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ABSTRACTS

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EPNS21-120 Oral or poster
Epilepsy: Diagnosis and Investigations

Development and validation of a clinical-genetic prediction model to facilitate early diagnosis of *SCN1A*-related epilepsies

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Objective: Pathogenic variants in the sodium channel α 1 subunit (*SCN1A*) gene are associated with a spectrum of epileptic phenotypes ranging from the severe Dravet syndrome (DS), marked by drug-resistant seizures and intellectual disability to the milder genetic epilepsy with febrile seizures plus (GEFS+). Our objective was to develop and validate a prediction model using clinical and genetic biomarkers to aid early diagnosis of *SCN1A*-related epilepsies.

Methods: We retrospectively reviewed clinical and genetic data for 1022 *SCN1A*-positive DS and GEFS+ patients consecutively referred for genetic testing (March 2001-June 2020) in seven countries. We computed a novel *SCN1A* genetic score for missense variants combining paralog conservation of the mutated amino acid position with the physicochemical properties of the observed substitution. Using a supervised machine learning approach, a training cohort was used to develop multiple prediction models that were validated with two independent blinded cohorts. Our primary outcome was the discriminative accuracy of the models at predicting DS over GEFS+.

Results: The frequency of DS was 616/743 (83%) in the training cohort, 147/203 (72%) in validation cohort 1 and 60/72 (83%) in validation cohort 2. DS was associated with a higher *SCN1A* genetic score ($p < 0.001$) and earlier age of seizure onset than GEFS+ ($p< 0.001$). A model combining the '*SCN1A* genetic score' and seizure onset separated DS from GEFS+ more effectively [area under the curve (AUC): 0.89 (95% CI: 0.86-0.92)] than all other models (AUC: 0.79-0.85; $p < 0.001$). The performance of the model was replicated in both validation cohorts 1 [AUC: 0.94 (95% CI: 0.91-0.97)] and 2 [AUC: 0.92 (95% CI: 0.82-1.00)].

Conclusions: The prediction model provides an objective estimation at disease onset of whether a child will develop DS or GEFS+. It will assist clinicians with prognostic counselling and in making decisions on instituting precision therapies early in the DS disease course, before cognition impairment emerges.

Keywords:
SCN1A; Dravet syndrome; GEFS+; Prediction; Risk Model

EPNS21-396 Oral or poster
Epilepsy: Diagnosis and Investigations

Comprehensive genetic testing in patients undergoing epilepsy surgery for malformations of cortical development. A pilot study.

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Objective: Malformations of cortical development represent the most common aetiology of drug resistant epilepsy in paediatric epilepsy surgery series; however, the diagnostic yield of genetic testing in real-life epilepsy surgery programs has not yet been clearly established.

Methods: Patients <19 years of age who underwent epilepsy surgery for drug-resistant epilepsy for malformations of cortical development (MCD) were included. Targeted gene panel sequencing and whole-exome sequencing for detection of germline variants and deep target capture sequencing for detection of somatic variants in unmatched brain tissues were performed. Germline variants were confirmed by Sanger sequencing, and segregation analysis was performed in patient-parents trios.

Results: Sixty-four patients underwent germline genetic testing, 29 patients somatic genetic testing. In five patients (5/29, 17.2%), we were able to detect (likely) pathogenic somatic variants. In seven patients (7/64, 10.9%), we detected (likely) pathogenic germline variants. Germline variants most frequently involved genes of GATOR1 complex (DEPDC5, NPRL2, NPRL3); somatic variation was observed in mTOR genes and SLC35A2.

Conclusions: Our study shows, despite a limited patient population, that patients with genetic structural epilepsies represent at least one tenth to one fifth of paediatric surgical population. These results highlight the important role of diagnostic genetic testing in epilepsy surgery programs.

Keywords:
epilepsy surgery, GATOR1 complex, mTOR, germline genetic testing, somatic genetic testing

EPNS21-586 Oral or poster
Epilepsy: Diagnosis and Investigations

Detection of deregulated miRNAs in childhood epileptic encephalopathies

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Objective: The pathogenesis of epileptic encephalopathies (EEs), independent of epilepsy, can be defined by genetic control mechanisms. Understanding what controls gene expression may open new avenues for the treatment or prevention of EEs. Therefore, the development of new treatment targets and strategies in EEs will reduce the risk of mortality and morbidity due to seizures and drugs used by individuals with this disease. For this purpose, identifying the relevant pathways and molecular mechanisms that coordinate gene expression is crucial for a better understanding of the pathogenic process and the development of new therapeutic approaches.
This study aimed to investigate the use of miRNAs as serum biomarkers for the determination and discrimination of EEs.

Methods: Whole blood samples obtained from 54 individuals in 2 groups designated as EEs patients group (n=24) and healthy controls (n=30) were included in this study. The expression levels of 10 miRNAs were determined using qRT-PCR. After the determination of expression levels, in neuron the correlation of upregulated miRNA levels and Ki67 index was calculated using the Pearson correlation test.

Results: The comparison of the EE patients group with healthy controls revealed the upregulation of one miRNAs (hsa-miR-324-5p) and downregulation of three miRNAs (hsa-miR-146a-5p, hsa-miR-138-5p, hsa-miR-187-3p).

Conclusions: It has been determined that miRNAs with altered expression are an important factor in the formation of epileptic seizures and seizure-induced neuronal death. The fact that processes that play a key role in epileptogenesis are under the control of miRNAs causes miRNAs to become meta-controllers of gene expression in the brain. Using this study as a starting point may enable the discovery of a test to determine to diagnosis for childhood EE. Especially, hsa-miR-146a-5p, hsa-miR-138-5p, and hsa-miR-187-3p can be used as biomarkers in the diagnosis of EE. A study on miRNA expression only in cases with EE was not found in the literature review.

Keywords:
Epileptic encephalopathy, Pediatric Neurology, Biomarker, microRNA

EPNS21-666 Oral or poster
Epilepsy: Diagnosis and Investigations

Diagnostic yield of next-generation sequencing in neonatal onset epilepsies. Impact on clinical management

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Objective: Neonatal seizures (NS) are the most common neurologic symptom in newborns. Glass et al., 2016 found that 9% of NS had a genetic origin. We evaluate the diagnostic yield of Next Generation Sequencing (NGS) in a population of NS of unknown etiology, analyze the clinical phenotype and study the impact of genetic diagnosis on the implementation of a targeted therapy.

Methods: Retrospective observational study of patients with NS of unknown aetiology followed at Pediatric Neurology Dpt. SJD Hospital between January 2012 and January 2021. Family history, perinatal data, epilepsy history, Video-EEG, metabolic screening, Brain MRI, and genetic tests (Panel, Clinical Exome (CES) or Whole Exome (WES)) were collected from electronic medical record and an anonymized database was created.

Results: Forty patients fulfilled inclusion criteria. Thirty-one underwent NGS genetic tests (20 epilepsy panel; 10 CES; 1 WES). NGS study detected pathogenic variants in 28/31 patients (diagnostic yield of 90%). The most frequent causes were KCNQ2 (14/28) and SCN2A (5/28). All patients had normal pregnancy, delivery and physical exam. Two patients (KCNQ2) had a familiar history for seizures. Seizures onset within first and third day of life and were sequential or tonic. Interictal neurologic exam was abnormal. 5/14 patients with KCNQ2 presented developmental and epileptic encephalopathy. Patients with KCNQ2 and benign neonatal familial epilepsy had normal neurological examination. Seizures started within first and fifth day and were sequential or clonic. Intercritical neurological examination was normal. All patients had normal neurodevelopment. Complete response to sodium channel blockers was obtained in KCNQ2, KCNA1 and SCN2A channelopathies.

Conclusions: In our series, the diagnostic yield was 90%. Channelopathies were the most prevalent cause. Genetic tests are crucial to obtain a diagnosis, to avoid unnecessary diagnostic test, to provide prognostic information and to establish a targeted therapy.

Keywords:
Neonatal onset epilepsy, next generation sequencing, targeted therapy

EPNS21-715 Oral or poster
Epilepsy: Diagnosis and Investigations

Clinical, health economic and environmental evaluation of a secure, carer recorded, clinical video transfer system for paediatric neurology

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Objective: An interactive cloud based platform allowing patients and carers to upload smartphone video and linked metadata for neurological diagnosis was designed by paediatric neurologists with a technology partner and established in 21 paediatric centres; the first from 1/5/2020. We describe the clinical utility, health economic and environmental impact of the technology (www.vcreate.tv/neuro).

Methods: Parent/carers are invited to register by their clinical team and utilise a password and passcode for access. Videos are uploaded with a structured history. The clinician classifies using drop-down menus of seizures and other events. Users and clinicians completed online evaluations. Government health economists evaluated the impact of the system. Distance travelled saved and carbon savings were calculated based on postcode to hospital and a small average family car.

Results: To 26/10/21, 8089 paediatric video uploads from 3054 patients. Five to 600 videos are uploaded per month. 353 physician/nurse users are registered. Postcode derived deprivation scores indicate equitable use across socio-economic groups. Videos classified as non-epileptic(59%), epileptic (33%), unknown(8%). Seizure types include: focal impaired awareness (23%), generalised tonic clonic(17%), epileptic spasms(11%). Non-epileptic events include: tics(7%), normal behaviour(11%), functional disorders (6%). Carers (523) report system easy or very easy to use (88%) with 2% finding the technology difficult. Clinicians (297) report video very useful (67%) or useful (25%) for diagnosis and prevented investigations in 44%. Video quality high (88%) or adequate(11%). Cost savings to health service estimated at £550 per patient. A minimum of 374,735km travel and 70 tonnes of CO2 was saved. Patients/Carers avoided a half-day (8%)or full-day absence (12%)off school or work.

Conclusions: The system facilitates remote care, communication & rapid diagnosis. Investigations are prevented or prioritised with efficiencies in patient pathways and cost saving.

Keywords:
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EPNS21-148 Poster only
Movement Disorders

POOLED EFFICACY AND SAFETY ANALYSIS OF INCOBOTULINUMTOXINA IN THE TREATMENT OF UPPER- AND LOWER-LIMB SPASTICITY IN CHILDREN WITH SEVERE CEREBRAL PALSY (GMFCS LEVELS IV AND V)

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Objective: This pooled analysis assessed the efficacy and safety of incobotulinumtoxinA for lower-limb (LL) and upper-limb (UL) spasticity in children and adolescents with cerebral palsy (CP) and Gross Motor Function Classification System (GMFCS) level IV or V using data from the first injection cycle in 2 randomized Phase 3 studies, TIM (NCT01893411) and XARA (NCT02002884).

Methods: Non-ambulant patients (pts; aged 2-17 years; uni- or bilateral CP; Ashworth Scale [AS] score >=2 in clinical patterns for treatment) with GMFCS level IV or V were analyzed.
Pts were randomized to 3 incobotulinumtoxinA dose groups: 8, 6, 2 U/kg body weight, maximum 200, 150, 50 U, per LL clinical pattern in TIM, and per UL in XARA. Additional multipattern treatment was allowed in both studies with total body doses up to 16 U/kg (<=400 U). Changes from baseline in AS score and Global Impression of Change Scale (GICS) scores at Week 4 were assessed in pts who had LL treatment (TIM and XARA) and pts who had UL treatment (XARA). Adverse events (AEs) were assessed.

Results: Of pts with GMFCS level IV or V, 164 had LL treatment and 108 had UL treatment. Statistically significant improvements in AS score for the pes equinus and flexed elbow/wrist and investigator's GICS for the LL and UL were seen with all incobotulinumtoxinA doses at Week 4 (P<0.0001 vs baseline). AS and GICS improvements were numerically greatest in the high-dose group. Efficacy was largely similar in patients with GMFCS level I-III.
AE frequency was generally <30.0% across dose groups and GMFCS levels I-V. The most common AEs for pts with GMFCS level IV or V were nasopharyngitis (7.0%) and pharyngitis (3.2%). Few treatment-related AEs (n=1), serious AEs (n=5), or AEs of special interest (n=2) occurred in pts with GMFCS level IV or V.

Conclusions: In children with severe CP (GMFCS level IV or V), incobotulinumtoxinA is effective, safe, and well-tolerated for multipattern/multilevel treatment of LL and UL spasticity.

Keywords:
GMFCS levels IV-V; Cerebral palsy; IncobotulinumtoxinA; Spasticity; Pediatric; Safety

EPNS21-187 Oral or poster
Neuro rehabilitation

MRI after hypoxic events in childhood: Temporal dynamics of cerebral diffusion restrictions

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Objective: Unlike perinatal asphyxia, little is known about MRI in children who suffered a hypoxic event during childhood or adolescence (e.g., by near-drowning, foreign body aspiration, cardiac arrythmia or strangulation). Here, we describe the time course of MRI diffusion restrictions (indicating cytotoxic oedema) in the early phase (0-90 days) after such post-neonatal hypoxic events.

Methods: We retrospectively analysed DWI (diffusion weighted imaging) and ADC (apparent diffusion coefficient) maps of 60 MRIs (42 previously healthy children, aged 29 days to 18 years when suffering the hypoxic event). For defined intervals after the hypoxic event (0-1 d; 2-3 d; 4-5 d; 6-7 d; 8-14 d; 15-30 d; 31-60 d; 61-90 d) and 10 anatomical structures we determined the ratio "number of MRIs with diffusion restriction of the analysed structure" to "total number of available MRIs in the analysed time period".

Results: On day 0-1 we found diffusion restrictions in putamen and caudate, as well as in primary sensorimotor, visual and auditory cortex, peaking at days 2-3. Then, starting at days 4-5, we found diffusion restrictions in the deep white matter and in the corpus callosum, with a peak at days 6-7. Diffusion restrictions of the hippocampus also started at days 0-1 but showed no clear peak.

Conclusions: The appearance of diffusion restrictions in cerebral MRI in the early phase after a hypoxic event suffered in childhood or adolescence takes place in a characteristic temporal sequence. 1st peak: grey matter (striatum + primary cortical areas) on days 2-3; 2nd peak: white matter on days 6-7.
Hence, when assessing diffusion restrictions in the early phase after a hypoxic event, it is crucial to be aware of this characteristic temporal sequence to better understand the overall impact of the injury. Ongoing analyses will have to elucidate the prognostic value of these patterns.

Keywords:
MRI, hypoxia, hypoxic, diffusion, near-drowning

EPNS21-518 Oral or poster
Neuro rehabilitation

PowerVR: A New Intervention Tool in Pediatric Neurorehabilitation to treat Social Deficits

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Objective: The aim was to determine the structure of acquired social deficits (SD) in children with neurological disorders (ND) and designate efficacy of PowerVR, a novel rehabilitation tool.

Methods: 60 children with SD and ND aged 8-13 years participated: 28 with epilepsy, 10 TBI, 3 tic disorders, 3 stroke, 16 with other ND. 16 patients (M=10.5 yrs, SD=1.8) completed trainings with pre- and postintervention assessments. 44 patients in Delayed treatment group participated at Baseline assessment (M=10.2 yrs, SD=1.6).
PowerVR combines Multitouch-Multiuser TableTops (MMT), Social Virtual Reality (SocialVR) and NeuroVR platforms. Intervention consists of 10 sessions guided by therapist. Paired training (with 2 age-matched patients) includes interactive apps on MMT: Snowflake and NoProblem to develop social skills. In individual training, SocialVR and NeuroVR programs were used. Authors developed 10 VR metaphors to practice socially challenging situations (anxiety level was monitored by BP and heart rate). Improvements were assessed with NEPSY-II, FOS, BRIEF-2, Sentence Completion Task, Spence Anxiety Scale.

Results: The most impaired social domain was verbal theory of mind (ToM) skills. 64% of children presented behavioral problems related to executive dysfunctions based on parental questionnaires. Patients lacked conflict resolution abilities (38% out of 100%) and empathy (25%).
After the training, communication and cooperation skills, friendship, and conflict resolution improved up to 62%. Verbal ToM and understanding false beliefs improved ($p<0.005$), and social anxiety decreased. In NeuroVR (Mirror/Ball; Electric Track) fine motor skills, hand-eye cooperation were practiced. Based on self-reports, starting conversations and making friends became easier, bullying decreased.

Conclusions: PowerVR is a novel and motivating technology, which enables children to improve communication skills in a safe environment. Combined MMT/VR method increases power for the multicomponent training of socio-communicative skills.

Keywords:
neurorehabilitation, children, socio-communicative deficit, virtual reality, neurological disorders, technology-based training

EPNS21-524 Oral or poster
Neuro rehabilitation

Efficacy of Virtual Reality Therapy assisted Modified Constraint Induced Movement Therapy in children with hemiparetic cerebral palsy using fMRI - An open labelled, randomized controlled trial

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Objective: To evaluate the efficacy of 8 weeks of VRT reinforced mCIMT versus mCIMT alone, in improving upper limb function as per increase in total Quality of Upper Extremity Skill Test(QUEST) scores and changes in cortical and functional reorganization in terms of changes in fMRI parameters in children (>/= 5-18 years) with hemiparetic cerebral palsy

Methods: This is an open-labeled, randomized controlled, parallel design, superiority trial wherein 49 children between 5-18 years were enrolled and randomized into intervention (n=25; VRT assisted mCIMT) and control (n=24; only mCIMT) groups. The intervention was provided for 8 weeks as supervised therapy, and 4 weeks of unsupervised therapy. Improvement in hand function at the end of 8 weeks was analyzed using the QUEST score. VRT was delivered through a Kinect motion sensor system. Functional cortical activation was analyzed pre, and post-supervised intervention sessions (8 ± 1 week).

Results: There was a significant improvement in the total QUEST and subdomain scores in both the groups ($p<0.05$), with children in intervention group having a greater improvement compared to control group (MD, 95% CI- 8.58(1.56-15.60), $p<0.05$) at the end of 8 and 12 weeks. The effect size was 2.05 (1.3-2.7). FMRI analysis in VRT group showed some positive changes in the BOLD cluster activation in right hemiparetic patients with activation of ipsilesional motor cortex on follow up compared to the baseline, whereas there were no significant alterations in the mCIMT group and no statistically significant difference between the groups

Conclusions: VRT assisted mCIMT can bring about significant increments in the functional outcomes, compared to mCIMT alone in children with hemiparetic cerebral palsy, however without any significant structural and functional cortical changes.

Keywords:
hemiparetic cerebral palsy, virtual reality, functional MRI

EPNS21-532 Oral or poster
Neuro rehabilitation

Next-Generation Therapist - Social Robot Pepper in Paediatric Neurorehabilitation

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Objective: The aim of the study was to develop and deploy social robot Pepper as a therapist in the rehabilitation process in children with communication and speech disorders

Methods: Neural speech synthesis technology Neurokone (text-to-speech solutions) with synthetic children's voices was used to deliver a talk-based treatment program with an embodied robot. Using Software Framework we programmed and implemented relevant behavioral and communication rehab models.
Training with Pepper consisted of ten 30-minute sessions with different social, language, and movement tasks. 22 children (12 boys /10 girls) aged 5-7 yrs with epilepsy, TBI or movement disorders and social deficit (assessed by NEPSY-II Social domain) participated. Child-like Pepper (h 120 cm, w 28kg; created by Softbanks 2014), conducted training as a therapist.

Results: All children (22/22) were quickly engaged in training, without needing extra motivation. Children, who showed defiance (4/22) prior to rehab, immediately started to cooperate. Improved verbal and non-verbal communication skills: children used full sentences, held eye-contact, laughed etc. Effectiveness of training was demonstrated by individual enhanced vocabulary, cooperation skills, and empathy. Educational tasks on the Pepper's tablet screen attracted children, with improving cognition, emotional skills and social attention. 100% compliance and children's positive feedback showed suitability of artificial intelligence (AI) involved in speech and social skills multi-session treatment program. Still, at the moment a need for therapist exists for guiding child through training process.

Conclusions: Social robots that can communicate and interact with children have opened a new era in pediatric neurorehabilitation. Robot-delivered sessions were attractive, motivating and helped children change their behaviours. In future the automation of therapeutic sessions using humanoid Pepper makes the work of therapists more efficient and less time-consuming.

Keywords:
social robot, children, neurorehabilitation, social deficit, Pepper, speech disorders

EPNS21-352 Oral or poster
Cerebrovascular Disorders

Pediatric stroke: Clinical presentation, risk factors and outcomes. A single tertiary center 10-years retrospective review from the UAE

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Objective: Epidemiological data on childhood stroke from Middle East remains limited, This is a first-time ever data on the aetiology, type and predictors of outcome of paediatric stroke in Emirati children.

Methods: Retrospective review of children, 1 month to 16 years, admitted in Sheikh Khalifa Medical City hospital in UAE, from 2011 to 2020.

Results: 79 children with stroke were identified, 46(58.3%) were males. 50 % were older than 6 years of age. Underlying risk factors included cardiac diseases (38%), congenital vasculopathy (23%), infections and haematological diseases each (17%). 15% of the cohort were previously healthy with no underlying predisposing factors. The cardinal presenting symptoms were focal deficits (53%), altered level of consciousness (52%), seizures (33%), headache (23%), dysarthria, vomiting and visual changes (37%) collectively. Ischemic strokes were more prevalent than hemorrhagic and mixed strokes; 49.4% 34.1%, and 16.5% respectively. Most common affected vascular territory was the left middle cerebral artery (50.6%) in ischemic strokes. The use of MRI versus CT as a first diagnostic tool showed statistical difference of sensitivity (P= 0.03). The median time from symptom onset to diagnosis was 8 hours. The overall mortality was 20%, evident among hemorrhagic stroke 37.5% (p= 0.007), and inversely correlated with GCS (P=0.01). Among those who survived, 58% had severe to moderate functional disability (modified Rankin Scale-3) at the time of discharge, of which 26% persisted at 6 month and 16% at one year. 40% of our cohort had variable degrees of learning difficulties and behavioural difficulties and need for special schooling post stroke. Recurrence within one year of initial diagnosis was found in 6%.

Conclusions: This study highlights that prognosis varied with the aetiology of stroke, time to diagnosis and conscious level at presentation. No significant role of age, focality and location of stroke (Cortex, brain stem, basal ganglia and cerebellum) on outcomes was noted.

Keywords:
Stroke

EPNS21-426 Oral or poster
Cerebrovascular Disorders

Recanalization Treatments In Pediatric Stroke: Safety and Efficacy Data From The French KIDCLOT Study

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Objective: Safety and efficacy of recanalization treatments, i.e. intravenous thrombolysis (IVT) and/or mechanical thrombectomy (MT), have to be refined in pediatric stroke.

Methods: The French KIDCLOT multisourcing nationwide retrospective study (NCT03887143) collected data of consecutive children aged >28 days and <18 years old with acute arterial ischemic stroke who had a recanalization treatment, during a 41 month-period.

Results: 68 patients, 44 boys (64.7%), median age at stroke onset 11.5 years old, were included. Pre-stroke mRS was 0 for 89.7%. Main stroke etiologies were cardio-embolic (30.9%), focal cerebral arteriopathy (FCA, 25%), cervical (carotid/vertebral) arteriopathy (13.2%), and thrombotic (11.8%). 70 pediatric procedures were recorded: IVT alone (n=31), MT alone (n=23), combined IVT and MT (n=14), and digital subtracted angiography without recanalization treatment (n=4). Median stroke onset to first recanalization treatment delay was shorter when the patient was managed in adult stroke units than in pediatric wards (188 vs. 264 minutes respectively, p=0.0087). An early complication was reported for 6 procedures, including two significant intracranial hemorrhages. After MT, cardio-embolic stroke patients achieved good arterial recanalization more frequently than FCA patients (88.9% vs 33.3%). Although high initial severity markers (median NIHSS = 13.5, decreased consciousness in 52.2%, decompressive craniectomy in 17.1%), outcome was relatively good in the 65/68 survivors (median mRS = 1 and PSOM = 1 at 12 month-follow-up).

Conclusions: This study provides encouraging safety data despite severe stroke presentations. It suggests potential ways to improve recanalization treatments efficacy in children: reducing management delays in pediatric wards and optimizing etiological orientation since the hyperacute phase, as cardio-embolic strokes seem to display a better recanalization rate profile.

Keywords:
stroke, thrombolysis, thrombectomy, focal cerebral arteriopathy

EPNS21-453 Oral or poster
Cerebrovascular Disorders

Early MRI diagnosis of Sturge Weber Syndrome type 1 in infants

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Objective: Patients with Sturge-Weber syndrome type 1 (SWS1) have a port-wine birthmark (PWB) as cutaneous hallmark. Up to 35 % of neonates with a high risk PWB in the first trigeminal branch develop SWS1. Clinical manifestations are severe and often progressive. Especially early onset seizures are associated with worse neurocognitive outcome. Identification of pre-symptomatic SWS1 patients is hampered because standard brain MRI in the first months of life does not always show the for SWS1 characteristic leptomeningeal angiomatosis (LMA).
Therefore, the objective of this study was to identify sensitive and specific MRI predictors for early SWS1 diagnosis.

Methods: In this retrospective single centre study, we included 24 SWS1 patients and 20 controls. We studied specificity and sensitivity for SWS diagnosis of LMA and indirect MRI signs such as choroid plexus (CP) size and thickness, white matter hypermyelination, lobar cerebral atrophy, ischemia and cortical calcifications.

Results: In SWS1 patients CP thickness and CP thickness ratio on non-contrast brain MRI was significantly increased. The optimal cut-off value of 5.6 mm on the affected side corresponded with a sensitivity of 91.7% and a specificity of 100% for confirmation of SWS1 diagnosis. In 21% of children aged < 3 months with a later confirmed SWS1 diagnosis, LMA on initial MRI could not be discerned but CP thickness > 5.6 mm on the affected side confirmed SWS1 diagnosis.

Conclusions: CP size ratio and thickness are sensitive and specific signs additional to LMA to confirm SWS1 diagnosis in young infants and may be of use to reliably select pre-symptomatic patients.

Keywords:
Sturge Weber syndrome, prediction, MRI diagnosis, choroid plexus, leptomeningeal angiomatosis, infant

EPNS21-613 Oral or poster
Cerebrovascular Disorders

Royal College of Paediatrics and Child Health (RCPCH) Stroke in Childhood Guidelines adherence in South Wales

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Objective: RCPCH Stroke guidelines were proposed in 2017 to improve the recognition and management of childhood stroke cases commensurate with adult stroke cases.Paediatric stroke is an important cause of death and long-term disability, estimated to affect 400 children per year in the UK.

Methods: We audited the adherence to RCPCH Stroke in Childhood guidelines for the acute management of children diagnosed with stroke in South Wales over four years (June 2017 to June 2021). Information on patient demographics, presenting symptoms, types of stroke, assessment of the Paediatric National Institute of Health Stroke Severity (PedNIHSS) score, time interval to conduct brain imaging, and outcomes was collected.

Results: The audit identified seventeen patients over the four years, with 9 girls and 8boys.Age at presentation ranged between 2to16 years.At presentation,14 out of 17 patients were FAST (Face, Arms, Speech and Time) positive.
PedNIHSS score was documented in one case.

Three patients had brain imaging within one hour of presentation.However, only one of these patients had CT angiogram,as recommended by the guidelines.

Nine patients had an acute ischaemic stroke, the majority of which involved the middle cerebral artery territory. One patient had a posterior circulation stroke. Eight patients had stroke presentations related to a vascular malformation or haemorrhage, of which two patients died. In the cohort, seven patients had residual neurologic sequelae, while three had complete resolution of symptoms.

Conclusions: Most children with stroke attended with FAST clinical sign at presentation, which unfortunately did not trigger timely recognition or management of these cases.
There is an urgent need to improve stroke awareness by developing regional pathways and targeted training for clinicians to improve guideline adherence and outcomes for children with stroke.

Keywords:
Stroke in Childhood, FAST, PedNIHSS

EPNS21-656 Oral or poster
Cerebrovascular Disorders

Neonatal Arterial Ischemic Stroke: a fifteen-year-long multicentre study.

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Objective: Aims of this study are:
i) to report for the first time the case series of neonates who presented an arterial ischemic stroke (nAIS) and were enrolled in the Italian Registry of Infantile Thrombosis (RITI);
ii) to perform literature review on nAIS and to compare the results with our population.

Methods: RITI is an observational, longitudinal, multicentre study that includes patients who presented nAIS from January 2007 to May 2021 and were admitted to one of the 25 paediatric hospital participating in the study.
Studies on Pubmed concerning nAIS in form of registry or case report were analysed and then compared with our case series through descriptive analysis.

Results: RITI population consist of 152 patients; 4589 patients were instead identified from the literature review.
Male prevalence is common; mean age of onset of symptoms is 5 days (vs 0.8-4.2 d from literature review, LR).
Multifactorial aetiology of stroke has been confirmed: in our population 60% of patients has two or more risk factors. They are maternal infection (14.4% vs 8-30% LR), prolonged rupture of membranes (15.3% vs 6-37% LR), congenital heart disease (39.5% vs 0-38%) and perinatal infections (19.1% vs 3-26% LR).
Seizures are the most frequent onset presentation (73.6% vs 31-100% LR).
nAIS is typically characterized by a single lesion in the left hemisphere and it requires antithrombotic therapy in 16% of patients (vs 2-19% LR).
After a mean hospitalization of 22 days, 42% of RITI patients reported neurological deficits, similar to literature studies' population (23-49%).
At the least available follow up (average duration 2.9 y vs 2-8 y LR) neurological deficits persist in 40% of RITI's cases (vs 8-68% LR). Long-term mortality is low (4% RITI vs 0-4% LR).

Conclusions: RITI registry, that is the fifth in the world for numerosity, lays the foundation for deepening our knowledge on thrombosis and to improve diagnosis and management of these pathologies.

Keywords:
neonatal stroke

EPNS21-163 Oral or poster
Neuromuscular

Onasemnogene Abeparvovec for Presymptomatic Infants with Spinal Muscular Atrophy and Two Copies of SMN2

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Objective: The Phase III SPR1NT study investigated onasemnogene abeparvovec efficacy and safety in presymptomatic patients at risk of spinal muscular atrophy type 1 (SMA1).

Methods: Fourteen presymptomatic patients (biallelic *SMN1* deletions, 2 *SMN2* copies) were enrolled. Primary endpoint was independent sitting for ≥30 seconds (Bayley-III #26) by 18 months. Secondary endpoints were survival (no death/permanent ventilation) at 14 months and maintaining body weight (≥3rd WHO percentile) without feeding support at any visit. Exploratory endpoints included CHOP INTEND and Bayley-III assessments. Safety evaluations included adverse events (AEs), concomitant medications, physical examinations, vital signs, cardiac indices, and laboratory data. Primary and secondary outcomes were compared with a Pediatric Neuromuscular Clinical Research (PNCR) natural history cohort.

Results: All primary and secondary endpoints were statistically significant compared with the PNCR cohort ($p<0.001$). All 14 patients sat independently (11/14 within WHO-MGRS developmental window), all survived without permanent ventilation, and 13 (93%) maintained body weight without feeding support. No patient used nutritional/respiratory support (including cough assist). Eleven patients stood (Bayley-III #40) and nine walked (Bayley-III #43) (7/11 and 5/9 within WHO-MGRS developmental windows, respectively). All 14 patients achieved CHOP INTEND score of ≥58 (max score=64) during ≥1 follow-up visit. All 14 demonstrated ≥15-point increase in Bayley-III scores. All patients had AEs. Pyrexia, upper respiratory tract infection, and constipation were most common. Ten patients had ≥1 treatment-related AE. No serious AEs were considered treatment-related by investigator.

Conclusions: Onasemnogene abeparvovec was efficacious and well-tolerated for presymptomatic patients at risk of SMA1. All patients survived without nutritional/respiratory support. All sat independently, most within the normal developmental window. No new safety signals were identified.

Keywords:
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EPNS21-192 Oral or poster
Neuromuscular

Onasemnogene Abeparvovec in Presymptomatic Spinal Muscular Atrophy (SMA): SPR1NT Study Update in Children with Three Copies of SMN2

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Objective: SMA causes loss of motor and respiratory function because of *survival motor neuron 1* (*SMN1*) gene deletion/mutation. Copies of *SMN2* modify disease severity. A range of phenotypes may occur with three *SMN2* copies, and approximately 85% of patients develop symptoms in infancy and are unable to walk independently without intervention. SPR1NT (NCT03505099), a multicentre, open-label, Phase III study, evaluated the safety and efficacy of onasemnogene abeparvovec in presymptomatic SMA patients with three copies of *SMN2*.

Methods: Presymptomatic patients expected to develop SMA (biallelic *SMN1* deletions, three *SMN2* copies) received a one-time intravenous infusion of onasemnogene abeparvovec and were assessed through 24 months. Primary outcome was standing unassisted for ≥3 seconds by 24 months of age. Secondary outcome was independent walking by 24 months. Safety outcomes included incidence of adverse events (AEs)/serious AEs. Primary and secondary outcomes were compared with a cohort from the Pediatric Neuromuscular Clinical Research (PNCR) natural history data set.

Results: Fifteen patients were enrolled, and all completed the study. Primary and secondary endpoints were statistically significant compared with the PNCR cohort ($p<0.001$). All patients were alive, and none used ventilatory or feeding tube support at any time. All 15 patients achieved the ability to stand alone (14 within the WHO-MGRS developmental window). Fourteen patients also walked alone (11 within the WHO-MGRS developmental window). All patients had AEs. Eight patients (53%) had at least one treatment-related AE, and three patients had serious AEs. No serious AEs were considered treatment-related by investigator.

Conclusions: Onasemnogene abeparvovec was efficacious and well-tolerated for presymptomatic SMA patients with three *SMN2* copies. All patients survived, and none used ventilatory or feeding tube support. All achieved the ability to stand alone, most within the normal developmental window. No new safety signals were identified.

Keywords:
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EPNS21-261 Oral or poster
Neuromuscular

Treatment with onasemnogen abeparvovec in spinal muscular atrophy: an observational, multicenter cohort study

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Objective: To date there are limited data on efficacy and safety data available in children with spinal muscular atrophy (SMA) >24 months, >8.5 kg and after pre-treatment with nusinersen on the gene replacement therapy (GRT) with onasemnogene abeparvovec. We aimed to provide data on efficacy and safety, especially liver dysfunction, in a real-world cohort.

Methods: In this prospective, multicentre observational study, children with SMA who received gene replacement therapy between 09/2019 and 04/2021 at 18 neuropediatric centres in Germany and Austria were examined over at least six months according to the German consensus paper. Motor function 6 months before, at the time of and after GRT (CHOP INTEND / HFSME) was analyzed with respect to age (>=8 months, >8 and < =24 months, >24 months), SMA type, SMN2 copy number, sex and pre-treatment with nusinersen. Furthermore, clinical side effects and laboratory values were evaluated, and the duration and amount of steroid therapy required.

Results: 76 children with SMA (58 pre-treated with nusinersen, 18 treatment-naïve) with a median age/weight of 16.8 months (0.8-59 months)/9.1 kg (4.0-15.0 kg) were treated with onasemnogene abeparvovec. CHOP INTEND and HFSME scores improved significantly in 49/60 children, especially in children <24 months. 45 children pre-treated with nusinersen also significantly improved after switching therapy. Adverse effects included fever, vomiting and thrombocytopenia during the first week after GRT. Six patients developed (sub)acute liver dysfunction, one of whom acute liver failure. The increase in liver enzymes correlated with increasing age and weight at the time of therapy. The median time of treatment with prednisolone was increased to15.7 weeks compared to the manufacturer's information.

Conclusions: SMA patients <=24 months of age benefit significantly from GRT with onasemnogene abeparvovec, regardless of pre-treatment with nusinersen. Severe side effects may occur and require close follow-up at a specialised centre.

Keywords:
Spinal muscular atrophy, onasemnogene abeparvovec, liver dysfunction

EPNS21-602 Oral or poster
Neuromuscular

Corticosteroid regimens for Duchenne Muscular Dystrophy: results of an international comparative safety and efficacy randomized controlled trial

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Objective: According to Care recommendations, corticosteroids should be discussed with all patients who have been diagnosed with Duchenne Muscular Dystrophy (DMD). Although the benefits of corticosteroids are well established, there is still uncertainty regarding the best regimen and dosage. This has led to inconsistency in corticosteroid prescription in DMD affecting clinical care and confounding the results of clinic trials.

Methods: We completed a randomized, double blind, parallel-group clinical trial comparing benefits and side effects of the three most commonly prescribed corticosteroid regimens in boys with DMD. Participants were randomized 1:1:1 to receive daily prednisone (0.75 mg/kg), daily deflazacort (0.9 mg/kg), or intermittent prednisone (0.75 mg/kg 10 days on/10 days off). Boys were evaluated for three years. The three-dimensional primary outcome comprised rise from the floor velocity, forced vital capacity, and participant/parent global satisfaction with treatment. Secondary efficacy outcomes included time to walk/run 10 meters, distance walked in 6 minutes, and North Star Ambulatory Assessment total score. Safety outcomes included height and weight, behavioral measures, and adverse events.

Results: the study was run at 32 sites across 5 countries and enrolled 196 boys with DMD not previously treated with corticosteroids. The mean age at randomization was 5.9 (standard deviation, SD 1 year). Comparative trajectories of the functional outcome measures and frequency and severity of reported adverse events including steroid-associated side effects over the 3 year duration of the study will be presented.

Conclusions: The data from this study should support the standardization of corticosteroid prescription in DMD. Moreover, the study describes the benefit and side effect profile of corticosteroids which can be useful to design clinical trials and assess the effects of new interventions and treatments.

Keywords:
Duchenne, corticosteroids, prednisone, deflazacort, regimen

EPNS21-621 Oral or poster
Neuromuscular

Efficacy and safety of Vamorolone in Duchenne muscular dystrophy (DMD)

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Objective: Vamorolone is a first-in-class steroidal drug that shares some activities with the corticosteroid class, with the additional potential of improved safety.

Methods: We conducted a randomized, double-blind, placebo and prednisone controlled, confirmatory efficacy and safety trial of vamorolone in steroid-naïve 4-<7 years boys with DMD(VBP15-004).

Results: The study showed significant motor function improvement over 24 weeks for the 2.0 and 6.0 mg/kg/day dose groups as confirmed by change from baseline to week 24 vs placebo on time to stand velocity (vamorolone 6.0 mg/kg/day p=0.002, 2.0 mg/kg/day p=0.017) 6-minute walk test (6.0 mg/kg/day p=0.003, 2.0 mg/kg/day p=0.009) and time to run/walk 10 meters velocity 6.0mg/kg/day p=0.002).
Deceleration of growth was seen in prednisone but not in vamorolone-treated participants (least square means [standard error] prednisone -1.58%tile [1.41] vs. vamorolone 6.0 mg/kg/day +3.40%tile [1.55]; p=0.02). Bone remodeling biomarkers were reduced by prednisone, but not by vamorolone (p<0.001 for all comparisons).
A previous open-label, 24-week trial (VBP15-003, n=48; age 4- <7 years) with a 24-month long-term extension (VBP15-LTE) in DMD also showed that vamorolone 2.0 and 6.0 mg/kg/day improves some motor outcomes as compared with corticosteroid-naïve individuals and does not cause growth deceleration.
When comparing 2-year treatment period of vamorolone (VBP15-LTE) vs. real-world corticosteroid data from two large DMD cohorts (NorthStar UK Network and CINRG Natural history study in DMD) no significant differences were observed in motor outcomes.

Conclusions: Vamorolone appears to be an effective and safer alternative to standard-of-care corticosteroids in DMD. Data from all studies demonstrates similar disease-modifying effect to corticosteroid real-world treatment data over a 2-year treatment period while limiting side effects. Period 2 data from VBP15-004 will provide further prospective, blinded safety and efficacy data

of vamorolone for the treatment of DMD.

Keywords:
Duchenne, vamorolone, prednisone, safety

EPNS21-188 Oral or poster
Inflammatory Disease of the CNS

Safety and efficacy of therapeutic apheresis in pediatric neurology: a French retrospective multicentric study

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Objective: To demonstrate safety and efficacy of therapeutic apheresis, i.e. therapeutic plasma exchange (TPE) and immunoadsorption (IA), in acute pediatric neurologic disorders.

Methods: This retrospective cohort study recruited 126 children less than 18 years undergoing TPE or IA across 9 French tertiary centers between 2014 and 2019. Patient characteristics, treatment schedules, complications and outcome were reviewed.

Results: Median age at initiation of TPE or IA was 7 years (0,7 - 18). Twenty-seven children underwent IA and 100 children underwent TPE. Indications included acute demyelinating syndromes (n=47), auto-immune encephalitis (n=50), myasthenia gravis (n=7) and peripheral nervous system disorders (n=26). Patients underwent a median of 9 procedures (range 3-60). Modified Rankin Score (mRS) reduction was significant by completion of therapeutic apheresis (median mRS before procedure 5 ± 0.9 vs median mRS after procedure 3 ± 1.2, $p<0.01$), and by 6 months follow-up (median 2 ± 1.4, $p<0.01$).
Adverse effects during procedure occurred in 23 % of cases during TPE and 37% of cases during IA.

Conclusions: This large multicentric national study confirms safety and efficacy of therapeutic apheresis in acute pediatric neurologic disorders.

Keywords:
Children, apheresis, therapeutic plasma exchange, immunoadsorption, safety, efficacy, pediatric neurology

EPNS21-202 Oral or poster
Inflammatory Disease of the CNS

Neurologic and radiographic findings associated with Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS) in Children

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Objective: Our aim was to report neurological manifestations of children with Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS- TS)

Methods: Patients (<18yrs) presenting to Great Ormond Street Hospital between April 4, 2020, and May 1, 2021 fulfilling PIMS-TS criteria, were included. Clinical and paraclinical features were retrieved retrospectively from electronic patient records

Results: Data was available for 125 patients who presented during the study period. Median age was 10 years (IQR 7, 12), 71 (56.8%) were male and 96 (76.8%) were of non-white ethnicities. New-onset neurological symptoms were reported in 68/108 (63.0%); headaches (n=47), encephalopathy (n=41), hallucinations (n=15), ataxia (n=12), dysarthria/dysphonia (n=12), peripheral nerve involvement (n=3), and seizures (n=1). Thirteen patients had CSF examined; one patient had 118 leukocytes in CSF. Abnormalities were noted in 16/32 patients with neuroimaging, with splenium of the corpus callosum signal changes most commonly seen in 9 patients. An excess of slow activity was found in 78/98 who had an EEG; 38 mild, 34 moderate and 7 had severe encephalopathy on EEG. Myopathic and neuropathic changes were seen 7/12 who underwent nerve conduction studies and electromyography (EMG). Children with neurological involvement had higher peak inflammatory markers and were more likely to be ventilated and require inotropic support in PICU ($p<0.05$).

Conclusions: Children with PIMS-TS presented with new neurological symptoms involving both the central and peripheral nervous systems, in the absence of respiratory symptoms. Neurological symptoms were seen more frequently in more severe presentations.

Keywords:
SARS-CoV-2 , PIMS-TS

EPNS21-339 Oral or poster
Inflammatory Disease of the CNS

Severity Scoring for Paediatric Autoimmune Encephalitis: PASS

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Objective: The modified Rankin Scale (mRS) is widely used to score disease severity but is coarse (7-point) and insufficiently weighted to non-motor aspects of autoimmune encephalitis (AE). To test the clinimetric properties of the 30-point Paediatric AE Severity Score (PASS), recently developed by international collaboration, we evaluated its discrimination of AE subtypes and relationship with key clinical variables (duration of hospitalisation, long-term outcome) in comparison to mRS.

Methods: Patients admitted to our tertiary centre since 2015 with new onset AE according to consensus diagnostic criteria were included. Weekly PASS and mRS scores were assigned retrospectively by review of electronic patient records over the first 2 months of disease. Statistical analyses utilized Spearman's correlation, Mann Whitney U-test and Wilcoxon signed-rank test.

Results: 284 scores were analysed in 23 patients (8 with NMDA-receptor antibody encephalitis [NMDARE]). Median (IQR) PASS was 13 (4-20.5) at peak versus 8 (1-12) at discharge ($p=0.01$); median mRS was 5 (2.5-5) at peak versus 2 (2-2.5) at discharge ($p=0.01$). Peak PASS showed stronger correlation with duration of hospitalization compared to mRS ($r=0.843$ vs 0.707, both $p<0.001$). Longitudinal PASS plots revealed generally worse severity and longer plateau in NMDARE compared to other AE subtypes, with significant differences at days 0 (12 vs 5, $p=0.007$), 7 (14 vs 5, $p=0.026$), 35 (16 vs 7, $p=0.004$) and 2 months (13 vs 7, $p=0.020$). Both peak PASS and mRS correlated only weakly with long-term outcome (not statistically significant).

Conclusions: In comparison to mRS, application of PASS in acute AE enabled better delineation of disease severity, which correlated strongly with duration of hospitalization, and revealed significant differences between NMDARE and other AE subtypes. We envisage that PASS could be useful both in clinical trials and to help inform treatment escalation decisions in routine clinical practice.

Keywords:
Autoimmune encephalitis, NMDA-receptor antibody encephalitis, Paediatric autoimmune encephalitis severity scoring, PASS

EPNS21-597 Oral or poster
Inflammatory Disease of the CNS

Real life application of diagnostic criteria for pediatric autoimmune encephalitis: preliminary data from a large Spanish cohort

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Objective: To test the accuracy of the most recent criteria for pediatric autoimmune encephalitis (AE).

Methods: Application of international criteria for encephalitis (Venkatesan's Criteria 2013 (VC)) and for pediatric AE (Cellucci's criteria 2020 (CC)), in a cohort of children with suspected AE prospectively recruited from a multicenter study in Spain, between 2012-2021. Antibody (Ab) testing was performed by immunochemistry on rat brain tissue, cell-based assays, and cultures of neurons.

Results: 705 patients (52% males, median age 7yo (IQR 3-11yo) were enrolled. 486 (69%) patients met VC. The main diagnosis in those 219 (31%) that did not fulfill VC included psychiatric primary disorders and epilepsy. Prior to paraclinical studies, 432 (61%) fulfilled criteria of "possible AE" according to CC, but only 345 (49%) had also evidence of paraclinical inflammation that would have recommended empirical immunotherapy. After Ab results, 217 (31%) fulfilled the criteria as "probable Ab negative AE" and 143 (20%) as "defined Ab positive AE".
CC for "possible AE" with evidence of paraclinical inflammation had 94% sensitivity and 52% specificity for the final diagnosis of Ab positive AE. Among the 273 that did not fulfill CC, only 10 (4%) had a final diagnosis of AE associated with neuronal or glial antibodies (6 MOG, 3 GFAP, 1 GlyR).

Conclusions: International criteria for possible AE are useful and sensitive guiding at the initial diagnostic process. However, specificity is low for final diagnosis of Ab positive AE. This has to be taken into account when guiding immunotherapy given the high prevalence of non-inflammatory disorders (e.g. psychiatric primary disorders, epilepsy) in cohorts of children with initial suspicion of AE.

Keywords:
Autoimmune encephalitis, encephalitis criteria, ADEM, MOG, NMDAR.

EPNS21-609 Oral or poster
Inflammatory Disease of the CNS

Anti-NMDAR encephalitis in patients younger than 2 years old

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Objective: Anti-N-methyl-D-aspartate (NMDAR) encephalitis has been recognized as one of the most frequent autoimmune encephalitis (AE) in children. Diagnosis in a child, especially in those under two years of age, is a challenge. Here study the disease in this group of patients.

Methods: Patients <2yo with suspected AE sent to our laboratory for antibody testing from 2011-2021 were reviewed. NMDAR antibody testing was performed by immunohistochemistry and cell based assays. Comparision of AE triggers was performed with a cohort of older children (2-18yo) with anti-NMDAR encephalitis recruited in our center over the same period.

Results: From 260 children <2 yo with suspected AE, 47 were diagnosed with anti-NMDAR encephalitis (median age 12 months, IQR 9-21mo). Twenty-seven (57%) had history of herpes virus encephalitis in the previous weeks before AE onset (HSE group), and in 20(33%) no previous trigger (viral or tumoral) was identified (non-HSE group). The frequency of HSE-triggered NMDAR encephalitis was much higher in children < 2yo than in children >2yo, 57% vs 6%, p <0.001. First symptom at presentation was different between children with and without HSE history (behavioral alteration in the HSE group and seizures in the non-HSE group, p = 0.03541). Epileptic spasms were seen in both groups at onset of AE although they were more frequent in the HSE group (8 [30%] vs 1[5%], p= 0.05861). The HSE group showed worse outcome at last follow-up (median mRS 4 IQR [4-5] vs median mRS 2 IQR [1.25-3-75], p=0.009679). The need of nasogastric tube at onset was a risk factor for bad outcome (p=0.01389), but immunotherapy or need for admission to the intensive care unit were not related with outcome.

Conclusions: HSE-triggered NMDAR encephalitis is much frequent in children <2yo than in older children. This group of patients have different symptom presentation and worst outcomes than children with non-related HSE NMDAR encephalitis.

Keywords:
NMDAR, CHILDREN, PEDIATRIC, Herpes virus encephalitis

EPNS21-131 Oral or poster
Epilepsy: Miscellaneous

Predictors of health-related quality of life in Dravet syndrome: a ten-year follow- up study

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Objective: Dravet Syndrome (DS), caused by mutations in the SCN1A gene, is a severe developmental and epileptic encephalopathy, leading to reduced health related quality of life (HRQOL). This 10-year follow-up study investigated long-term predictors of HRQOL in DS.

Methods: Clinicians of 141 SCN1A-positive patients recruited in 2009 were contacted, 140 responded. 10 patients were lost to follow up, 7 patients died, 10 patients had non-DS SCN1A-related phenotypes. The remaining 113 families completed questionnaires used in the original study: Epilepsy & Learning Disabilities Quality of Life, Impact of Pediatric Epilepsy, Pediatric Quality of Life and Strength and Difficulties.

Results: 68 families responded. 28 were aged 10-15 years and 40 were aged over 16 at follow-up. Patients 0-5 years old at baseline showed significant decline in mean scores on the PedsQL total ($p=0.004$), physical ($p< 0.001$), cognitive ($p=0.011$), social ($p=0.003$), and eating ($p=0.03$) scores. This was not the case for patients over 6 years old at initial assessment. On multivariate regression, epilepsy severity and a high initial SDQ total score were associated with lower short (adj. $R2=.49$) and long-term (adj. $R2=.183$) HRQOL for the whole cohort. In the younger patient group, younger age at 1st seizure and increased severity of epilepsy were associated with a lower short-term HRQOL (adj. $R2=.346$) but were no longer significant factors on follow-up. In the older age group epilepsy severity at baseline ($F=6.399$, $p=0.016$, adj. $R2=.137$) and the use of sodium-channel blockers at baseline ($F=4.122$, $p=0.05$, adj. $R2=.082$) were independently associated with a lower HRQOL at follow-up.

Conclusions: This study highlights the sharp cognitive, social and physical decline which particularly affects younger patients with DS. Early diagnosis and management of DS, including avoidance of sodium channel blockers, appears to be especially important in mitigating factors that negatively impact long-term HRQOL in DS patients.

Keywords:
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EPNS21-412 Oral or poster
Epilepsy: Miscellaneous

Efficacy of low frequency repetitive transcranial magnetic stimulation(rTMS) therapy among children with focal onset drug refractory epilepsy - A Randomized sham controlled clinical study

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Objective: To analyse the effect of low-frequency repetitive Transcranial Magnetic stimulation(rTMS)on seizure control,cognition and behaviour in children with drug-refractory focal epilepsy

Methods: Forty-nine children(5-18 years)with drug-refractory focal epilepsy with more than 4 seizures/month were randomly assigned to active(n=25)and sham treatment arm(n=24).The patient and outcome accessors were blinded.The seizure focus was localized with interictal,ictal VideoEEG,Brain MRI,PETscan.Cognition was assessed through Malin's Intelligence scale for Indian Children (MISIC)and behavior by Childhood behavior checklist(CBCL).rTMS protocol used 10 days daily 45min session of 0.5Hz,1200 pulses(2trains of 600 pulses)at 110% of resting motor threshold(RMT)over seizure focus using figure-of-8 coil.RMT was calculated over motor cortex of dominant hemisphere.The clinico-electrographic outcome was assessed at 8week post-therapy

Results: Baseline characteristics were comparable in the two groups.In active arm 76%(19/25)children achieved >50% seizure reduction verses12.5%(03/24)in sham arm($p<0.0001$);effect size 63.5%(95% CI:42.1%-84.8%);mean weekly seizure reduced by74.8±30.2% in active compared to 12.8±23.1% in sham group($p<0.001$).Active arm had median percentage reduction in Spike-wave-index of 33%(17.6, 55.5;$p<0.0001$)vs0(-13.3,6.7)insham arm.Between active and sham group mean change in IQ was 3.5±0.5vs-0.91±0.3($p<0.0001$);CBCL scores improved in behavioral domains of inattention(-5.7±3vs 0.41±0.7;$p<0.0001$),hyperactivity(-4.3±2.2vs-0.5±0.2;$p<0.006$)and aggression(-3.1±0.5vs0.37±0.1;$p<0.0001$).Interestingly,motor cortex became more excitable/disinhibited after active TMS therapy as RMT got reduced by 7.84±0.12vs-1.05±0.26.No major adverse events observed

Conclusions: Targeted low frequency rTMS therapy is effective in inducing short term seizure control and improvement in cognition and behavior in children with drug refractory focal epilepsy.rTMS therapy elevates the refractory epilepsy induced motor cortex inhibition

Keywords:
rTMS, epilepsy, sham, drug refractory, cognitive, behavioural

EPNS21-448 Oral or poster
Epilepsy: Miscellaneous

Genotype-phenotype associations in a large cohort of SCN1A-related epilepsies

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Objective: SCN1A variants cause epilepsy syndromes ranging from mild genetic epilepsy with febrile seizures plus (GEFS+) to severe Dravet syndrome (DS). Most variants are de novo making early phenotype determination difficult. We investigate genotype-phenotype
relationships through examination of variant characteristics, clinical data, and in-silico tools.

Methods: We assessed data from a retrospective cohort of 1022 individuals with SCN1A-related epilepsies. We explored how variant type, position, in-silico (CADD, REVEL), physicochemical (Grantham) scores and seizure type related to phenotype and age of onset.

Results: DS has earlier median onset than GEFS+ (5.4 v 12 months, $p<0.001$). Truncating variants were associated with earlier median onset than missense variants (5 v 6 months,
$p<0.001$). Mean Grantham (95.4 v 72.5) and in-silico variant scores (CADD 30.8 v 27.1, REVEL 0.91 v 0.85) were higher in DS vs GEFS+ phenotypes ($p<0.001$) and negatively correlated with age of onset (Grantham [-0.111, $p=0.015$], CADD [-0.169, $p<0.001$] and REVEL [-0.197, $p<0.001$]). The diagnostic value of status epilepticus as first seizure indicating a DS phenotype in SCN1A positive epilepsies was as follows: Specificity 95.2% (76.2-99.9), Sensitivity 32.7% (27.7-38.6), Positive Predictive Value 98.9% (94.1-100), Negative
Predictive Value 9.7% (6-14.5). Missense variants in functionally important coding regions (S4, S5, S5-6, S6) were associated with earlier median seizure onset than those found elsewhere in the gene (6 v 7 months $p<0.001$). Identical variant carriers exhibited less variability in age
of onset compared to non-identical variant carriers (1.88 v 2.9 months SD, $p=0.001$).

Conclusions: These findings add to current understanding of genotype-phenotype associations in SCN1A-related epilepsies. Variant type and position are reflected in clinical presentation. In-silico and physico-chemical variant scores are related to onset and phenotype. The identification of highly specific early disease features aids early diagnosis.

Keywords:
Dravet Syndrome, SCN1A, Genetic Epilepsy

EPNS21-578 Oral or poster
Epilepsy: Medical & Surgical Treatment

Epilepsy surgery in children and adolescents and genetic findings

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Objective: Epilepsy surgery is the only way to cure drug resistant structural epilepsy with postoperative seizure-freedom in about two-thirds of cases selected carefully through pre-epilepsy surgery assessments. In those receiving complete resection it remains unclear why some do not reach seizure-freedom. Genetic testing prior to epilepsy surgery to evaluate an additional genetic epilepsy cause is not offered routinely. Here we evaluated genetic findings offered as routine assessment to all patients undergoing preoperative diagnostics at our center.

Methods: We performed a retrospective data analysis of all patients operated at our epilepsy center who accepted a genetic workup as part of the epilepsy surgery assessment. Genetic workup included chromosome analysis, CGH array analysis, and whole exome sequencing.

Results: Of 52 children and adolescents who underwent epilepsy surgery, 19 (36.54%) patients accepted a genetic workup. Negative results were obtained in eight patients (34.8%), while 11 patients (57.9%) carried abnormal genetic findings. The latter included variants in eight genes/microdeletion linked to epilepsy, three linked to brain malformation or infarction leading to epilepsy. Seizure freedom in our total cohort was 84.2% at a current median observation period of 20.7 months, with 87.5% (7/8) seizure-freedom in patients lacking abnormal genetic findings and seizure-freedom 81.8% (9/11) in patients with positive findings. The presence of abnormal genetic findings strongly influenced patient and family counseling and tapering of anti-seizure medication (ASM) postoperatively.

Conclusions: In our cohort, an additional genetic cause was identified in two-thirds of patients with structural epilepsy. The genetic results influenced counseling and postoperative ASM decisions. We anticipate that increased use of genetic testing in pediatric epilepsy patients will aid to identify those that will presumably require ASM postoperatively despite complete resection.

Keywords:
epilepsy, epilepsy surgery, genetics, outcome, pediatrics, drug resistant epilepsy

EPNS21-594 Oral or poster
Epilepsy: Miscellaneous

Computational modelling: an opportunity in rare epilepsies

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Objective: We aimed to discuss the possible contribution of computational modelling in the understanding of underlying mechanisms of genetic epilepsies.

Methods: We used computational models at different scales to study the physiopathology of pathogenic variant of KCNT1, a major cause of epilepsy with migrating focal seizure in infancy. This approach enabled us to go from a microscopic (detailed models) to a mesoscopic (interconnected neural masses) scales mimicking the functional impact of a given pathogenic variant at the cellular level, to the network level and ending with producing a comparable EEG to patients harboring the mutation. At each stage of this work, the simulated results were compared with data from in vivo and in vitro data.

Results: First, we identified, using detailed models of neurons and interneurons, that pathogenic variants of KCNT1 result in a decrease in the frequency of discharges from these neurons. However, this alteration was more pronounced in interneurons resulting in hyperexcitability of microscopic networks. Then, we developed an original approach to adapt mesoscopic neural masses to take into account of the impact of the pathogenic variant on the different subtypes of neurons. By adapting certain features of interconnected neural masses to reflect brain immaturity, we were able to simulate the abnormal EEG of individuals with KCNT1 pathogenic variant. Suppression of the effects of the pathogenic variant in the different neuronal populations resulted in a near-normalization of the EEG pattern. Finally, we were able to reproduce the migrating pattern of the seizures, a key feature of this epilepsy, by introducing dynamic GABA into our mesoscopic network.

Conclusions: This study is one of the first to use computational modelling to go from functional impact of a pathogenic variant to the resulting EEG. It illustrates the value of computational models as an additional model to understand the epilepsy mechanisms and to test possible therapies.

Keywords:
Models, developmental epileptic encephalopathy, physiopathology

EPNS21-198 Oral or poster
Inflammatory Disease of the CNS

Postherpetic autoimmune encephalitis

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Objective: The purpose of our study was to find relevant clinical data predicting autoimmune encephalitis (AIE) after herpes simplex encephalitis (HSE).

Methods: A retrospective study of patients treated with HSE and postherpetic AIE between 1998 and 2021. 37 events of 33 pediatric patients with proven HSE were included. Diagnosis was based on either positive CSF HSV PCR or detection of intrathecal HSV antibody production. Two groups were compared: group A with only HSE (24), group B with HSE and AIE (13 cases). The data of HSE and AIE episodes were studied separately in group B. HSE recurred in 3 patients, AIE in 2 patients. Prodromal period, symptoms, laboratory - especially CSF -, MRI and EEG findings, therapy and outcome were studied. Chi square and T probe was used for analysis, significance was at p lowe than 0.05.

Results: Average age of HSE onset was 5 yrs in group A, 10 months in group B. Delay of diagnosis was 3.6 and 9.8 days in the two groups, respectively. Seizures were more often the presenting symptoms in group B. Occurrence of status epilepticus was significantly higher in group B (p: 0.0105). Elevation of CSF protein was significantly less common in Group B (p: 0.049) at the time of HSE. The use of steroids (p: 0.015), cognitive impairment (p: 0.002) and epilepsy (p: 0.005) in the outcome were also significantly higher in group B. AIE started on average day 25 with sleepiness followed by insomnia and feeding difficulties. Choreoathetosis was present in all cases. Two patients developed 2nd HSE during AIE. All 13 cases had data proving intrathecal antibody production. In 8 cases combined immunotherapy was needed.

Conclusions: Predictors for development of AIE in our data were: delay in diagnosis, younger age, status epilepticus and near-normal CSF protein with elevated IgG/albumin ratio.

Keywords:
herpes, autoimmune, encephalitis, CSF protein

EPNS21-2079 Oral or poster
Inflammatory Disease of the CNS

Temporal dynamics of MOG-antibodies in children with acquired demyelinating syndrome

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Objective: To assess clinical and laboratory prognostic parameters for a risk of relapse and the temporal dynamics of MOG-IgG titers in children with MOGAD in correlation with clinical presentation.

Methods: In this prospective multicenter hospital-based study 116 children with a first demyelinating attack and a complete data set comprising clinical and radiological findings, MOG-IgG titer at onset, clinical and serological follow-up data were included. Serum samples were analyzed by live cell-based assay and a titer level of greater or equal 1:160 was classified as MOG-IgG positive.

Results: 116 children (female:male=57:59) with MOG-associated disorder (MOGAD) were included and initially diagnosed with ADEM (n=59), monolateral optic neuritis (ON) (n=12), bilateral ON (n=16), myelitis (n=6), Neuromyelitis optica spectrum disorder (n=8) or encephalitis (n=6). Median follow up time was 3 years in monophasic and 5 years in relapsing patients. 44/116 patients (38%) had a relapsing disease course with the first relapse occurring after a median of 0.5 years. There was no significant association between disease course and MOG-IgG titers at onset, sex, age at presentation or clinical phenotype. Seroconversion within 2 years of the initial event showed a significant risk reduction for a relapsing disease course. 47/116 patients (monophasic n=30, relapsing n=17) had serial MOG-IgG testing in year 1 and 2 after the initial event. In contrast to relapsing patients, monophasic patients showed a significant decrease of MOG-IgG titers during the first and second year, often with seroconversion to negative titers. During follow up MOG-IgG titers were persistently higher in relapsing than in monophasic patients. In our cohort no patient experienced a relapse after seroconversion.

Conclusions: Declining MOG-IgG titers are associated with a reduced relapse risk. Patients with seroconversion to MOG-IgG negative titers (<1:160) seem to have a stable clinical remission without further relapses.

Keywords:
MOGAD, children, MOG-antibodies, outcome, relapsing, monophasic

EPNS21-374 Oral or poster
Inflammatory Disease of the CNS

Immune response to COVID-19 mRNA vaccination in pediatric- and adult-onset multiple sclerosis

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Objective: Few data are available on disease-course of pediatric-onset multiple sclerosis (POMS) patients with COVID-19, similarly there is currently no data on vaccine response in POMS patients.
Aim of this study was to investigate humoral immune responses to COVID-19 mRNA vaccinations in POMS and adult-onset MS (AOMS) on various disease-modifying therapies (DMTs).

Methods: We analyzed seroconversion rates and SARS-CoV-2 specific antibody levels in a cohort of POMS (age at MS onset <18 years and age at vaccination <21 years) and AOMS patients. Immune response was tested using the Elecsys® Anti-SARS-CoV-2 S immunoassay.

Results: 20 POMS (15 female) and 107 AOMS (72 female) received two COVID-19 mRNA vaccine doses.
We did not observe any new or unexpected side effects in the pediatric population. No relapses occurred following vaccination.
All patients with no treatment or baseline DMTs generated robust immune responses to vaccination (POMS: seroconversion in 9/9, median titer: ≥ 2500 BAU/ml, IQR: 0 BAU/ml; AOMS: no treatment: 13/13, ≥ 2500 BAU/ml, 585 BAU/ml; baseline DMT: 9/9, ≥ 2500 BAU/ml, 0 BAU/ml). Similar good response was seen in AOMS patients on alemtuzumab (5/5, ≥ 2500 BAU/ml, 0 BAU/ml) and cladribine (13/13, ≥ 2500 BAU/ml, 811 BAU/ml).
Patients on fingolimod (POMS: 2/2, 116 BAU/ml, 106 BAU/ml; AOMS: 8/8, 75,5 BAU/ml, 444,7 BAU/ml) showed lower antibody levels; patients on anti-CD20 therapies (POMS: 7/9, 51 BAU/ml, 170 BAU/ml; AOMS: 39/59, 14,9 BAU/ml, 958,3 BAU/ml) showed lower conversion rates and lower antibody levels compared to untreated patients.

Conclusions: Generally, mRNA vaccinations were well tolerated in POMS and AOMS patients with and without DMTs. Immune response was reduced in patients treated with anti-CD20 therapies and fingolimod. The response in patients treated with anti-CD20 therapies was higher in the pediatric population. Our data supports consensus recommendations on COVID-19 vaccinations in MS.

Keywords:
multiple sclerosis, pediatric-onset multiple sclerosis, COVID-19, vaccine, vaccination, SARS-CoV-2, mRNA

EPNS21-495 Oral or poster
Inflammatory Disease of the CNS

MR-imaging in children with MOGAD, NMOSD, absent antibodies and MS presenting with transverse myelitis

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Objective: To analyze the imaging findings of children presenting with transverse myelitis (TM) with a special focus on patients with antibodies to myelin oligodendrocyte glycoprotein (MOG-abs).

Methods: Children with a first clinical event of an acquired demyelinating syndrom (ADS) and clinical as well as radiological involvement of the myelon, a complete data set including MOG-IgG and AQP4-IgG antibody measurement, cerebrospinal fluid (CSF) cell count and/or oligoclonal bands (OCBs) and at least spinal imaging were eligible for the study.

Results: 100 patients (54 females, 46 males, age range 0.6 to 17 years) were included and divided into 4 groups: MOG-IgG positive (n=33), NMOSD (n=7), seronegative transverse myelitis/longitudinally extensive TM (LETM) (n=34), including 3/34 children with acute disseminated encephalomyelitis (ADEM), and MS (n=26). Patients with MOG-antibody associated diseases (MOGAD) were younger ($p<0.001$), had rarely OCBs (13%), the highest CSF cell count ($p<0.001$) and presented mainly with ADEM + TM/LETM (42%) or isolated LETM (30%). MRI was characterized by LETM (55%) with involvement of only the grey matter (73%). The presence of leptomeningeal enhancement with or without nerve root enhancement was highly predictive of MOGAD (15/26; 57%). MS patients were older ($p<0.001$), had the lowest CSF cell count ($p<0.001$) and often OCBs (96%). Spinal MRI showed single short (50%) or multiple short lesions (46%) with involvement of both grey and white matter (69%). Cerebellar lesions were mainly present in children with MS compared to the other groups (46%). Seronegative children mainly presented with LETM (74%) and brain lesions were found less likely compared to the other groups (30%).

Conclusions: Children with a first ADS presenting with involvement of the spinal cord reveal important radiological differences between MOGAD, NMOSD, MS and double seronegative patients.

Keywords:
transverse myelitis, acquired demyelinating syndrome, MOG, pediatric, radiologic, neuroinflammation

EPNS21-2041 Oral or poster
Miscellaneous Topics

The Guanabenz Trial: Treatment of Patients with Early-Childhood Onset Vanishing White Matter

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Objective: Vanishing White Matter (VWM) is a leukodystrophy caused by variants in the genes EIF2B1-5, encoding eIF2B. This is a key factor in the integrated stress response (ISR), a protective response activated by physical stresses. VWM leads to chronic progressive neurological dysfunction characterized by ataxia, spasticity and cognitive decline. Additionally, there are episodes of subacute major neurological decline, provoked by stresses like febrile infections, which can lead to coma and death. In VWM, the ISR is continuously abnormally activated downstream of eIF2B. Guanabenz, an old alfa2-adrenergic antihypertensive drug, decreases ISR activation. In a mutant VWM mouse model, beneficial effects of Guanabenz were observed on motor function, brain white matter integrity and ISR activation. We currently conduct an open-label clinical trial with a historical control group using Guanabenz in children with early onset VWM.

Methods: Children with genetically proven VWM with clinical onset <6 years of age and brain MRI compatible with VWM, who are still be able to walk 10 steps or more, are included in the trial. We evaluate (1) safety and tolerability of Guanabenz, (2) pharmacokinetic profile, (3) efficacy (clinical outcome and quantitative brain MRI parameters), and (4) potential biomarkers for future studies. We expect that in 2 years 30-40 patients can be included. The total trial duration will be 4 years.

Results: The first patient was included on May 31, 2021. By January 1st 2022, 9 patients were treated with Guanabenz (dose range 1.05-1.78 mg/kg/day). Median age at time of inclusion was 7 (range 2-11) years and median disease duration at start of the trial was 2 (range 1-8) years. Common side-effects were drowsiness, fatigue, nausea and nightmares. In all patients, tolerance was observed. Until now, one patient lost the ability to walk.

Conclusions: Preliminary results suggest that Guanabenz is tolerated by VWM patients. Longer follow-up is needed to evaluate efficacy.

Keywords:
Guanabenz; Treatment; Trial; Vanishing White Matter; Leukodystrophy; Children

EPNS21-338 Oral or poster
Movement Disorders

Paediatric tic-like presentations during the COVID-19 pandemic

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Objective: Clinical centres have seen a sudden increase in tic-like movements during the COVID19 pandemic. The aim of this paper is to describe the characteristics of a series of children and adolescents presenting with phenotypes which include functional movements.

Methods: This is a clinical evaluation of 34 paediatric patients, seen during a period of 6 months (10/2020 to 04/2021), across Tourette services in England and Canada who presented with sudden onset or significant exacerbation of existing 'tics' or tic-like movements. A retrospective chart review, multidisciplinary interviews, neurological and psychiatric assessments were performed. Characteristics of patients with and without diagnosis of previous tics were compared.

Results: 94% of patients were female with an average age of sudden onset or increase of tic-like movements at 13.7 (SD 2) years. 44% had a previous diagnosis of tics. There was a high frequency of copro-, pali- and echolalia (77%) and a high mean Yale Global Tic Severity Score of 62.6 (SD 19). Tics waxed and waned in only 32% and were suppressible in less than 60%. Almost half of patients (47%) initially presented to an emergency department. Comorbid psychiatric and neurodevelopmental disorders were reported in 91% with 68% reporting anxiety.

Conclusions: We highlight a dramatic presentation of sudden onset functional tic-like movements in predominantly female adolescents. This phenotypic description should help inform identification and management. There is an urgent need to research the neurobiological underpinnings and environmental exacerbating factors leading to these presentations and to explore effective therapeutic strategies.

Keywords:
Tics, functional tic-like movements, COVID19, neurodevelopmental vulnerability, functional movement disorder, tic-like movements

EPNS21-433 Oral or poster
Genetics

Clinical and genetic spectrum from a prototype of ciliopathy: Joubert syndrome

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Objective: Defects of the primary cilium which are a microtubule-based extension of cellular membranes found in nearly all cell types are called ciliopathies. The importance of ciliary function in neuronal development was recognized when Joubert syndrome (JS) was classified as a ciliopathy in the last decade. We would like to describe a clinical and genetic spectrum of patients with JS which is a prototype of ciliopathy, also including some very rare and unreported variants.

Methods: We retrospectively collected the data of 16 clinically and/or molecularly diagnosed JS patients. The molecular diagnosis was ascertained by clinical exome or whole-exome studies when possible.

Results: Pathogenic and/or likely pathogenic variants could be identified in 13 (%81) patients. The most common variants were in the *CPLANE1* gene, followed by *KIAA0586*. Other causative genes were *TMEM67*, *AHI1*, *CSPP1*, *CEP290*, *CEP41*, *KATNIP*, *RPGRIP1L*, and some of the variants in these genes were not reported before in the literature. All of the patients without a molecular diagnosis had molar tooth sign. Eye (%25) was the most common extra-neurological organ involvement including Leber's congenital amaurosis. Portal hypertension, esophageal varices as liver and polycystic kidney disease, nephronophthisis as kidney involvement were also encountered in our cohort. A mild phenotype was observed in one patient with novel compound heterozygous variants in *KATNIP* gene with hypophyseal hormone deficiencies without molar tooth sign.

Conclusions: Some rare variants were first reported in our cohort of JS which display prominent genetic heterogeneity with variable severity. In our study cohort of 16 JS patients, *CPLANE1* and *KIAA0586* were the most commonly affected genes. JS as a ciliopathy is possible without a molar tooth sign like in very rare *KATNIP* gene-affected patients.

Keywords:
ciliopathy, Joubert syndrome, KATNIP, molar tooth sign

EPNS21-487 Oral or poster
Epilepsy: Diagnosis and Investigations

Inter-observer agreement between Primary Care Physicians and Pediatric Neurologists in classifying epilepsy among children aged one month to 18 years using AIIMS modified INDT EPI Tool according to ILAE 2017 classification scheme

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Objective: Primary care physicians are the most common first health care contact for children with epilepsy. Correct identification and initiation of appropriate, timely treatment is imperative to reduce morbidity and mortality related to epilepsy. To develop and validate a questionnaire-based tool to identify the seizure semiologies as per ILAE 2017 classification system for epilepsy and to calculate inter-observer agreement between the Pediatric Neurologists and Primary Care Physicians for epilepsy classification.

Methods: To the existing AIIMS Modified INCLEN Diagnostic Instrument for Epilepsy, 6 new questions were added by expert group of Pediatric Neurologists to cover all semiologies in the ILAE 2017 classification scheme. Construct validity of the modified tool was done in 20 patients. Subsequently, MD students (MD) and undergraduate interns (UG), surrogates for primary care physicians (PCP), were trained to classify epilepsy using the modified tool, their classification of epilepsy was compared with that of pediatric neurologists (PN). Inter-observer agreement using kappa agreement was calculated for both set of observers.

Results: A total of 144 children (97 males) with confirmed epilepsy were enrolled. Classification of the epilepsy was done by each evaluator using AIIMS Modified INCLEN Diagnostic Instrument for Epilepsy tool. Kappa agreement was 0.52 at first level and 0.28 at second level of classification between the MD and PNs. Between UG and PN Kappa agreement was 0.45 at first level and 0.30 at second level of classification.

Conclusions: The AIIMS Modified INCLEN Diagnostic Instrument for Epilepsy is appropriate for broad classification of seizures into generalized, focal, multiple and unclassified seizures but not for detailed semiology classification as per ILAE-2017 classification. Focused pediatric and neurology training is associated with better semiology identification.

Keywords:
Epilepsy classification, inter-observer agreement

EPNS21-590 Oral or poster
Epilepsy: Diagnosis and Investigations

Thalamic volumetric analysis in Encephalopathy associated with Status Epilepticus in Sleep (ESES): A cross-sectional study

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Objective: Thalamic affection (structural or functional) is proposed to be responsible for sleep potentiated epileptiform discharges and rapid synchronization characteristically observed in Encephalopathy associated with Status Epilepticus in Sleep (ESES). We compared thalamic volume (TV) of children with ESES with age matched children with well-controlled epilepsy (WCE).

Methods: Children (5-12years) with steroid-naïve ESES {spike-wave-index (SWI) in sleep >= 50%} and typically developing children with WCE (seizure free period of 1-year) were enrolled. Presenting complaints, cognition (SQ-VSMS), behavioral profile (CBCL) and EEG characteristics were documented. Brain MRI was performed in all. High-resolution T1-weighted sequences were analyzed by a pediatric neuro-radiologist for gross visual assessment (GVA), which were subsequently assessed for segmentation and quantitative volumetric assessment (QVA) using the online "volBrain" software. Relative TV after correcting for the total intracranial volume (TIV), was also compared between the two groups.

Results: Twenty-children each with ESES (14 boys; mean age: 8.05$\pm$1.76 years) and WCE (15 boys; mean age: 9.1$\pm$1.74 years) were analyzed. All the children had neurobehavioral symptoms and cognitive decline, while only 60% had active seizures in the ESES group. The mean duration between seizure onset and onset of neuroregression was 6.2$\pm$6.03 months, while the mean duration between onset of neuroregression to diagnosis was 6.6$\pm$4.13 months. The mean SWI was 86.25$\pm$13.56%. On GVA, thalamic injury was seen in 6/20; other structural lesions in 10/20, no structural abnormality in 4/20. The mean TV of ESES was significantly lower compared to WCE (7.65$\pm$1.7cm3 vs 11.17$\pm$1.22cm3) ($p<0.0001$). The mean relative TV in ESES group was significantly lower (0.73$\pm$0.15% vs 0.87$\pm$0.05% in WCE) ($p=0.0003$).

Conclusions: Thalamic volume is reduced in children with ESES. Even those with normal appearing thalamus have reduced volume on quantitative volumetry.

Keywords:
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EPNS21-304 Oral or poster
Inflammatory Disease of the CNS

The Swiss Paediatric Inflammatory Brain Disease Cohort Study: Setting up a national registry for children and adolescents with paediatric onset MS and related disorders

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Objective: Paediatric onset MS (POMS) is a severe disease affecting children and adolescents in a period of essential brain development. Timely diagnosis and treatment initiation minimize neurological sequelae and improve patient outcomes. However, the diagnosis of POMS can be challenging, especially in young children. A systematic approach to the assessment of POMS patients versus patients with other inflammatory brain diseases (IBrainDs) will allow faster and more reliable diagnosis. A national registry will improve our understanding of POMS epidemiology, clinical presentation, and management.

Methods: Multicentre cohort study including prospective and retrospective data. Inclusion criteria: patients with POMS or another specified IBrainD with an onset before 18 years of age. Exclusion criteria: patients with 1) infectious diseases of the CNS; 2) genetic/metabolic causes of central demyelinating diseases; 3) neurological symptoms due to Guillain-Barré-Syndrome. Demographic and medical data are centrally collected.

Results: After the ethics committee approval at the end of 2020, ten out of the 11 participating centres have already been initiated. So far, we identified 194 potential participants with an IBrainD. Of those, 84 (43.3%) have a POMS diagnosis. Currently, 37 patients and/or families from seven centres have consented to participate in the registry. Retrospective patient identification was challenging due to a lack of systematic and unified coding approaches.

Conclusions: The national registry will answer pressing questions about the epidemiology and clinical phenotypes of POMS and related diseases in Switzerland. It also offers the opportunity to assess treatment and outcomes of paediatric IBrainD patients in a longitudinal fashion. Furthermore, the registry facilitates the national and international collaboration by providing a research platform.

Keywords:
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EPNS21-567 Oral or poster
Inflammatory Disease of the CNS

Neurofilament light chain and disease activity in pediatric multiple sclerosis

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Objective: Neurofilament light chain (NfL), a neuron-specific protein, is elevated in serum following axonal damage. Study aim was to investigate if pre-treatment serum NfL levels correlate with disease presentation and course in pediatric multiple sclerosis (pedMS).

Methods: Retrospective cohort study of 178 pedMS patients (115 females) with mean age at MS onset 13.7 years and mean follow-up 43.9 months. For each patient, NfL level was analysed in a stored serum sample collected prior to treatment using single-molecule array technology and compared with presenting features and disease course parameters.

Results: Pre-treatment median sNfL in 178 pedMS patients was 21.4 pg/ml (IQR 9.6, 55.7) compared to 4.6 pg/ml (3.7, 6.7) recently reported for 301 healthy controls.(Reinert et al. 2020) Levels were significantly higher in patients with a relapse within 90 days of sampling (median 29.3 pg/ml vs 17.6 pg/ml, (n = 177, p = .007) and also correlated with number of pre-treatment relapses (p = .006). Higher sNfL values were associated with higher numbers of T2-weighted (n =169, p < .001) and contrast enhancing lesions (n = 166, p < .001) on baseline cranial MRI, poorer recovery from the first attack (median sNfL in patients with sequelae 6 months after first attack 42.6 pg/ml vs 17.0 pg/ml in fully recovered patients, n = 19 vs 132, p = .007), a shorter first inter-attack interval (n = 151, p < .001) and higher Expanded Disability Status Scale scores at last follow-up (n = 170, p < .001). Consistently, patients escalated to a second-line therapy had significantly higher levels than non-escalated patients (median 27.9 pg/ml vs 11.9 pg/ml, n = 109, p < .001).

Conclusions: Findings indicate prognostic potential of sNfLs in identifying children with pediatric MS at risk of more active disease and may help to choose the appropriate treatment at the time of diagnosis

Keywords:
Multiple sclerosis. NfL

EPNS21-618 Oral or poster
Inflammatory Disease of the CNS

Interferon pathway activation in patients with autoimmune encephalitis post-herpes simplex encephalitis

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Objective: Herpes simplex virus (HSE) encephalitis is the most frequent cause of sporadic infectious encephalitis. More than 25% of patients with HSE develop autoimmune encephalitis (AE) post-HSE, most of them associated with NMDAR antibodies. It is urgent to understand the immunemechanisms underlying this severe complication as these patients have a poorer prognosis and a suboptimal response to immunotherapy compared with patients with NMDAR encephalitis not related to HSE.

Methods: Patients with confirmed diagnosis of HSE from a multicenter prospective spanish study were included. Blood samples were collected using PAXgene® Blood RNA Tubes (Qiagen) at HSE onset, 21 days, and at 2,6,12 months. Total RNA was extracted, and expression levels of 28 interferon -induced genes and 4 housekeeping genes were measured using the nCounter® Digital Analyzer (NanoString). The type I interferon signature (IS) was calculated using the median of the Z scores7 of the 6 genes mainly involved in AGS previously reported by Rice et al., and the median of the Z scores of the 28 genes described by Kim et al; both were considered positive if higher than 1.96 (+2SD).

Results: The IS was positive in all patients during the viral phase (11/11, 100%), in 4/14 (29%) at 21 days after HSE onset, and in any patient at longer follow-up. In patients that developed antibodies post-HSE IS was higher at 21 days than in patients that did not develop antibodies (median IS Z score 1.99, IQR 0.3-7.8 vs -0.44, IQR -0.78 - -0.34, p=0.0027).

Conclusions: Persistence of interferon pathway activation after 3 weeks of HSE onset was identified in patients that later would develop AE post-HSE encephalitis. Type I IS could be used as a biomarker to predict AE post-HSE in patients with HSE, and to help to find new therapeutic strategies.

Keywords:
Herpes virus encephalitis, children, autoimmune encephalitis, interferon signature

EPNS21-644 Oral or poster
Inflammatory Disease of the CNS

Early factors predicting risk of relapse and outcome in paediatric MOG-antibody associated disorders

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Objective: We strove to identify early factors predictive of subsequent relapses and outcome in an Italian multicenter paediatric myelin oligodendrocyte glycoprotein antibody-associated disorders (MOGAD) cohort.

Methods: Patients with paediatric-onset (< =18 yrs) MOGAD were retrospectively collected. Factors at onset were compared in patients with monophasic vs relapsing disease (including cases with follow-up >=12 months after onset or relapse at any time), and in patients with Expanded Disability Status Scale (EDSS) 0 vs EDSS >0 at last follow-up (including cases with follow-up >3 months after last event or EDSS 0 at any time). Statistical tests were the Mann-Whitney U test for continuous and ordinal data, and chi square or Fisher's exact tests for nominal data.

Results: 59 patients were included (median age at onset 7.9 yrs, range 1.8-18.6; 49.2% males).
Onset events were acute disseminated encephalomyelitis (45.8%), optic neuritis (with/without CNS lesions) (37.3%), neuromyelitis optica (3.4%), encephalitis (3.4%), other CNS demyelination (10.2%). Worst EDSS at onset was median 4.5 (range 1-8.5).
At onset, 94.9% of patients received immunotherapy (IT) (< =10 days from onset in 71.7%): corticosteroids (93.2%), immunoglobulin (16.9%), plasma exchange (1.7%), rituximab (3.4%), mycophenolate mofetil (3.4%) (>=2 different agents in 22%). Time on IT at onset was median 6 weeks (range 0-248).
At last follow-up (median 30 months from onset, range 1-126), 42.4% relapsed, and median EDSS was 0 (range 0-6) (EDSS 0 in 71.2%).
Factors at first event significantly associated with risk of relapses were late IT initiation >10 days after onset (p=0.007), use of only 1 type of IT (p=0.04), and shorter time on IT (p=0.038). Higher EDSS at onset was associated with risk of EDSS >0 at last follow-up (p=0.009).

Conclusions: Outcome is overall good in paediatric MOGAD, but relapses can occur in >40% of cases. Early treatment, use of multiple ITs and longer time on IT at onset were associated with lower risk of subsequent relapses.

Keywords:
MOG, myelin oligodendrocyte glycoprotein antibody-associated disorders, immunotherapy, relapses, outcome

EPNS21-705 Oral or poster
Inflammatory Disease of the CNS

Novel mutations in RNU7-1 weaken secondary RNA structure, induce MCP-1 and CXCL10 in CSF and result in Aicardi-Goutières syndrome with severe end-organ involvement

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Objective: Aicardi-Goutières syndrome (AGS) is a type I interferonopathy usually characterized by early-onset neurologic regression. Biallelic mutations in LSM11 and RNU7-1, components of the U7 small nuclear ribonucleoprotein (snRNP) complex, have been identified in a limited number of genetically unexplained AGS cases. Impairment of U7 snRNP function results in misprocessing of replication-dependent histone (RDH) pre-mRNA and disturbance of histone occupancy of nuclear DNA, ultimately driving cGAS-dependent type I interferon (IFN-I) release. We performed a clinical, genetic and immunological workup of 3 unrelated patients with uncharacterized AGS.

Methods: WES and targeted Sanger sequencing of RNU7-1 were performed. Primary fibroblasts were used for mechanistic studies. IFN-I signature and STAT phosphorylation were assessed in peripheral blood. Cytokines were profiled on serum and cerebrospinal fluid (CSF). Histopathology was examined on brain and kidney tissue.

Results: Sequencing revealed compound heterozygous RNU7-1 mutations, resulting in impaired RDH pre-mRNA processing. The 3' stem-loop mutations reduced stability of the secondary U7 snRNA structure. We observed a discrete IFN-I signature in peripheral blood, aberrant STAT1 phosphorylation and significant upregulation of MCP-1 and CXCL10 in CSF. Histopathological analysis of the kidney showed thrombotic microangiopathy. Clinical overview of all currently known patients with RNU7-1-related disease revealed high mortality and high incidence of organ involvement compared to other AGS genotypes.

Conclusions: Targeted RNU7-1 sequencing is recommended in genetically unexplained AGS cases. CSF cytokine profiling represents a supportive diagnostic tool to identify an IFN-I signature. Clinical follow-up of RNU7-1-mutated patients should include screening for severe end-organ involvement including liver disease and nephropathy.

Keywords:
Aicardi-Goutières syndrome, AGS, Type I interferon, IFN-I, cGAS, U7 snRNP, small nuclear RNA, RNU7-1

EPNS21-161 Oral or poster
Metabolic Disorders

Lentiviral Haematopoietic Stem and Progenitor Cell Gene Therapy for Metachromatic Leukodystrophy (MLD): Clinical Outcomes from 38 Patients

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Objective: MLD is a fatal demyelinating lysosomal storage disease due to arylsulfatase A (ARSA) deficiency. We report results of 38 patients (pts) with early-onset MLD (20 late infantile [LI], 18 early juvenile [EJ]) treated with haematopoietic stem cell-based gene therapy (atidarsagene autotemcel, "arsa-cel") across 2 prospective clinical trials and expanded access programs.

Methods: Arsa-cel consists of autologous CD34+ cells transduced ex vivo with a lentiviral vector encoding the human ARSA gene. Following myeloablative busulfan conditioning, arsa-cel was administered intravenously. Key endpoints were compared to an untreated natural history (NHx) cohort.

Results: Of 38 pts with 0.08-8.85 years of follow-up, 35 are alive; 2 died from disease progression, 1 from cerebral stroke, all unrelated to arsa-cel. There were no treatment-related serious adverse events, malignancies, abnormal clonal expansion, or evidence of replication-competent lentivirus. All pts achieved haematological recovery. Stable engraftment of gene-corrected cells and restoration of ARSA activity in the haematopoietic system and cerebrospinal fluid was observed in all pts with 3 or more months follow-up. Most pts treated pre-symptomatically maintained long-term walking capability and normal cognitive development. Also, early-symptomatic EJ pts treated before entering the phase of rapid decline showed better motor and cognitive scores or slower rate of decline versus NHx.

Conclusions: Data from 38 early-onset MLD pts with up to 8.85 years of follow-up demonstrated that arsa-cel was generally well-tolerated and effective in modifying the disease course of early-onset MLD. Arsa-cel [tradename: Libmeldy(TM)] was approved by the EMA in 2020 and is indicated for the treatment of children with LI or EJ forms without clinical manifestations of the disease, and in children with the EJ form, with early clinical manifestations of the disease who still have the ability to walk independently and before the onset of cognitive decline.

Keywords:
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EPNS21-302 Oral or poster
Movement Disorders

Intracerebral gene therapy in 2 patients with aromatic-L acid decarboxylase (AADC) deficiency

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Objective: Aromatic L aminoacid decarboxylase (AADC) deficiency is a rare disorder due to pathogenic variants of the dopa-decarboxylase (DCC) gene, resulting in decreased synthesis of dopamine and serotonin. Clinical spectrum includes early-onset developmental delay, hypotonia, oculogyric crisis and others movement disorders, autonomic dysfunction, mood and sleep disturbances We report the results of bilateral intraputaminal delivery of a gene vector expressing the DDC gene in two patients with AADC.

Methods: 2 patients aged 10 and 11, and exhibiting a severe classical phenotype, recieved convective bilateral intraputaminal injections of the viral vector (eladocagene exuparvovec, 1.8 x 1011 vector genomes, infusion volume 4x80microlitres, 2 per putamen). Patients were assessed at base line, and prospectively after gene therapy with a follow-up of 9 months (patient 001) and 6 months (patient 002).

Results: Sleep disturbances, irritability and cognitive development improved by week 4. At last follow-up, both patients exhibited improvement of axial tonus, voluntary movements and motor function. Oral feeding was possible for the patient who was exclusively fed by a stomy before gene delivery. Brain imaging did not show any complication. Transient dyskinesias were noticed from week 5-6 after gene therapy. No serious adverse event has been reported.

Conclusions: Intraputaminal gene delivery in the 2 patients with AADC deficiency has been safe and well-tolerated, and resulted in significant improvement in motor and non-motor symptoms of the disease. Longer follow-up is mandatory. Dedicated team for adequate perioperative management and specialized skills for close monitoring of gene therapy are recommended.

Keywords:
AADC deficiency; gene delivery; oculogyric crisis; eladocagene exuparvovec

EPNS21-444 Oral or poster
Metabolic Disorders

Altered autophagy mechanisms associated with neurodegeneration: study of a cohort of patients with BPAN (Beta-propeller protein-associated neurodegeneration)

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Objective: To describe the clinical, biochemical, radiological, and genetic profile of patients with genetically confirmed BPAN. Demonstrate defects in the autophagy pathway in BPAN patients.

Methods: Observational study in a cohort of BPAN patients. Clinical, biochemical, and radiological data were assessed. Genetic studies of the WDR45 gene. Autophagy markers in fibroblasts were investigated using western blot techniques and immunofluorescence.

Results: A total of 9 BPAN patients were assessed, 2/9 male, with ages ranging from 2.6-16 years. The main symptom at onset was global neurodevelopmental delay, also associated with seizures in relation to fever (n = 3), language regression (n = 2) and hypotonia (n = 1). The age of onset was less than 15 months in all cases. The course was variable, including different degrees of developmental delay/intellectual disability (9), epilepsy (7), and parkinsonian signs (2). Elevated liver transaminases were present in 6 cases. Brain MRI showed: T2 and SWI hypointense signal symmetrically in globus pallidus (n = 5) and delayed myelination (n=2). The patients presented de novo pathogenic variants in the WDR45 gene, with the exception of one hemizygous case, whose mother showed mosaicism for the variant investigated in oral mucosa DNA. CSF study showed low level of homovanilic acid in the elder patient. Fibroblasts showed alterations in all the autophagy marker that are compatible with a defect in the autophagy flux (LC3BI/II ratio, LAMP1 and p62).

Conclusions: We describe a cohort of Spanish BPAN patients, including two male patients with a recognizable and particular phenotype. All the patients showed abnormal neuroimaging, most of them including an abnormal iron deposition in the nigrostriatal pathway. The data set of these patients contribute to explain that the dysfunction of the intracellular autophagy determines the developmental defect and the neuronal degeneration.

Keywords:
Autophagy; BPAN; NBIA; Neurodegeneration

EPNS21-52 Oral or poster
Metabolic Disorders

BCKDK deficiency: A treatable neurodevelopmental disease amenable to newborn screening

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Objective: BCKDK deficiency reduces BCAA concentration and causes a clinical picture of developmental delay, autistic features and epilepsy. Few cases have hitherto been reported. Goal: to describe the clinical presentation, long-term outcome, and treatment response in an international patient cohort.

Methods: We included twenty patients with pathogenic BCKDK variants. We analyzed patients' phenotypes using a detailed clinical questionnaire. BCAA were analyzed by ion-exchange chromatography and in dried blood spot.

Results: The mean age of diagnosis was 5.4 years (range: 8mo-19y, 53% female). At birth, no patients had microcephaly. At diagnosis, the average of BCAA were below the reference value in plasma and in CSF. All patients had global neurodevelopmental delay, 18/20 had gross motor function impairment (GMF III or more in 5/18), 15/15 intellectual disability, 16/16 language impairment, 10/15 autism, 9/10 epilepsy, 12/14 clumsiness. All patients presented a post-natal head circumference decreasing reaching microcephaly in 13/17 of them. Regression was reported in 4/5 patients. After treatment, high protein diet and BCAA supplementation (100-260 mg/kg/day), plasma BCAA increased significantly ($p < 0.001$), motor functions stabilized/improved in 12/12 patients. None of the 3 patients with follow-up data who started the treatment before 2 years of age developed autism. 5/12 presented head circumference increase, two of them reaching normocephaly. The patient who started treatment earlier (8 months) experienced a significant improvement (almost normal development at 3 years old). NBS filter cards identified BCAA significantly lower than the normal population.

Conclusions: This is the largest series of BCKDK patients reported. Progressive microcephaly, developmental delay, and autism are the most common traits. Dietetic treatment, in particular early introduction, improves symptoms, leading to an almost normal development in the patient who started earliest, which motivates the necessity of newborn screening.

Keywords:
BCKDK deficiency, developmental delay, autism, microcephaly

EPNS21-598 Oral or poster
Metabolic Disorders

Real-world clinical outcomes of intraventricular cerliponase alfa in CLN2 disease: 4.5-year update from an independent ongoing observational study

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Objective: Neuronal ceroid-lipofuscinosis type 2 (CLN2) disease, characterised by rapid psychomotor decline, epilepsy and vision loss, is caused by deficiency of the lysosomal enzyme tripeptidyl peptidase 1 (TPP1). Intraventricular enzyme replacement therapy with recombinant human TPP1 (cerliponase alfa) is the only approved treatment since 2017.

Methods: Out of our cohort of 59 treated CLN2 patients, we evaluated 24 patients (14 female, 10 male) with (i) late infantile phenotype, and (ii) treatment with cerliponase alfa for at least 6 months outside clinical trials. Unlike the clinical trial cohorts, our cohort also consisted of patients who were pre-symptomatic as well as patients in more advanced diseases stages. Disease progression was monitored by performing the CLN2 clinical rating scale every 3 months as well as Denver developmental testing, electroencephalogram, cerebral MR imaging, and ophthalmologic exams including ocular coherence tomography every 6 months.

Results: Mean age at treatment start was 61.3 months (SD 27.4) with the youngest pre-symptomatic patient being age 6 months. The mean treatment duration was 24.4 months (SD 14.9) with a maximum duration of 51 months. Disease progression was analysed similar to previous clinical trials using the motor and language domain of the CLN2 clinical rating scale (ML score). Mean ML score at treatment start was 3.9 (SD 1.6). Treated patients showed an annual decline of 0.52 (SD 0.4) scores compared to an annual decline of 1.81 scores as previously shown in natural history data from untreated patients. In addition, our data evaluated treatment efficacy with regard to neurocognitive development, brain volumetrics, and visual function.

Conclusions: Data from this independent study are based on the largest cohort of patients receiving cerliponase alfa treatment outside clinical trial settings. They analyse treatment efficacy not only based on outcome measures used

Keywords:
Neuronal ceroid lipofuscinosis, Batten disease, neurodegeneration

EPNS21-206 Oral or poster
Epilepsy: Medical & Surgical Treatment

Efficacy and safety of long-term treatment with stiripentol in children and adults with drug-resistant epilepsies: a cohort study of 196 patients and a review of the literature

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Objective: Stiripentol is an antiseizure medication with multiple potential mechanisms of action, indicated as adjunctive therapy in Dravet syndrome (DS), whose seizures are not adequately controlled with clobazam and valproate. However, there is a reasonable amount of data on its efficacy in other epilepsy aetiologies and types.

Methods: We previously reported our single-centre experience on the efficacy of adjunctive stiripentol treatment in a cohort of 132 patients with different types of refractory epilepsies. Here we expand our analysis to a larger cohort of 196 patients with long-term follow-up (range 0.5-232.8 months). We retrospectively evaluated long-term efficacy, tolerability and predictors of treatment response. We also performed a systematic review of the literature on long-term response to stiripentol (15 studies, n=1156 patients, of which 781 with DS).

Results: In our 196 patients with long-term follow-up, we observed a responder rate of 53% including seizure freedom in 9%. We found that both epilepsy type and aetiology are associated with sustained response over time, with generalised (44%) and combined focal and generalised epilepsies (28%) showing a higher responder rate than focal (20%) epilepsies, and DS being the aetiology with the highest responder rate (64%) among the other syndromes (13-38%). The highest relapse free-survival was observed when stiripentol was initiated at the youngest age (0-4 years) or in adulthood.

Conclusions: Based on the available evidence and our novel findings, we conclude that stiripentol can be an effective and well-tolerated therapeutic option in DS and other epilepsy syndromes with or without an established genetic aetiology, with sustained response over time.

Keywords:
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EPNS21-378 Oral or poster
Epilepsy: Medical & Surgical Treatment

Magnetic Resonance-Guided Laser Interstitial Thermal Therapy (MRg-LiTT) of three different epileptogenic lesions: report of eight pediatric cases

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Objective: To test the efficacy and safety of Magnetic Resonance-guided Laser Interstitial Thermal Therapy (MRg-LiTT) in a series of different epilepsy-determining brain lesions: Hypothalamic Hamartoma (HH), Tuberous Sclerosis, Dysembryoplastic Neuroepithelial Tumour (DNET) affecting pediatric patients. The aim is to investigate seizure outcome, complications rate, hospital stay length and behavioural and cognitive outcome.

Methods: In this prospective study we describe a series of 8 pediatric patients (mean age: 6 years, 11months -15 years) suffering from epilepsy who underwent MRg-LiTT in our Centre. Clinical evaluation, vEEG, neuroimaging and validated questionnaires investigating behaviour and development were administered (Vineland Adaptive Behavior Scales II - only in patients with a 1 year follow-up) before and after the procedure.

Results: None of the patients suffered post-surgical complications. The mean hospital stay was 6 days, and 100% of patients regained normal preoperative motility and activity on the second day after the procedure. The mean follow up was 8 months. Postoperative seizure outcome, as characterized by the Engel Outcome Scale, ranged from class I to class IV. Three of the eight patients (two HH, one DNET) were completely seizure-free after the procedure. The patient with TSC experienced significant reduction of seizure frequency. Neurodevelopmental assessment before and after the surgical procedure showed improvement in cognitive and social behavior.

Conclusions: Our data are consistent with data reported in literature in terms of seizure outcome, complication rates and hospital stay length. MRg-LiTT is an expensive technology, but indirect cost savings (lower complications rate, shorter hospitalization) must be considered. MRg-LiTT may represent first line of minimally invasive treatment of a range of diseases associated with drug-resistant epilepsy. This consideration is particularly pertinent for those brain lesions difficult to access with the methods of traditional surgery.

Keywords:
epilepsy surgery, pediatric, laser, magnetic resonance, MRg-LiTT

EPNS21-393 Oral or poster
Epilepsy: Medical & Surgical Treatment

Precision treatment in epilepsy after whole-exome sequencing diagnosis in clinical practice

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Objective: Whole-exome sequencing (WES) allows to make a diagnosis in a substantial subset of individuals with epilepsy. We analyzed how treatment approach was adjusted after WES-based diagnosis.

Methods: In the past 22 months diagnostic WES (Illumina) was performed in 205 individuals with epilepsy. In 6 individuals with suspicion of a new-onset developmental and epileptic encephalopathy (DEE), rapid analysis was requested. Variants were filtered using an in-house developed pipeline (VariantDB software; Vandeweyer et al., 2014) analyzing a set of 296 genes known to be implicated in epilepsy, and additional genome-wide Human Phenotype Ontology (HPO)-based filtering (MOON software, Diploid).

Results: Pathogenic variants were identified in 28 of 205 individuals (14%), including in 5/6 (83%) for whom rapid analysis was requested. Pathogenic variants were identified in 23 different genes, with recurrent variants in DEPDC5 (3), PRRT2 (2), SCN2A (2), and CHD2 (2).
Based on literature, precision treatment was a theoretical possibility in 19/28 individuals (68%) but was only implemented in 7/19 (37%). In three of them precision treatment was already started upon clinical suspicion, prior to genetic diagnosis. Hurdles to implementation included absent reimbursement (4), availability restricted to clinical trials (4), clinical seizure control (2) and unknown (2). Precision treatment included: enzyme replacement therapy (1), adjustment of anti-seizure medication (2) and ketogenic diet (1).

Conclusions: In our cohort, precision treatment was a possibility in the majority of cases (68%) for whom a WES-based genetic diagnosis could be made. However, precision treatment was only implemented in 37%. These findings are in line with previous studies, and show that the translation of a genetic diagnosis into treatment decisions requires more attention.

Keywords:
Whole-exome sequencing, epilepsy, precision treatment

EPNS21-403 Oral or poster
Epilepsy: Diagnosis and Investigations

A Window in the Brain: Detecting seizures using 8-channels EEG montage and phase synchronisation

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Objective: Phase synchrony on multi-channels electroencephalogram (EEG) changes before and during seizures. No prior study has attempted to detect seizures using phase synchrony calculations on low-density EEG montage (e.g. less than 19 channels), which is required for translation of this quantitative seizure detection method into acute care clinical settings where a round-the-clock neurophysiology service is undeliverable. In this project, we aim to test the seizure detection performance of phase synchronisation calculations using only 8 channels of the routinely collected multi-channels EEG.

Methods: Retrospective data science analysis of fully anonymised routinely generated clinical multi-channels EEG was performed. 40 EEG recordings with seizures were randomly selected from the clinical EEG database in one Scottish paediatric hospital for this study. These recordings are reported by consultant neurologist and neurophysiologist with seizures marked on the EEG. All patient identifying details were removed on EEG extraction. The fully anonymised EEG was processed automatically using the BrainsView seizure detection software which used phase synchrony index (PSI) calculations to identify seizures. BrainsView software only used 8 of the standard 64 channels on the extracted EEG for PSI calculation to detect seizures. Seizures identified by PSI were then compared with the gold-standard neurologist identified seizure markings on the EEG to determine its seizure detection performance.

Results: Using PSI calculations on 8-channels on standard clinical EEG, seizures were detected with 65.5% precision and 70.9 % specificity in the Delta band when compared to the gold-standard seizure detection. Considering other bands did not improve the algorithm's seizure detection accuracy.

Conclusions: Ictal activity can be captured quantitatively using only 8-channels montage on EEG. Further investigations on decreasing the required number of EEG channels and validating its seizure detection performance are warranted.

Keywords:
PhaseSynchrony AutomatedSeizureDetection nonlinear

EPNS21-435 Oral or poster
Epilepsy: Diagnosis and Investigations

Heart rate variability alterations in Dravet Syndrome: the role of status epilepticus and a possible association with mortality risk

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Objective: Preliminary data suggest that patients with Dravet Syndrome (DS) have a reduced heart rate variability (HRV). This seems particularly evident in patients who experienced Sudden Unexpected Death in EPilepsy (SUDEP). This study aims at confirming these finding in a larger cohort and at defining clinical, genetic or electroencephalographic predictors of HRV impairment in DS patients.

Methods: This is a prospective study on all consecutive DS patients followed at our Institution. Patients performed a 24h-ECG Holter to derive HRV parameters. We used as control population patients with epilepsy (PWEs) and healthy controls (HCs). To compare individual HRV parameters among groups (DS, HC, PWE) we used Kruskal-Wallis test and Mann-Whitney test for pairwise post-hoc comparisons. Multiple comparisons were adjusted with Bonferroni correction. In DS patients, we assessed the impact of different clinical, neurophysiological and genetic features on HRV alterations through multiple linear regression. After a mean follow-up of 7.4+/-3.2 years since the HRV assessment all DS patients were contacted to record death or life-threatening events.

Results: 56 DS patients had a significantly reduced HRV compared to both HCs and PWEs. A recent history of status epilepticus (SE) was the only significant predictor of lower HRV in the multivariate analysis. At follow up, only one patient died; her HRV was lower than that of all the controls and was in the low range for DS patients.

Conclusions: We describe for the first time an association between SE and HRV alterations is DS. Further studies on other SCN1A-related phenotypes and other epilepsies with frequent SE will help clarify this finding. Compared to the literature, our cohort showed better HRV and lower mortality. Although limited, this observation reinforces the role of HRV as a biomarker for mortality risk in DS.

Keywords:
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EPNS21-176 Oral or poster
Genetics

PLA2G6-Associated Neurodegeneration (PLAN): A Retrospective Natural History Study

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Objective: To define the PLAN disease course through an international multicentre retrospective natural history study.

Methods: PLAN patients were identified by (i) monthly notifications sent to all paediatric neurology consultants through a national surveillance unit study from 2017-2020 (ii) collaboration with 20 international centres from 5 continents. Clinical details were obtained for each case through standardised, anonymised proformas. Non-parametric statistical tests were used to compare between groups.

Results: 220 PLAN cases were identified: 174 Infantile Neuroaxonal Dystrophy (INAD), 33 atypical Neuroaxonal Dystrophy (aNAD) and 13 dystonia-parkinsonism (DP). The median age at symptom onset differed significantly according to phenotype (INAD=1.2years, aNAD=3years, DP=20years $p<0.01$). The commonest presenting symptoms were developmental regression(49%), gait abnormalities(22%), developmental delay(11%) and eye abnormalities(9%). All aNAD and DP patients learnt to walk independently but most INAD patients(63%) did not; those who achieved it lost ambulation earlier than the aNAD group (median age 2vs7years, $p<0.01$). The median age at motor regression varied significantly (INAD=1.5years, aNAD=4years, DP=20years, $p<0.01$). There were significant differences in death rate (25% INAD, 15% aNAD, 0% DP), median age of death (INAD=9years, aNAD=22years, $p<0.01$) and Kaplan-Meier survival curves. Genotype-phenotype correlations were evident. Nearly all the aNAD and DP cases harboured 2 missense variants. For PLAN patients with 2 missense variants, there was a significant difference in the mean total CADD scores between subgroups (INAD=59.29, aNAD and DP=54.74, $p<0.01$).

Conclusions: This is the largest ever PLAN natural history study, improving the understanding of the disease natural history and phenotypic differences for this ultra-rare, neurodegenerative condition. In the absence of objective biomarkers of disease progression, this data can aid evaluation of upcoming novel precision therapies.

Keywords:
PLA2G6, INAD, aNAD, DP, NBIA, PARK14, Infantile Neuroaxonal Dystrophy, atypical Neuroaxonal Dystrophy, Dystonia-Parkinsonim, Neurodegeneration with Brain Iron Accumulation

EPNS21-186 Oral or poster
Genetics

Utility of genetic testing in children with leukodystrophy

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Objective: Leukodystrophies are rare monogenic disorders primarily affecting the central nervous system white matter. Although imaging characteristics were reported suggestive of specific genetic etiology, there is a significant phenotypic overlap leading to diagnostic challenges. In Israel, since 2018, exome sequencing (ES) is clinically available for patients with leukodystrophy (LD) and negative chromosomal microarray (CMA). We report the diagnostic yield of genetic tests and time to diagnosis in a LD clinic at a pediatric tertiary care center.

Methods: Seventy patients with brain MRI suggestive of a LD, symptom onset before the age of 18 years and genetic workup, were identified from a cohort of patients referred to a LD clinic between June 2019 - September 2021. Clinical data were retrieved form medical records.

Results: Pathogenic variants were identified in 63/70 (90%) patients. ES showed the highest diagnostic yield (38/43,88%) followed by single gene sequencing (11/20,55%), LD panel (1/3,33%), and CMA (2/25,8%). Seven patients tested positive for known familial disease causing variants. Diagnostic method was unavailable for 4 patients. A mean of 1.6±0.7 tests per patient were done prior to diagnosis.
Common diagnoses included: Aicardi Goutières syndrome (20%); metachromatic LD (11%); Hikeshi (8%), Canavan (6%), Alexander (6%), and Pelizaeus-Merzbacher (6%) disease; mucolipidosis IV (5%); IBA57, VPS11, POLR3, and TUBB4A related disease and vanishing white matter (3% each). Three patients (3/70, 4%) were diagnosed with Menkes, ECHS1 and DDX3X related disorders and not a LD. One patient has a non-genetic etiology and 6 patients (6/70, 8.5%) are currently undiagnosed.
Time from symptom onset to diagnosis was 26±30 months. In patients presented prior to 2018 time to diagnosis was longer (35±35 vs 12±9 months, $p<0.001$).

Conclusions: Next generation sequencing carries the highest diagnostic yield with faster time to diagnosis. Rapid diagnosis is crucial as advanced targeted treatments are becoming available.

Keywords:
Leukodystophy, Genetics, Next Generation Sequencing, White matter

EPNS21-189 Oral or poster
Genetics

PHENOTYPIC HETEROGENEITY OF RNA POLYMERASE III-RELATED DISORDERS

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Objective: To study the clinical and radiologic spectrum of RNA polymerase III (Pol III or POLR3)-related disorders with pediatric onset.

Methods: Retrospective review of diagnosed patients at our institution with pathogenic variants in POLR3A, POLR3B, or POLR1C genes (years 2017-2021).

Results: Our cohort is composed of 7 patients. Patient 1 is a 10-year-old boy who shows tremor, dysarthria, and severe ataxia. He has a homozygous mutation in the POLR3B gene (c.496+3A>G). Patient 2 is a 14-year-old boy who only has difficulties in visomotor skills without cognitive impairment. He carries two mutations in the POLR3A gene (c.2376_2377delAT and c.2081G>A). Patient 3 is a 12-year-old girl with dysarthria, mild ataxia, and mild cognitive involvement. Two mutations were detected in the POLR1C gene (c.193A>G and c.836G>A). Patient 4 is a 3-year-old girl with severe global developmental delay, hypotonia and choreic movements. She carries two mutations in the POLR3A gene (c.3381delT and the intronic variant c.1771-6C>G). Patients 5 and 6 are siblings, a 25-year-old woman and his 32-year-old brother. During adolescence they started with progressive disabling tremor and axial dystonia. Both share a homozygous intronic variant in the POLR3A gene (c.1771-7C>G). Patient 7 is a 31-year-old man who began in childhood with alcohol-responsive tremor, followed by spastic ataxia. He carries two mutations in the POLR3A gene (c.2737G>A and the intronic variant c.1909+22G>A). Regarding brain MRI, patients 1-3 show supratentorial diffuse hypomyelination associated with T2 hypointensity of the optic radiations and the thalami. In Patient 4 there is a combination of atrophic and T2-hyperintense striatum, while Patients 5-7 have no relevant cerebral findings.

Conclusions: Pathogenic variants in genes encoding subunits of Pol III are characterized by high phenotypic heterogeneity, with manifestations ranging from severe childhood-onset conditions, as hypomyelinating leukodystrophy or extrapyramidal syndrome, to milder disorders.

Keywords:
POLR3, hypomyelinating leukodystrophy, ataxia, extrapyramidal syndrome

EPNS21-558 Oral or poster
Genetics

Delineation of laminopathies with progeroid and neurodevelopmental disorders due to deficient nucleophagy

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Objective: Background: Autophagy is an intracellular degradation pathway that is essential for quality control in post-mitotic tissue such as neurons. Macroautophagy either occurs in bulk or cargo-selective pathways, e.g., clearance of deficient mitochondria ('mitophagy') or cell nucleus components ('nucleophagy'). Congenital disorders of autophagy present a broad phenotype including neurodevelopmental disorders, microcephaly, epilepsy, and immunodeficiency. Recent studies in patient cells with EPG5-associated autophagy blockade implicated the nuclear component lamin as a driving factor for neurodegeneration due to perturbed nucleophagy (Baron et al., 2017).
Objectives: We delineate the clinical, molecular genetic and imaging spectrum of the biggest cohort yet with pathogenic variants in LMNB1 or LMNB2 and neurodevelopmental and/or progeroid features. Our hypothesis is such disorders overlap with those of EPG5-associated defective nucleophagy.

Methods: Patients with pathogenic variants in LMNB1/2 were identified from multi-centre clinics, GeneMatcher, ClinVar, and previously published reports. Deep phenotyping and massively parallel sequencing revealed two novel pathogenic variants and enabled genotype-phenotype correlation with phenotypic expansion.

Results: We identified a phenotypic spectrum in 40 patients with novel symptoms that range between neurological (epilepsy, leukencephalopathy, strabism, intellectual disability, brain malformation) and progeroid symptoms (microcephaly, lipodystrophy, skin abnormalities). Genomic profiling revealed mutational hotspots in evolutionary conserved domains in LMNB1/2 for progeroid symptoms.

Conclusions: We will explore possible links between LaminB1/2 and deficient nucleophagy that might impinge upon neurodevelopment with a range of progeroid symptoms. Via detailed genotype-phenotype correlation for LaminB-associated disorders, we can offer genetic counselling and anticipatory guidance for families and patients.

Keywords:
autophagy, progeria, neurodevelopmental disorders, nucleophagy, lamin, neurodegeneration

EPNS21-580 Oral or poster
Genetics

The expanding phenotypical spectrum of congenital disorders of autophagy due to recessive mutations in EPG5

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Objective: Autophagy is a fundamental biological pathway with important roles in intracellular quality control and homeostasis. The pathway is highly evolutionary conserved and involves engulfment of intracellular targets by double-membraned structures, autophagosomes, and delivery to lysosome for digestion and recycling. We previously reported recessive mutations in EPG5 with a crucial role in autophagosome-lysosome fusion as cause of Vici syndrome characterized by callosal agenesis, cataracts, hypopigmentation, immunodeficiency, and cardiomyopathy.

Methods: We present genetic, clinical and neuropathological features from the largest cohort of patients with EPG5-related disorders reported to date, complemented by proteomic data and experimental findings from C. elegans, D. melanogaster and murine models of EPG5 deficiency.

Results: We identified an international cohort of more than 100 patients with recessive mutations in EPG5, more than half unpublished. The associated phenotypical spectrum ranged from antenatally lethal presentations to classical appearance of Vici syndrome and less specific neurodevelopmental presentations at mildest end of range. Epilepsy, movement disorders and myopathic features were frequently associated and progression was variable. Genotype-phenotype studies suggested tentative correlations between predicted residual EPG5 expression and clinical severity. Organismic models showed neurodevelopmental, neurodegenerative and neurological features (incl. epilepsy), life span reduction and immune defects.

Conclusions: Our findings expand the phenotypical spectrum of EPG5-related disorders beyond Vici syndrome and suggest close clinical and molecular links with other disorders of defective autophagy and intracellular trafficking. Organismic models of EPG5 deficiency provide insights into the intricate relationship between neurodevelopment, neurodegeneration and defective immunity,

and may provide a therapy development platform for an important emerging group of neurodevelopmental disorders.

Keywords:
autophagy, neurodevelopmental disorders, neurodegeneration, drosophila melanogaster, caenorhabditis elegans, proteomics, vici syndrome

EPNS21-102 Oral or poster
Epilepsy: Medical & Surgical Treatment

Ganaxolone Significantly Reduces Major Motor Seizures Associated with CDKL5 Deficiency Disorder: A Randomized, Double-blind, Placebo-Controlled Phase 3 Study (Marigold Study)

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Objective: CDKL5 deficiency disorder (CDD) is a rare, genetically determined epileptic encephalopathy. The clinical characteristics commonly associated with a pathogenic CDKL5 variant include early-onset refractory epilepsy, hypotonia, intellectual and gross motor impairment. The Marigold Study is the first Phase 3, randomized, placebo-controlled trial to evaluate adjunctive investigational ganaxolone in patients with refractory epilepsy associated with CDD.

Methods: This was a randomized, double-blind, placebo-controlled trial conducted at 36 sites in 8 countries. Eligible patients were 2-21 years of age with a pathogenic CDKL5 variant and uncontrolled seizures. Enrolled patients prospectively tracked seizure frequency during a 6-week baseline period and were then randomized (1:1) to receive ganaxolone (n=50) or placebo (n=51) for 17 weeks. The primary endpoint was the percentage change from baseline in major motor seizure frequency during the treatment period.

Results: Enrolled patients were a median 6 years of age and comprised of 79% female and 21% male. Prior to the study, patients had tried a median of 7 prior anti seizure medications. In the baseline period, patients experienced a median 28-day major motor seizure frequency of 49.2 and 54.0 in the placebo and ganaxolone groups, respectively. Patients on ganaxolone experienced a median 30.7% reduction in major motor seizure frequency compared to a 6.9% reduction in the placebo group during the treatment period relative to baseline (p=0.0036, Wilcoxon Rank-Sum Test). Ganaxolone demonstrated improving trends but did not achieve statistical significance in the key secondary endpoints. Adverse events occurred in 86% of ganaxolone patients and 88% of placebo patients. Ganaxolone was generally well tolerated with a less than 5% discontinuation rate.

Conclusions: These data provide strong evidence that ganaxolone is effective and generally well-tolerated in the treatment of refractory epilepsy in patients with CDD.

Keywords:
CDKL5, CDD, Ganaxalone

EPNS21-402 Oral or poster
Epilepsy: Medical & Surgical Treatment

Stiripentol use in Dravet patients below 2 years of age: real world experience in France

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Objective: Evaluate the short- and long-term effect of stiripentol initiated in young Dravet patients by retrospectively reviewing the databases generated in France.

Methods: Cohort-databases of Dravet patients treated in France with stiripentol since 1991 were reviewed and those that fulfilled the following criteria were included: stiripentol initiated before 2 years, longitudinal data available, data either published or collected within the framework of a regulatory protocol, raw data fully accessible. Three databases were included: (1) a temporary authorization for use (TAU), (2) a European post-marketing survey (PMS) and (3) two successive cohorts of Dravet patients in Paris. Duplicates were eliminated and data regarding seizures, treatments and patients' condition were collected at stiripentol initiation, at short-term and at last visit.

Results: Data from more than 100 patients who started stiripentol at a mean age of 15 months were collected. Valproate and clobazam were the most common comedications. At short-term, responder rate (at least 50% decrease in convulsive seizure frequency) was above 50% in all cohorts, seizure duration and frequency of status epilepticus were significantly reduced, and no specific safety issues were reported. At the last visit, more than 90% of the patients were still receiving stiripentol, mostly (>90%) in combination with valproate and/or clobazam, and one third of the patient received topiramate. Loss of appetite and somnolence were the most frequently reported adverse events, and less than 10% of the patients discontinued stiripentol due to poor tolerance.

Conclusions: Real-world efficacy and safety data collected in this large cohort of Dravet patients started with stiripentol before 2 years were comparable to those already reported in older children. Additionally, stiripentol was shown to have a significant effect on the number of episodes of status epilepticus in these young patients.

Keywords:
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EPNS21-463 Oral or poster
Epilepsy: Diagnosis and Investigations

Infantile spams. Clinical description and genetic landscape in a series of 96 pediatric patients. Early predictors of poor outcomes.

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Objective: To describe the deep clinical phenotype and pathogenic molecular findings in a cohort of patients with infantile spams (IS). We also evaluate early predictors of poor prognosis.

Methods: This is a retrospective observational study. Ninety-six patients diagnosed with IS between January 2012 and January 2020, followed at Pediatric Neurology Department (Hospital Sant Joan de Déu). Family history, perinatal antecedents, neurological exam at onset, spasms characterization, ictal and inter-ictal video-EEG, brain MRI, metabolic tests, molecular findings, and neurodevelopment outcome were collected from electronic medical record and an anonymized database was created. Data were analyzed using IBM SPSS Statistics.

Results: fifty-seven patients were male. Mean age at IS onset was 5.7 months (SD 2.1 months) Developmental delay before spasms onset observed in 42.7 %, and developmental regression in 36.5 %. Global hypotonia was the predominant neurological feature. Inter-ictal multifocal epileptiform discharges in 83 %, and hypsarrhythmia pattern in almost 50%. Brain MRI was abnormal in 52%. De novo pathogenic variants in clinical exome sequencing were found in 18 patients: SYNGAP1, PAFAH1B1 (2), SLC35A2, KIAA2022, KCNB1, CDKL5 (4), TSC1, TSC2, NR2F1 (2), DYNC2H1, DYNC1H1, EEF1A2, and SPTAN1. Down syndrome (5). Chromosomal rearrangements in aCGH (4): NDS1 deletion, dup MECP2, del (15q13) and del (4q13). At follow-up, refractory epilepsy in 58.1 % patients, intellectual disability in 75.3 %, and 57 % with autism spectrum disorders.Psychomotor delay or abnormal neurological examination at diagnosis but also structural or genetic etiology were the most significant early prognostic factors for poor outcome.

Conclusions: IS are one of the main seizure type of early onset epilepsies. Heterogeneous genetic etiologies with different synaptic mechanisms have been described and related to poor outcome. In this study we reaffirm the concept of developmental and epileptic encephalopathy (Scheffer et al 2017).

Keywords:
infantile spams , Psychomotor delay, encephalopathy

EPNS21-571 Oral or poster
Epilepsy: Diagnosis and Investigations

Early childhood epilepsies: high precision syndrome and aetiological classification

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Objective: 1.Describe the epidemiology of epilepsies presenting before 3 years of age
2.Report incidences for individual epilepsy syndromes
3.Report underlying aetiologies in relation to epilepsy syndrome

Methods: A prospective national cohort study, using capture-recapture methodology, including the entire population of Scotland. Participants were recruited using two independent strategies: 1) referral via clinicians and 2) Review of EEG records. Patients were extensively investigated for underlying aetiology, including a 104 gene epilepsy panel offered to all patients with unknown cause. Whole genome sequencing was offered for those with therapy resistant epilepsies without cause found on gene panel. 24 months after initial presentation clinicians were contacted to classify each epilepsy as per the ILAE 2017 Classification. They were also asked to report on seizure control and any developmental comorbidity.

Results: 390 children <3 years with epilepsy were prospectively recruited. Incidence of epilepsies <3 years was 240 per 100,000 live births (95% confidence intervals 216-265). Epilepsy syndrome was classified in 54% and aetiology identified in 54%. Only 30% could not be classified by either syndrome or aetiology. The incidence for syndromes, per 100,000 live births, was: Infantile Spasms Syndrome (ISS), 30.7 (95%CI 22.9-40.2), Dravet syndrome, 6.5 (95%CI 3.2-10.0); Early Infantile (onset < 3 months) Developmental and Epileptic Encephalopathy (EIDEE), 10.0 (95%CI 5.8-16.0). Aetiology was identified in 69% of patients with ISS, 76% with EIDEE, 100% with Dravet syndrome, and 87% with otherwise unclassified DEE. Aetiology was the strongest predictor of adverse outcomes in terms of both seizure control and developmental impairment. Failure to identify aetiology in ISS was associated with significantly better outcomes.

Conclusions: Early childhood epilepsies require precision syndrome and aetiological classification. Yield from genetic testing is high in ISS and all DEEs. Identifying aetiology guides prognosis.

Keywords:
Epilepsy, Syndrome, Aetiology, Outcome, Developmental, Spasms

EPNS21-95 Oral or poster
Epilepsy: Medical & Surgical Treatment

Interim Analysis (IA) Safety, Pharmacokinetics (PK), and Cerebrospinal (CSF) Exposure Data from the Ongoing Phase 1/2a MONARCH Study of STK-001, an Antisense Oligonucleotide (ASO), in Children and Adolescents with Dravet Syndrome (DS)

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Objective: DS is a severe and progressive genetic epilepsy that is generally caused by spontaneous, heterozygous loss of function mutations in the *SCN1A* gene, which encodes the voltage-gated sodium channel subunit type 1 α ($Na_V1.1$). STK-001 is an investigational ASO designed to upregulate $Na_V1.1$ protein expression in brain by leveraging the non-mutant (wild type) copy of *SCN1A* to restore physiological $Na_V1.1$ levels, thereby potentially reducing seizure frequency (SF) and non-seizure comorbidities.

Methods: Patients (N=21) with DS were grouped by age (2-12 and 13-18 yrs) and SF was evaluated for 28 days (baseline) before CSF collection. During the pre-treatment period, patients had a high rate of convulsive SF (median=17). STK-001 was administered intrathecally on Day 1 as a single dose (SAD; 10, 20, or 30mg) or on Day 1, Wk 4, and Wk 8 as multiple ascending doses (MAD; 20mg).

Results: 18/21 were taking ≥3 concomitant anti-seizure medicines as maintenance therapy, and 14/21 were taking ≥4. Adverse events (AEs), SF, and plasma PK were monitored throughout. At the time of the IA, three patients had study drug-related treatment-emergent (TE) AEs; none in 30mg SAD or 20mg MAD cohorts, and four patients had serious TEAEs, none related to study drug. In addition, 8/11 SAD patients experienced a reduction in convulsive SF from Day 1 to Days 29-84. Dose-proportional increases in plasma exposure and CSF concentration were observed. Modelling data suggest that >95% of patients are predicted to have pharmacologically active STK-001 brain levels with three monthly 30mg doses.

Conclusions: At the time of the IA, STK-001 was well-tolerated with no study drug-related safety concerns observed. MONARCH IA provides initial positive safety data and more clarity on STK-001 doses likely to be pharmacologically active in patients with DS, supporting continued development of STK-001 as the first disease modifying precision medicine for DS.

Keywords:
mRNA, splicing, TANGO

EPNS21-449 Oral or poster
Fetal and Neonatal Neurology

Diagnostic yield of exome sequencing in fetal callosal abnormalities

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Objective: Counseling for fetal callosal abnormalities remains very challenging since outcome is diverse and depends on the presence of additional (extra)neurological features and underlying genetic diagnosis. Rapid prenatal exome sequencing (ES) has proven to be a promising diagnostic tool for providing a timely genetic diagnosis. In this study, we investigated the diagnostic yield of ES when callosal abnormalities are detected on prenatal ultrasound.

Methods: This is a single center, retrospective study from 1/1/17 til 1/10/21. Parents, that were referred to the neurologist for counselling due to fetal callosal abnormalities detected on prenatal ultrasound, were included.

Results: Forty fetuses of 39 pregnancies were included. Two patients showed a dilated cavum septum pellucidum vergae (CSPV; 5%), two cavum septum pellucidum agenesis (CSPA; 5%), ten hypoplasia of the corpus callosum (HCC;25%), ten isolated agenesis of the corpus callosum (ACCi; 25%) and 16 complex ACC (ACCc). Genetic evaluation was performed in 34 cases (85%), and 27 had additional ES (79%). In one of the 2 CSPA cases a deletion/terminal duplication was found. In 8 of the 10 HCC cases (80%) a genetic diagnosis was established (1 terminal deletion and 7 pathogenic variants); in only 1 case out of 10 ACCi cases (10%) a mutation was found. In 11 of the 16 (69%) ACCc cases a diagnosis was established (1 trisomy 18, 2 deletions, 8 pathogenic variants). Termination of pregnancy (TOP) was performed in 43% of cases and 1 intra-uterine fetal demise took place (2%). A genetic diagnosis was helpful in parental decision making: 5 out of 5 abnormalities in micro-array (100%) and 13 out of 16 ES abnormalities (81%) resulted in discontinuation of the pregnancy.

Conclusions: We show that ES had a high diagnostic yield when fetal callosal anomalies were present, especially in HCC or ACCc cases. Moreover, ES had a substantial clinical impact on parental decision making. This warrants implementation of ES in the routine care in fetal callosal abnormalities.

Keywords:
fetal callosal agenesis exome sequencing

EPNS21-461 Oral or poster
Fetal and Neonatal Neurology

Outcome and genetics of fetal ventriculomegaly diagnosed at neurosonography

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Objective: Fetal ventriculomegaly (VM) is one of the most frequent abnormalities of the evolving nervous system of the fetus. The main purpose of this study is to investigate the outcome and genetic diagnosis of fetuses with VM in order to improve prenatal counselling of parents with a fetus with VM.

Methods: This is a retrospective cohort study performed in 2 university medical centers from January 01, 2015 to September 01, 2020. VM was classified as mild, moderate or severe. Genetic diagnosis was offered during pregnancy including microarray and rapid prenatal exome sequencing (pES). Outcome was the percentage of babies born alive, termination of pregnancy and/or fetal demise.

Results: Parents of 229 fetuses with VM were counseled: 109 (47.6%) with mild-, 60 (26.2%) with moderate-, and 60 (26.2%) with severe VM. Progression of VM during pregnancy occurred in 45 cases (29.4%), predominantly in severe VM (53.6%). In 123 cases (53.8%) progression of VM occurred when dilatation of third and/or fourth ventricle was present. In severe VM, corpus callosum defects and cerebellar malformations were seen in 50.0% and 45.5% of the cases, respectively. Hundred-one out of 229 (44.1%) fetuses with VM were born alive: 50.5% with mild-, 35.0% with moderate-, and 41.7% with severe VM, 12 (5.2%) fetal demises occurred. Genetic analysis (QF-PCR and micro-array) was performed in 117 out of 229 fetuses (51%), and pES in 57 of 229 cases (25%). An abnormal karyotype or micro-array was detected in 23 (19.7%) fetuses: 14 (11.9%) in mild VM, 5 (4.3%) in moderate VM, and 4 (3.4%) in severe VM. Fifteen of the 57 fetuses that had pathogenic variants in pES, of which 6 (40.0%) fetuses in the mild category.

Conclusions: Fetuses with mild VM have the highest chance to survive. Third and fourth ventricle dilatation is a risk factor for progression of VM. This study confirms the clinical relevance of additional genetic investigations, especially for the mild VM group. Further larger prospective research is needed to confirm these results.

Keywords:
fetal ventriculomegaly; genetics; prenatal exome sequencing; micro-array; karyotype; survival; termination of pregnancy; fetal demise

EPNS21-569 Oral or poster
Genetics

BRAT1 - encephalopathy mimicking hyperekplexia in neonates

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Objective: *BRAT1* mutations cause a spectrum of severty ranging from lethal neonatal rigidity and multifocal seizure to a less severe late-onset presentation. Neonates may present with myoclonic seizures, encephalopathy, hypertonia and microcephaly, and progression to bouts of apnea and bradycardia, cardiac arrest and death. Here we report three unrelated neonates with novel variants in *BRAT1* initially misdiagnosed with hyperekplexia.

Methods: We analyzed the clinical, neurophysiological neuroradiological findings of three unrelated neonates who presented at birth with hypertonia and erratic, multifocal myoclonic jerks. Neuropathological findings were obtainded for one patient. Whole exome sequencing confirmed homozygous or heterozygous compound mutations in *BRAT1*.

Results: All infants presented with hypertonia and erratic subcontinuous myoclonic jerks in the first days of life. Early EEGs were normal and no seizures were recorded. The myoclonus was increased by tactile and acoustic stimuli, leading to a diagnosis of hyperekplexia. Intractable seizures occurred after the first 12-21 days of life. Interestingly, at seizure onset the EEG background remained fairly organized. During the course of the disease, they developed acquired microcephaly, progressive apnea and bradycardia episodes, and early death. Neuropathology in one patient revealed marked delay in myelination and severe and diffuse astrogliosis.

Conclusions: *BRAT1* pathogenic variants are associated in neonates with congenital hypertonia and early-onset myoclonic jerks. EEG can be falsely reassuring initially, misleading to the diagnosis of hyperkplexia. Acquired microcephaly, encephalopathy, and the evolution into intractable seizures, apnea and bradycardia, suggest *BRAT1* encephalopathy. Pathological findings suggest a primary disorder of astrocytes and astrogliosis with the upper layer of the cortex relatively preserved, which could account for the initially normal EEG.
Videos with events' semiology will be part of the presentation.

Keywords:
BRAT1 Seizures Myoclonus Hypertonia Hyperekplexia

EPNS21-610 Oral or poster
Metabolic Disorders

Patterns of abnormal movements in inherited metabolic disorders with neonatal presentation: Study following video analysis and volumetric brain MRI

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Objective: To describe motor pattern abnormalities in newborns with inherited metabolic disorders (IMDs) to provide practical helpful clinical diagnostic and pathophysiological clues.

Methods: Observational and retrospective study of 47 neonatal patients with a defined diagnosis of IMD. IMD categories were considered according to the "International Classification of Inherited Metabolic Disorders (ICIMD)" (2021). Medical records were reviewed and video analysis was performed. Literature was reviewed. A neonatal volumetric brain MRI study was performed in 7 patients.

Results: A total of 47 patients (0-90 days;mean age: 27.9 days) were assessed. A hypokinetic pattern was observed in 22 patients, corresponding mainly to disorders of amino acid metabolism (n=5), followed by disorders of cofactor metabolism (n=4), complex molecule degradation (n=3) and peroxisomal disorders (n=3). A hypokinetic-rigid syndrome was present in 12 patients. A hyperkinetic pattern was observed in 14 patients, corresponding mainly to disorders of amino acid metabolism (n=9), and myoclonus and tremor were the most common phenomena. Abnormal ocular movements were described in 16 patients from different categories. Volumetric brain MRI analysis in patients with amino acid disorders showed abnormal reduction of putamen and caudate nucleus.

Conclusions: This is an initial approach to neonatal IMDs and the motor and movement disorder phenomenology. The hypokinetic pattern was prominent in this cohort, followed by the hyperkinetic pattern. Abnormal ocular movements were also frequent. We have found distinctives patterns that may allow an earlier detection of the IEM. Further studies with different IMDs categories with a systematic assessment of a larger number of patients will be required.

Keywords:
Inherited metabolic disorders, Neonatal period, Motor pattern, Movement disorder

EPNS21-698 Oral or poster
Epilepsy: Diagnosis and Investigations

Neonatal seizures: use of the last ILAE Classification.

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Objective: Neonatal seizures are the most common neurological emergency in newborns. The majority of seizures occur in response to an acute brain insult. A smaller number of cases are due to non-acute genetic or malformative etiologies. The aim of this study was to classify our patients' seizures according to the last ILAE classification (2021).

Methods: This was a retrospective observational cohort study of all
the neonatal cases with video EEG-confirmed seizures, recorded between January 2015 and August 2021 at Bambino Gesù Children's Hospital. During this period, 886 newborns (494M) required a neurological evaluation in the Neonatal Intensive Care Unit; among them, 11.6% (103, 60M) presented seizures. Perinatal history, primary and secondary diagnosis, age at onset, semiology and duration of seizures, EEG features were analysed, applying the last ILAE classification for neonatal seizures.

Results: A total of 39 (21M) cases with video-EEG seizures recorded were included. Median age at onset was 7.8 days (range: 1-28 days). Most infants (28/39) were born at term. The most frequent etiologies were HIE (15), stroke (7) and DEE (5). The duration of EEG recordings ranged from 30 minutes to 48 hours. We recorded 138 single seizures and 12 Status Epilepticus. The majority of seizures (67) were electrographic-only, due to HIE in 7 patients; the second more frequent type (25) has been clonic, due to stroke in 3. Myoclonic and tonic seizures were mainly observed in patients with DEE and inborn error of metabolism

Conclusions: The new ILAE classification appears to be comprehensive. Using seizures type and descriptors, we were able to include all our patients in a specific category. At this age, a classification based on the predominant clinical features, allows a better definition of the phenotype and a possible correlation with the etiology, as well as starting a therapy based on precision medicine as soon as possible.

Keywords:
newborn, classification, neonatal seizures, EEG

EPNS21-114 Oral or poster
Neuromuscular

Apitegromab in Spinal Muscular Atrophy (SMA): An Analysis of Multiple Efficacy Endpoints in the TOPAZ Trial

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Objective: Apitegromab is an investigational, fully human, monoclonal antibody that specifically binds to proforms of myostatin, promyostatin and latent myostatin, thereby inhibiting myostatin activation.

Methods: The TOPAZ study is a 3 cohort, phase 2 study (NCT03921528).
We report the results of 58 patients with later-onset SMA dosed with IV apitegromab Q4W for 52 weeks.

Results: In the Type 2 cohort initiating nusinersen before age 5 (>2 years, n=17) patients were randomized, double-blind, 1:1 to 2mg/kg or 20mg/kg apitegromab. 63% of patients on 20mg/kg in this cohort experienced >6-point gains in HFMSE with a mean improvement from baseline of +7.1-points in HFMSE on top of background therapy. The magnitude of (1) increase in serum latent myostatin (2) increase in motor function scores, and (3) time to reach HFMSE motor function benefit correlated with higher dose.

In the second cohort, nonambulatory Type 2/3 patients 5-21 years (n=14) receiving 20mg/kg apitegromab, 64% obtained greater than or equal to 1-point increases and 29% greater than or equal to 3-point increases in HFMSE from baseline. In both nonambulatory cohorts, improvements in RULM were achieved.

In the ambulatory cohort the effect of 20mg/kg apitegromab (5-21 years, n=23) receiving chronic nusinersen or not was studied. Functional stabilization was maintained in both groups, but overall 39% obtained greater than or equal to 1-point and 22% obtained greater than or equal to 3-point increases from baseline in RHS. Substantial correlations were observed between RHS scores and target engagement marker, serum latent myostatin. Overall, greater improvements in motor function inversely correlated with characteristics of advanced disease, i.e. presence of scoliosis and contractures.

The incidence and severity of AEs were consistent with the underlying patient population and background therapy

Conclusions: Apitegromab has the potential to be the first muscle-directed therapy to address motor function impairment affecting patients with SMA.

Keywords:
SMA, spinal muscular atrophy, apitegromab, muscle, myostatin, neuromuscular disorder

EPNS21-23
Neuromuscular

Oral or poster

Are neurofilaments suitable biomarkers in Spinal Muscular Atrophy?

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Objective: Neurofilament light (Nf-L) has been proposed as a biomarker for different neurodegenerative disorders. The study aims were to analyze how Nf-L is altered in different Spinal Muscular Atrophy (SMA) types and how concentrations change with nusinersen therapy.

Methods: We determined Nf-L in CSF by enzyme immunoassay, of patients with SMA (Type I: N=18, II: N= 32 and III: N=8) ranging in age from 0-33 yrs at baseline, and during nusinersen treatment. Baseline data were compared to those of 44 controls.

Results: Baseline Nf-L was increased in 34 patients (59%) and was higher in the patient group, when compared to the control group ($p<0.001$). Patients with SMA I showed higher values than patients with SMA II, SMA III and controls ($p<0.05$). Patients with SMA II had higher values than controls ($p<0.05$), whereas NF-L concentrations differed not significantly between patients with SMA III and controls. NF-L values were significantly lower after 6 mths of treatment compared to baseline for the entire SMA group. Regarding SMA types, NF-L concentrations declined significantly in the SMA II but not in the SMA III group. Patients with SMA I also showed lower NF-L values under treatment. Baseline NF-L values were distinctly lower in SMA I subjects with disease duration longer than 6 mths, as compared to those with shorter disease duration.

Conclusions: These data suggest that NF-L is principally suitable as a biomarker for SMA, but SMA type and disease duration have to be taken into account when interpreting NF-L concentrations and response to treatment.

Keywords:
spinal muscle atrophy, nusinersen, Neurofilaments, NF-L

EPNS21-401 Oral or poster
Neuromuscular

Nusinersen on respiratory progression in paediatric patients with spinal muscular atrophy type 2 and non-ambulant type 3

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Objective: Nusinersen treatment provides significant functional motor benefit in the milder forms of Spinal Muscular Atrophy (SMA). Treated patients demonstrate a clinical response as early as 6 months from first injection. However less is known on respiratory outcomes in Nusinersen treated patients. The available literature is from small, heterogeneous Nusinersen treated SMA cohorts with inconsistent results on the effect of 12 months of treatment on forced vital capacity (FVC).

Aim of this study is to identify the impact of Nusinersen on respiratory function across an international cohort of paediatric SMA2 and non-ambulant SMA3 patients (Italian SMA network, US PNCR, UK SMA REACH) when compared to the natural history data recently published by the consortium.

Methods: Five-year retrospective study of SMA2 and non-ambulant SMA3 paediatric patients (age 4-18years) within the iSMAc centres (UK, US, Italy) between 2016 and 2021 treated with Nusinersen. We collected: lung function (Forced vital capacity % predicted (FVC %pred), Non-Invasive ventilation requirement (NIV), use of cough device. Recumbent length/ulnar length were used as surrogate for height in FVC %pred. calculation.

Results: At the present time data were available for 81 patients: 64 SMA2, 17 SMA3. Mean (SD) age at first injection was 7.8(3.4) and 10.2(4) years respectively. At baseline 22/63 (35%) SMA2 and 1/17 SMA3 (6%) required NIV due to respiratory infections or hypoventilation and 43/64 (67%) SMA2 and 5/17(29%) SMA3 used cough device.

Up to age 13 years, when the respiratory decline is steeper, in treated SMA2 FVC% declined by 3.0% per year vs 4.2% in natural history and in treated SMA3 FVC% declined by 4.3% vs 6.3% in natural history.

Conclusions: In paediatric patients with SMA2 and non-ambulant 3, Nusinersen delays the rate of respiratory decline when compared to natural history. This study analyses the impact of Nusinersen on the respiratory function in the largest cohort of mild SMA published so far.

Keywords:
Spinal Muscular Atrophy, Nusinersen

EPNS21-61 Oral or poster
Neuromuscular

Predictive value of gross motor abilities at age of best performance in determining age at loss of ambulation in Duchenne Muscular Dystrophy

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Objective: To explore the predictive value of the North Star Abmulatory Assesment (NSAA) score and Timed Rise from Floor (TRF) recorded at age of expected peak in determining age at loss of ambulation (LOA) in Duchenne muscular dystrophy (DMD).

Methods: We included DMD patients enrolled in a large collaborative UK network (the North Start Network) database according to the following criteria: follow-up > 3 years, availability of one NSAA record between 6-7.5 years (defined as baseline visit), at least two follow-up visits, last visit > 8 years. Data regarding corticosteroid (CS) treatment, LOA, genotype, and functional scores (NSAA score, TRF) were analysed. Age at LOA amongst different groups based on NSAA and TRF was determined by log-rank tests. Cox-proportional hazard models were used for multivariate analysis.

Results: Two hundred ninety-three patients were included. Mean (SD) age at first and last visit was 5.5 (1.2) and 12.7 (2.9) years, respectively (median follow-up 7.3 years). The median NSAA score at baseline was 27. Higher NSAA scores were associated with older age at LOA ($P < 0.001$). For subjects with NSAA score <22, the probability (95% CI) of being ambulant at the age of 11 and 13 years was 0.32 (0.21-0.45) and 0.13 (0.05-0.34), respectively, while for NSAA 22-25 the probability was 0.42 (0.29-0.6) and 0.19 (0.09-0.38). For patients with a NSAA 26-28 the probability was 0.59 (0.46-0.76) and 0.34 (0.21-0.55), while for NSAA 29-31 the probability was 0.85 (0.75-0.96) and 0.34 (0.21-0.54). Finally, for NSAA 32-34 the probability was 0.82 (0.71-0.94) and 0.61 (0.47-0.79), respectively. TRF at baseline was positively associated with age at LOA (HR 1.13; 95% CI 1.09-1.17, $P<0.001$). In multivariate analysis, CS daily regimen (vs intermittent) and TRF were the most important predictive factors for LOA ($P = 0.01$).

Conclusions: Both NSAA score and TRF recorded before the expected decline phase are early predictors of age at LOA.

Keywords:
Duchenne muscular dystrophy, DMD, outcome, NSAA

EPNS21-696 Oral or poster
Neuromuscular

Characterization of missense variants in TTN-related congenital myopathies

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Objective: Mutations in TTN are a common cause of genetic myopathies. Diagnosis of a TTN-related myopathy is challenging due to clinico-pathological overlap with other myopathies and the prevalence of TTN variants, in particular rare missense variants, in healthy control population.We used a combined biochemical, biophysical and cellular approach to distinguish disease-causing from neutral TTN missense variants.

Methods: As part of an international collaborative effort,we identified 35 patients (age 10w-71y) with either 2 truncating variants,1 truncating and 1 missense variant,or homozygous missense variants in TTN.We assessed the effect of missense variants on domain solubility&thermal stability following expression of individual TTN domains in bacteria.For compound genotypes with 2 missense variants, we expressed affected domains in cardiac and skeletal myocytes,to assess the mutational effect on sarcomeric protein localisation,and aggregation and co-localisation with proteins implicated in proteostasis.

Results: Onset was typically from birth followed by variable progression of weakness,contractures,scoliosis&respiratory symptoms.Extraocular muscles were spared.Cardiac involvement depended on variant position.Histopathological abnormalities included cores,increased central nuclei,fibre-type disproportion.TTN missense variants either prevented correct domain folding and/or reduced thermal domain stability.Expression of 2 missense variants in cardiomyocytes resulted in protein mis-localisation.In skeletal myocytes recruitment of both P62/SQSTM1 (autophagy cargo adaptor) and conjugated ubiquitin (marker of proteins targeted for proteasomal/lysosomal degradation) to aggregates of the missense variant-containing protein was observed.

Conclusions: TTN-related myopathies have a characteristic clinico-pathological phenotype.Myopathy-associated TTN missense mutations are strongly destabilizing,exert their effect when inherited with a truncating TTN variant or when in homozygosity,and may affect correct proteostasis.

Keywords:
TTN, congenital myopathy, missense variants

EPNS21-130 Oral or poster
Movement Disorders

Delineation of the spectrum of movement disorders associated with CLN2 Batten disease

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Objective: To characterise the spectrum of movement disorders associated with neuronal ceroid lipofuscinosis type 2 Batten disease (CLN2).

Methods: A retrospective review of medical records, neuroimaging and videos were undertaken for 18 children (mean age 7.7 years, range 5-11) with genetically confirmed CLN2 attending a single tertiary metabolic centre for enzyme replacement therapy with cerliponase alfa. Patients were clinically assessed with a standardised structured history including the Unified Batten Disease Rating Scale (UBDRS) and a modified Abnormal Involuntary Movement Scale (AIMS). 15 examinations were video-recorded and independently rated by a second assessor. Two senior paediatric neurologists facilitated consensus agreement for divergent scoring.

Results: Ataxia (16/18) and myoclonus (14/18) were both common early disease features (median onset 4 years). Spasticity (10/18) and dystonia (10/18) were present in most though these developed later (6.5y and 5.5y respectively). Other hyperkinetic movements including chorea, athetosis, and orofacial dyskinesia were also frequently observed (11/18). Hypokinesia (8/18) became more evident with increasing age (>7y). These often followed a pattern from ataxia/myoclonus, to hykperkinesia/spasticity, to hypokinesa over time. For some, the first presenting feature was movement disorder (dystonia n=2, tremor n=1). The mean UBDRS Physical Assessment score was 44.4 and mean AIMS score 6.8. UBDRS had a mild correlation with age (R2=0.316). 9/18 received regular medications for their movement disorder, including Gabapentin (n=4, reportedly effective), Clonazepam (n=4) and Baclofen (n=3).

Conclusions: Movement disorders appear to be a core feature of CLN2 that are important to recognise. They can be the earliest presenting feature, manifesting before epilepsy and other classical features, and have potential to cause significant disability. Screening assessment and treatment of movement disorders should become standard clinical practice as children live longer.

Keywords:
CLN2, Batten disease, late infantile neuronal ceroid lipofuscinosis, neuronal ceroid lipofuscinosis, movement disorder, ataxia, myoclonus, dystonia, spasticity, hypokinesia

EPNS21-2060 Oral or poster
Epilepsy: Miscellaneous

Exome analysis focusing on epilepsy-related genes in children and adults with sudden unexplained death

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Objective: Previous studies indicate that 30% of sudden infant death syndrome (SIDS) and sudden unexplained death in children, adolescents, and young adults (SUD) may be attributed to a genetic disease. On the other hand, sudden unexpected death in epilepsy (SUDEP) is the main cause of death in patients with epilepsy. Its pathophysiology is unknown but likely multifactorial, including genetic causes such as voltage-gated channelopathies. This retrospective study aimed to breach the gap of knowledge by reanalyzing the whole exome sequencing (WES) data of a large cohort of SIDS and SUD cases with focus on epilepsy-related genes.

Methods: The study population consists of 153 SIDS and 45 SUD cases collected at the Zurich Institute of Forensic Medicine in Switzerland. The classification of SIDS and SUD cases has been performed according to international guidelines, including a review of the clinical history and of the circumstances of death, as well as a full autopsy. Targeted reanalysis of the available WES data focused on 365 epilepsy-related genes

Results: Analysis of the exome data identified pathogenic or likely pathogenic variants in 27.8% (42/151) of the SIDS cases and in 40% (18/45) of the SUD cases. None of the SIDS and 7 of the SUD victims had a known medical history of epilepsy or other underlying neurological diseases. Overall, 14 pathogenic or likely pathogenic sequence alterations, that are inherited in an autosomal dominant manner, were identified in 12 genes: ATN1, CACNA1E, COL4A1, DYNC1H1, GCK, KCNT1, NPRL2, OPA1, RAI1, SCN3A, SCN5A, TSC2.

Conclusions: By focusing on the postmortem analysis of epilepsy-related genes, this study has found pathogenic or likely pathogenic variants that might contribute to the pathology of the sudden death event in some of the SIDS and SUD cases. In the area of personalized management of genetic epilepsy, counselling regarding the risk and preventive measures of SUDEP should be addressed accordingly.

Keywords:
epilepsy; genetics; SUD; SIDS; SUDEP

EPNS21-292 Oral or poster
Miscellaneous Topics

Evaluation of the effectiveness of Melatonin and N acetylcysteine in ischemia-reperfusion injury caused by middle cerebral artery occlusion stroke model in adult rats.

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Objective: To evaluate the neuroprotective efficacy of melatonin and N-acetylcysteine (NAC) in experimental ischemia-reperfusion (I/R) injury induced as a result of cerebral artery occlusion (middle cerebral artery - MCA) in adult rats.

Methods: The study was planned to contain five groups [control, ethyl alcohol, melatonin, NAC, and melatonin+NAC]. Eight adult Wistar albino rats weighing 200-250 g were included in each group. In groups 2 (ethyl alcohol), 3 (melatonin), 4, [NAC)], and 5 (melatonin+NAC), reperfusion was established after 1-h cerebral artery occlusion. Thirty minutes before the experimental induction of I/R, these groups received ethyl alcohol, melatonin (15 mg/kg), NAC (50 mg/kg) and melatonin (15 mg/kg)+NAC (50 mg/kg) intraperitoneally, respectively. The experiment was concluded 24 h following I/R injury, and the experimental animals' brain tissues were removed for histopathological examination. Cellular eosinophilic pyknotic degeneration, vascular congestion, vacuolization, necrotic areas (infarct), edema, and apoptotic indices were evaluated at histopathological examination in cerebral cortex tissues. The Mann Whitney U and chi-square tests were applied for statistical analysis.

Results: While the application of melatonin caused no change in vascular congestion scoring, it caused decreases in the other histopathological scores. This decrease was significant for cellular eosinophilic, pyknotic degeneration, vacuolization, and edema scores ($p<0.05$). No statistically significant change was observed in histopathological scores in the group receiving NAC only compared to the ethyl alcohol group. However, significant decreases were observed in all histopathological scores in the group receiving NAC plus melatonin compared to the ethyl alcohol group ($p<0.05$).

Conclusions: The combined application of melatonin and NAC in experimental I/R injury following MCA occlusion further enhances the neuroprotective effects of melatonin.

Keywords:
melatonin, N-acetylcysteine, ischemia, reperfusion, rat

EPNS21-346 Oral or poster
Movement Disorders

Diagnosis and management of Myoclonus Dystonia Syndrome: a Survey of the European Reference Network for Rare Neurological Diseases.

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Objective: To evaluate the diagnostic and treatment strategies in Myoclonus Dystonia syndrome (MDS) used by experts from the European Reference Network for rare neurological diseases (ERN-RND), and to evaluate the diagnosis and management experience in patients with MDS.

Methods: A questionnaire was distributed among neurologists from ERN-RND and a specific-desgined one among patients and families with MDS.

Results: 29 adult and child neurologists (86% movement disorders experts) from 14 countries replied. 69% of patients were diagnosed in childhood. In 50% of cases, it took >3 years from the onset until the evaluation. 76% applied dystonia scales, but few myoclonus scales. Most assessed psychiatric symptoms, but only 25% referred for formal evaluation. Genetic diagnosis was offered in 75% (>50% SGCE). > 3 drug trials was reported in the majority. Botulinum toxin was used by 65% (25-75% efficacy). DBS was offered to severe cases(>50% efficacy).

29 patients, 22 parents/1 carer replied. Participants had a mutations in SGCE. Mean age was 29 years(4-75). 73% had positive family history. Median age of diagnosis was 7 years (0-57). 38/52 patients reported disability. More than half reported neuropsychiatric comorbidity (anxiety,depression OCD). Myoclonus was reported in 88%, predominantly in upper body and dystonia in 65%, as neck dytonia and writer's cramp. 11 patients received botox, with an improvement of pain and movement (54%). 6 patients received DBS with much improvement (90%).

Conclusions: MDS is well known among movement disorders experts. There're delays in referring patients to the specialist. Half of the patients awaited more than 3 years for a genetic confirmation. Experts follow a systematic assessment of the movement disorder. Most participants report myoclonus (rostro-caudal distribution) and focal/segmental dystonia. MDS has an impact on the majority of activities. Most patients suffer from anxiety, depression or OCD. Botulinum toxin and DBS are identified as effective options in selected patients.

Keywords:
Dystonia, Myoclonus, SGCE, Genetics

EPNS21-398
Basic Science

Oral or poster

North Sea- Progressive Myoclonus Epilepsy: towards rational treatment

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Objective: North Sea Progressive Myoclonus Epilepsy (NS-PME) is a rare condition caused by mutations in the GOSR2 gene, which encodes a vesicle docking protein at the Golgi apparatus. It is characterized by ataxia starting around the age of 2 years, followed by myoclonus and seizures, which persist despite combinations of anti-epileptic drugs. Here, we aim to optimize treatment of NS-PME through a large compound screen.

Methods: Previously, we generated a NS-PME Drosophila model with glial knockdown of membrin¸ (GOSR2 ortholog), which displays progressive heat-sensitive seizures. In this model, we tested the Prestwick Compound Library (PCL) with 1280 (mostly FDA-approved) compounds dissolved in DMSO. Flies were selected on eclosion and treated for 7 days on food media with either a PCL compound, sodium barbital as positive control or the solvent (DMSO) only as negative control. On day 8, flies were heat-shocked for 120s in a 40 degrees waterbath. First, we scored for seizure-like behavior at 120s by classifying paralysis (seizure) or walking (no seizure). Second, we analyzed which compounds reduced seizure events based on the presence of both criteria: 1. < 50% of flies seizing 2. >35% seizure suppression compared to DMSO control.

Results: 1) In flies treated with a compound, seizure proportion varied from 25% to 95%. When comparing seizure outcomes of compounds relative to matched DMSO controls, proportion changes varied from 79% increase (worsening) to 62% decrease (improvement).
2) Based on our criteria, we found 50 compounds that reduced seizure events in the NS-PME Drosophila model with the mode-of-action categories: Neurotransmitter, cardiovascular, antibacterial, anti-inflammatory and miscellaneous.

Conclusions: This unbiased drug screen is a first step towards optimizing treatment of NS-PME. We found distinct classes of compounds to improve seizures in the NS-PME Drosophila model. Currently, the obtained hits are validated and we aim to translate these findings into clinical studies for NS-PME.

Keywords:
Progressive; Myoclonus; Ataxia; Epilepsy; Drosophila model; Compound screen

EPNS21-105 Oral or poster
Movement Disorders

The Adapted Scale for Assessment and Rating of Ataxia for Toddlers

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Objective: In children with early onset ataxia (EOA), quantitative ataxia assessment by the Scale for Assessment and Rating of Ataxia (SARA) is influenced by physiological age-effects. To allow interpretation of pediatric SARA-scores, we have previously determined age-related SARA-performances in typically developing children (4-16 years of age). In toddlers, such data are still lacking.

Methods: In 42 typically developing toddlers (2-4 years of age), we explored the 1. feasibility of SARA-total in all SARA domains, 2. potential replacement of age-limiting performances that prohibit SARA-total assessment by compensation-scores, 3. SARA score-reliability, 4. longitudinal mathematical association between SARA-scores and age (from 2-16 years).

Results: In toddlers, the feasibility of SARA-performances increased with age from 0-92% ($p<.000$). After videotaping the SARA at two occasions (partially at home), and after replacement of unfeasible performances (heel-shin-slide and fast-alternating-hand-movements) that prohibited SARA-total assessment, the SARA became fully assessable at all ages. The SARA score-reliability was ICC.737, interpretable as substantial. Between 2-16 years, SARA-scores were mathematically associated with an exponentially decreasing trend line.

Conclusions: By providing compensatory scores for physiologically infeasible SARA-tasks, the SARA becomes fully assessable in toddlers. The age-adapted toddler's SARA-scale may enable longitudinal coordination assessment by the SARA from 2-16 years of age.

Keywords:
Scale for Assessment and Rating of Ataxia (SARA); child; feasibility; development; coordination; age; toddler; ataxia

EPNS21-108 Oral or poster
Movement Disorders

Pallidocortical and thalamocortical structural connectivity differs between children with genetic and acquired dystonia undergoing Deep Brain Stimulation.

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Objective: Deep Brain Stimulation (DBS) is an established therapy for the management of childhood dystonia. Differences in outcome occur following surgery, particularly influenced by dystonia aetiology. We aimed to explore whether differences in structural connectivity of the motor network accessed following electrode implantation could account for this differential response.

Methods: 22 children and young people (CAYP) undergoing DBS were prospectively recruited (6 genetic/idiopathic dystonia, 16 acquired). Pre-operative diffusion weighted images were acquired for all cases. Post-operative CT images were fused to preoperative structural MRI sequences, implanted electrodes automatically detected, and volumes of tissue activation (VTAs) derived from individual patient programming using the Lead-DBS suite. Whole brain anatomically constrained tractography was performed, supplemented by tractography seeded from VTAs. Fibre Bundle Capacity (FBC), a measures of structural connectivity, was calculated using spherical -deconvolution informed filtering of tractograms between VTAs and the putamen, thalamus, and pre- and post-central cortex. Additional measurements were obtained between the end points of VTA tracts to the thalamus and putamen and the pre- and post-central cortex.

Results: Significantly greater reduction in dystonia was observed in the Genetic/idiopathic group (Mann-Whitney U-test $P<0.05$). FBC between VTAs and the putamen and cortical regions did not differ between the groups. FBC between the putaminal and thalamic endpoints and cortical regions was lower in the acquired dystonia group (Mann-Whitney U-test, $P<0.05$).

Conclusions: Differences in pallido-cortical and thalamo-cortical structural connectivity were seen comparing genetic/idiopathic and acquired dystonia. Difference in response to DBS between these groups may be due to reduced structural connectivity in the motor network accessed by DBS, limiting propagation of the effect of stimulation beyond the local target volume to cortical regions.

Keywords:
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EPNS21-390 Oral or poster
Movement Disorders

Probabilistic Targeting for Paediatric Deep Brain Stimulation: "Hot Spot" or "Pot Shot"?

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Objective: Accurate electrode placement is a determinant of outcome following Deep Brain Stimulation (DBS) surgery, though the optimal target volume for stimulation remains debated. In adult patients, the Probabilistic Stimulation Mapping (PSM) approach has identified putative "hot spots" for stimulation. We aimed to apply PSM to a cohort of Children and young people (CAYP) following DBS surgery to see is a similar "hot spot" could be identified.

Methods: Pre-operative MRI and post-operative CT images were co-registered for 31 CAYP undergoing bilateral pallidal DBS with a diagnosis of genetic (DYT-TOR1A, DYT-SGCE, DYT-THAP and DYT-KMT2B) or idiopathic dystonia. DBS electrodes (n=62) were automatically detected, and Volumes of Tissue Activation (VTA) derived from individual patient stimulation settings within the Lead-DBS suite. VTAs were normalised to the MNI105 space and flipped to a single hemisphere. Normalised VTAs were weighted by percentage improvement in Burke-Fahn-Marsden Dystonia Rating scale (BFMDRS) one year post surgery. The mean improvement was calculated for each voxel, thresholding the resultant Probabilistic Stimulation Map to include voxels encompassed by 5 or more VTAs.

Results: Improvement in BMFDRS was seen with stimulation in voxels across a broad volume of the GPi. A spatial clustering of the upper 25th percentile of voxels in the Probabilistic Stimulation Map revealed a more delineated volume within the posterior ventrolateral GPi. The MNI coordinates of the centroid of this volume (X=23.0, Y=-9.7 and Z=-3.8) were posterior and superior to the typical target for electrode placement.

Conclusions: PSM in CAYP with genetic/idiopathic dystonia suggests the presence of a definable "hot spot" for electrode placement within the GPi. Further work is required to validate this hot spot, across different cohorts of patients, and particularly those with differing dystonia aetiology. Surgical targeting of a validated "hot spot" could potentially reduce variability in outcome following surgery.

Keywords:
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EPNS21-661 Oral or poster
Metabolic Disorders

Childhood Parkinsonism in Rare Genetic and Neurometabolic Diseases.

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Objective: Describe a series of pediatric patients from our center with extremely rare forms of Pediatric Parkinsonism(PP).

Methods: Retrospective review of 35 patients diagnosed with PP.Analysis of the clinical characteristics,measurement of neurotransmitters(NT)in CSF,neuroimaging,genetic etiology and response to L-Dopa were performed.

Results: 13 girls(37%)and 22 boys(62%)with a mean age of onset of symptoms of 1.8 years.The predominant clinical characteristics were:hypotonia(80%),bradykinesia(80%),rigidity(68%), hypomimia(71%),oculomotor abnormalities(63%).Depending on the age of presentation,the predominant symptoms were different:0-2 y.o with acute onset(diffuse hypotonia,hypokinesia,oculogyric crisis,generalized rigidity);2-10 y.o.with subacute onset:gait instability,hypomimia,hypokinesia,distal rigidity and dystonia;>10 y.o:conduct disorder;bradykinesia,rigidity, dystonia.30 patients(86%)had abnormalities in the NT profile:13(43%)with low 5-HIAA and HVA levels;7(23%)with low HVA and 4(13%)with decreased GABA.Our study revealed genotype-phenotype correlations in the following genes:mitochondrial diseases in 8 patients(22%):WARS2,NDUFAF6,GMF1,DNM1L(2),POLG, PTCD3,CHCHD6;Glutamatergic signaling deficit (GRIN1);Nucleotide metabolism defects:2(TREX1;RNASEH2B);Cell Traffic Defects(KIF1A);Channelopathies:4(CACNA1A;SCN3A;KCNT1;KCNQ3); miscellany of functions(TMEM240;AUTS2;FOXG1);10 patients had a favorable response to L-Dopa;5 nonresponders despite low HVA levels.The neuroimaging alteration had 24 patients (68%) with an unfavorable clinical progression.

Conclusions: Mitochondrial diseases were the most frequent in our series.It should also be noted the finding of a heterogeneous repertoire of genes with diverse neurobiological functions(neuronal signaling, channels and others).Many of them mimic,especially in early presentations,the primary deficits in neurotransmitter synthesis at the clinical and biochemical level(neurotransmitter depletion),which is why they must be considered in the differential diagnosis.

Keywords:
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EPNS21-93 Oral or poster
Movement Disorders

Comprehensive insights expanding the phenotypic spectrum of inherited disorders of biogenic amines

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Objective: Inherited disorders of neurotransmitter metabolism are rare neurodevelopmental diseases presenting with movement disorders and global developmental delay. They are caused by impaired biosynthesis, breakdown or transport of neurotransmitters, or of their essential cofactors, such as tetrahydrobiopterin.

Methods: Longitudinal data from 275 patients (224 new and 51 previously published cases) from 248 families with primary disorders of biogenic amine metabolism from the registry of the International Working Group on Neurotransmitter related Disorders (iNTD) were analyzed in a standardized deep phenotyping approach focusing on clinical and biochemical presentation at disease onset as well as the influence of diagnostic methods.

Results: An increased rate of prematurity was observed in aromatic L-amino acid decarboxylase deficiency (AADCD). Tyrosine hydroxylase (TH) and 6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiencies presented with high risk for being small for gestational age while patients with PTPS deficiency were also prone to symmetrical intrauterine growth restriction and congenital microcephaly. Age at diagnosis and the diagnostic delay are influenced by diagnostic methods, by presence of hyperphenylalaninemia and by disease-specific symptoms. Latency to diagnosis has decreased in recent years, possibly due to novel diagnostic approaches or raised awareness. Although each disorder has a specific biochemical pattern, we observed confounding exceptions to the rule.

Conclusions: The study provides comprehensive insights into pre-, peri- and postnatal presentations of inherited disorders of biogenic amines, as well as specific clinical and biochemical patterns in association with diagnostic processes. Our results highlight the importance of careful and systematic clinical evaluation and the value of standardized assessment in longitudinal registries to recognize the potential early signs in evolving phenotypic spectrum and to improve diagnostic approaches.

Keywords:
neurotransmitter, movement disorders, biogenic amines

EPNS21-117 Oral or poster
Neurodevelopmental

Parenting stress and adaptive behaviour in infants with early-onset epilepsies: A prospective population-based national cohort.

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Objective: To describe the levels of parenting stress (PS) and adaptive behaviour (AB) of infants with newly diagnosed seizures and explore relationships with clinical and demographic factors in identifying increased risk of developmental vulnerability.

Methods: 125/301 parent/carers of children who participated in a national prospective population-based study of genetic aetiologies in early-onset epilepsy. Index children were aged < 3 years presenting with: 1) new diagnosis of epilepsy, 2) >2 febrile seizures within a 24-hour period, 3) recurrent febrile seizures lasting >10 minutes, or 4) de novo febrile or afebrile status epilepticus. Parents completed the ABAS-2 and Parenting Stress Index-4 at baseline and 1-year follow-up. Clinical and demographic information was collated from a clinic proforma and parent/carer questionnaire.

Results: 22% of infants (n=120) had significant impairments (>2 sd) in AB at baseline (mean age 21 months), rising to 41% (n=68) at follow-up (mean age 41 months). Low levels of PS were found at baseline (n=125) and follow-up (n=68). AB was a significant predictor of PS at follow-up (p<.001) explaining 24% of the variance in total stress. Clinician rated global developmental delay (GDD) had a weak correlation with AB at baseline (r = -.361; P<0.001) but a strong correlation at follow up (r = -.607; P< 0.001). There was a significant relationship between identified aetiology (87% genetic) and drug resistant seizures (p=<.001), and with GDD (p<.001). 53% of participants resided in the lowest two quintiles of socioeconomic deprivation, and 67% received a diagnosis of epilepsy during the study.

Conclusions: Developmental vulnerabilities are common in infants with early onset seizures. Clinicians should consider using validated measures to assess development at presentation and involve multi-disciplinary colleagues when increased risk is observed. Whilst we found low-levels of PS, support is indicated for parents of infants with developmental vulnerability.

Keywords:
parenting stress, adaptive behaviour, early-onset seizures, developmental vulnerability

EPNS21-123 Oral or poster
Neurodevelopmental

Home treatment in children with neurodevelopmental disorders

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Objective: Children with neurodevelopmental disorders like trisomy 21, autism spectrum disorder or other genetic syndromes often show challenging behavioural problems, which can lead to significant parental stress and may affect the quality of life of all family members. Therefore we developed a home treatment programme that offers behavioural therapy with individualised parent training, aiming to achieve a reduction in problematic child behaviour, parental stress and enhanced positive parent-child-interaction.

Methods: To assess the effectiveness of home treatment a randomised controlled study with a wait-list control group was performed. 65 consenting families were randomised to eight weeks of home treatment consisting of targeted behavioural interventions, video analysis and psychoeducation or to treatment as usual (TAU). Primary outcome was a change in the total score of the developmental behaviour checklist (DBC, German version). Parental stress was evaluated using the German version of the parenting stress index (PSI) as a secondary outcome. The scores in DBC, PSI and PSI subscales in both groups were compared using a two-way ANOVA.

Results: There was a significant interaction between group membership and survey point in DBC total score (F(1)=24,786, p=.000), and PSI total score (F(1)=9,962, p=.003). After the intervention there was a significant decrease in DBC total score compared to the group receiving TAU (-14,73 ±11,724 vs. +0,95 ±8,172; p=.000). Similar effects were shown for PSI total score (-15,50 ±22,821 vs. +1,92 ±15,623; p=.003), parent scale (-9,28 ±16,107 vs. +1,00 ±9,956; p=.009) and child scale (-5,64 ±8,795 vs. +1,12 ±7,688; p=.005). In preliminary analysis stable therapeutic effects were discernible at three months follow up.

Conclusions: Home treatment is an effective treatment for children with neurodevelopmental disorders and behavioural problems and should be considered as treatment option. Further studies are needed to compare these results to the outcome after inpatient treatment.

Keywords:
neurodevelopmental disorder, home treatment, trisomy 21, autism, behavioral problems, interaction problems, behavioral therapy, home based intervention

EPNS21-281 Oral or poster
Neurodevelopmental

AXO-AAV-GM1 Gene Therapy for the Treatment of GM1 Gangliosidosis: Interim Results from a Phase 1/2 Trial

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Objective: To present interim results of AXO-AAV-GM1 for the treatment of GM1 gangliosidosis.

Methods: Ongoing, prospective, open-label, single-arm, dose-ranging Ph1/2 trial (NCT03952637). Following immune modulation, subjects were treated with intravenous AXO-AAV-GM1 low-dose (LD; $1.5x10^{13}$ vg/kg) or high-dose (HD; $4.5x10^{13}$ vg/kg).

The primary endpoint is safety/tolerability. Biomarkers (β-gal enzyme activity in serum and GM1 ganglioside in CSF) were assessed, and brain MRI was performed at Month 12. Clinical progression was measured by Vineland-3, Mobility Scores, Clinical Global Impression, and neurological exam.

Results: Presented are 12-month data for 5 LD subjects (n=4 late-infantile-onset; n=1 juvenile-onset), and 6-month data for 2 HD subjects (n=2 juvenile-onset). AXO-AAV-GM1 was generally safe and well-tolerated, with no treatment-related serious adverse events. 5 subjects had AST elevations (≤2.5X pre-treatment levels) and 1 had ALT elevation (≤2.3X upper limit of normal). None required clinical intervention or had clinical sequelae.

In HD subjects, CSF GM1 ganglioside was reduced to published normal levels, and serum β-gal enzyme activity increased above the lower limit of normal at 6 months. In LD subjects, CSF GM1 ganglioside remained below baseline in all subjects, and serum β -gal activity was above baseline levels in 2 of 5 subjects at 12 months. Volumetric MRI data showed maintenance of brain volume in 4 of 5 LD subjects at 12 months. There was no clinical evidence of disease progression in 4 of 5 LD subjects at 12 months, nor in the HD subjects at 6 months.

Conclusions: Both doses of AXO-AAV-GM1 were well-tolerated. Biomarker data showed normalized serum enzyme activity in HD subjects, and CNS penetration was demonstrated by reduced CSF GM1 ganglioside in all subjects. Clinical data showed signs of disease stability in most subjects at up to 12 months post-treatment. Further evaluation and enrollment of subjects with early infantile-onset are ongoing.

Keywords:
gene therapy; AAV; GM1; AXO-AAV-GM1; gangliosidosis; NCT03952637; sio; NIH

EPNS21-450
Basic Science

Oral or poster

Recombinant human growth hormone (rhGH) and erythropoietin (rhEPO) mediate neuroprotective effects by vasoproliferative and BBB stabilizing actions in hypoxic injury of the developing mouse brain

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Objective: Experimental in-vivo data confirmed anti-apoptotic, -excitotoxic, and anti-inflammatory rhEPO effects in neonatal rodent models of HI brain injury. Our recent studies demonstrated complementary neuroprotective actions of rhEPO and rhGH in a neonatal murine model of hypoxic brain injury. Here, we hypothesized that exogenous rhGH and rhEPO mediate stabilization of blood-brain-barrier (BBB) and regenerative vascular effects in hypoxic injury of the developing brain.

Methods: Using an established model of neonatal hypoxia (8% O2, 6 h), P7 mice were treated i.p. with rhGH (4,000 µg/kg) or rhEPO (5000 IU/kg) 0/12/24 h after hypoxic exposure. After a regeneration period (48h, 7 d), cerebral expression of vasoactive factors (qRT-PCR, ELISA), vessel structures (PECAM-1 IHC) and BBB integrity (occludin IHC) were analyzed.

Results: While hypoxia significantly reduced the numbers of occudin(+) cells in cortical vasculo-endothelial, occludin protein signal intensity significantly increased in response to rhGH (cortex, $p<0.05$) as well as rhEPO (cortex&hippocampus, $p<0.05$). Hypoxia did not significantly change mRNA levels of VEGF, VEGFR, and angiopoietins (ANGPT1/2) in comparison to controls. However, we found higher levels of VEGF-A in response to rhGH ($p<0.01$), while mRNA levels of VEGFR and the ANGPT/TIE2 system remained unchanged. RhEPO treatment resulted in an increase of VEGF-A ($p<0.05$) and ANGPT-2 mRNA ($p<0.05$), associated with decreased TIE-2 levels ($p<0.05$, vs. controls). There were no significant changes in vessel branching or length in both treatment groups compared to controls.

Conclusions: Present data indicate 1) protective effects on hypoxia-induced BBB disruption, and 2) regenerative vascular effects of rhGH and rhEPO during the subacute post-hypoxic period in the developing mouse brain.

Keywords:
Hypoxia, neonatal brain, vasculogenesis, BBB, EPO, GH, neuroprotection

EPNS21-478 Oral or poster
Neurodevelopmental

Gene Therapy With Eladocagene Exuparvovec Improves Cognition and Language in Patients With Aromatic L-Amino Acid Decarboxylase Deficiency

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Objective: Aromatic L-amino acid decarboxylase (AADC) deficiency is caused by mutations in the dopa decarboxylase gene leading to reduced AADC enzyme activity. Patients with AADC deficiency may experience delayed cognitive and speech development. Eladocagene exuparvovec is a recombinant adeno-associated viral vector serotype 2 carrying the coding sequence for the human AADC gene.

Methods: Eladocagene exuparvovec was administered via bilateral infusions to the putamen of 28 children with AADC deficiency in 3 clinical trials (AADC-CU/1601 [8 patients, completed], AADC-010 [10 patients, completed], and AADC-011 [10 patients at 26 February 2020 cutoff date, ongoing]). Patients received 1.8 × 1011 vg (n=21) or 2.4 × 1011 vg (n=7; AADC-011)]. Cognition and language changes were assessed using Comprehensive Developmental Inventory for Infants and Toddlers (CDIIT; N=8) and Bayley Scales of Infant Development, 3rd edition (Bayley-III; N=20). Both tools measure pediatric development and include cognitive and language subscales.

Results: CDIIT showed improvements in cognitive and language skills as early as 6 months, which were maintained up to 60 months. Bayley-III showed gradual, sustained improvement up to 60 months. Mean change from baseline, total language score was 46.5% after 12 months (n=17), 62.7% after 24 months (n=15), 80.5% after 36 months(n=10), 108.3% after 48 months (n=8), and 110.7% after 60 months (n=4). Significant improvements in subscale scores were observed 24 months post-treatment.

Conclusions: Results demonstrate the efficacy of eladocagene exuparvovec in improving cognition and communication in patients with AADC deficiency, indicating that gene therapy may successfully target neurotransmitters affected by AADC deficiency and may improve quality of life.

Keywords:
AADC deficiency; gene therapy; rare disease

EPNS21-128 Oral or poster
Epidemiology & Follow-Up

Long-term outcomes after cerebral thrombosis in children and adolescents - a nationwide study

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Objective: Cerebral thromboses, defined as arterial ischemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT), in childhood are rare but severe diseases.
Short time neurological sequelae were previously reported in 67% of the children with AIS.
The aim of our study was to examine mortality and long-term neurological and psychiatric sequelae in a nationwide cohort of children and adolescents with AIS and CSVT.

Methods: Patients 0-18 years of age diagnosed with a first AIS or CSVT between 1994-2006 were identified in the National Patient Registry. The diagnosis of AIS or CSVT was previously validated by record review. Retrospective long-term register-based follow-up were performed until December 2017. Cases were age and sex matched 1:10 with individuals from the general population. Follow-up information data was obtained from the National Patient Registry and the Civil Registration System.

Results: Mean length of follow-up in patients with previous cerebral thrombosis (n= 251) was 15.7 years (SD 5.4) versus, 16.9 years (SD 3.6) in the general population (n=2510).
The cumulative all-cause mortality was 9.2%; CI (5.6%-12.8%) in individuals with previous cerebral thrombosis versus 0.4%; CI (0.2%-0.6%) in the general population.

The cumulative risk of neurological and psychiatric diagnoses was increased in patients with previous cerebral thrombosis when compared with the matched general population. During follow-up period relative risk (RR) for respectively epilepsy was 14.36 times higher, with a 95% CI [10.44;19.76], psychiatric disorders 3.33 with 95% CI [1.65;6.74] and vision problems 15.50 with 95% CI [8.97;26.79] in patients with cerebral thrombosis versus the general population.

Conclusions: In our nationwide population we found a higher long-term mortality and risk of neurological and psychiatric diagnoses in children and adolescents with a history of AIS or CSVT when compared with the general population.

Keywords:
Children, adolescents, long-term follow-up, Arterial Ischemic Stroke, AIS, Cerebral Venous Thrombosis, CSVT, sequelae, mortality, nationwide, national cohort study

EPNS21-193
Movement Disorders

Oral or poster

Pathways in Early Onset Ataxia with comorbid myoclonus and epilepsy: evidence for common pathophysiology

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Objective: Early onset ataxia (EOA) concerns a heterogeneous disease group, often presenting with comorbid features such as dystonia, myoclonus or epilepsy. Genetic heterogeneity and phenotypic pleiotropy complicate the diagnostic process. The pathomechanisms underlying comorbid EOA phenotypes remain largely unknown. In EOA with dystonia, we described cerebello-basal ganglia-thalamo-cortical network involvement, with affected biological pathways involving neural signalling and neurodevelopment. This study aims to investigate key pathological mechanisms in EOA with myoclonus and epilepsy.

Methods: For 154 EOA genes from up-to-date gene panels, we investigated (1) associated phenotypes (2) reported anatomical neuroimaging abnormalities, and (3) functionally enriched biological pathways through in silico analysis. We assessed validity by outcome comparison with a recently described EOA cohort (80 patients, 31 genes).

Results: EOA associated gene mutations cause a spectrum of disorders including myoclonic and epileptic phenotypes. Cerebellar imaging abnormalities were seen in 86% of EOA genes independent of phenotypic comorbidity. Comorbid myoclonus/epilepsy was significantly associated with thalamocortical damage. EOA, myoclonus and epilepsy genes were enriched for neurotransmission and neurodevelopment pathways, both in the clinical and in silico genes. Gene subgroups with comorbid myoclonus/epilepsy revealed specific enrichment for lysosomal, lipid and synaptic processes.

Conclusions: The studied EOA phenotypes revealed changes in the cerebellum, thalamus and cortex, which suggests network involvement analogous to findings in EOA-dystonia. Damage at different network locations or interconnections might explain the phenotypic variety. The EOA phenotypes exhibit a shared biomolecular pathogenesis, with some phenotype-dependent pathways. These insights into the pathophysiology of EOA support whole exome sequencing over conventional single gene panel testing, and may have implications for new treatment strategies.

Keywords:
early onset ataxia, myoclonus, epilepsy, child, neurodevelopment, network, clinical genetics, phenotype, bioinformatics.

EPNS21-263 Oral or poster
Epidemiology & Follow-Up

Clinical Phenotyping, MRI and EEG Characteristics in Convulsive Status Epilepticus - a 2 Year Follow up of a Scottish Population Data-linkage Study

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Objective: Convulsive status epilepticus (CSE) is a common medical emergency. We have previously reported on a large prevalence cohort study (Mitchell et al., 2021). We followed this cohort for two years studying the detailed phenotype (clinical characteristics and antiepileptic drug prescriptions) as well as investigation data including EEG and MRI.

Methods: This study draws on a cohort of children who presented with CSE to a children's hospital in Scotland between January 2011 and December 2017.

We linked our CSE cohort using individual identifiers (CHI numbers) to electronic records of emergency care, outpatient neurology care and the EEG and MRI databases to obtain clinical phenotype details, anti-epileptic drug prescriptions, EEG and MRI features.

Results: There were 665 children with 1,234 presentations with CSE. 57.30% were male and the median age was 3.65 years (IQR 6.33). 60.45% of admissions were diagnosed with epilepsy, 24.40% were before the status epilepticus event and 75.60% after. EEG was carried out in 55.67% of admissions (30.28% normal, 40.47% abnormal and specific to epilepsy diagnosis, 29.26% abnormal but non-specific). MRI was carried out in 61.35% of admissions (49.80% normal, 41.08% abnormal and associated with epilepsy, 7.40% abnormal and possibly related to epilepsy, 1.72% unrelated abnormal). Maintenance anti-epileptic drugs were prescribed in 35% of patients. Of those 43.35% require polytherapy; the commonest antiepileptic drug was levetiracetam.

Conclusions: We describe a clinical phenotype for our large cohort of CSE using data-linkage. Sixty percent of the status epilepticus admissions were amongst children who either already have epilepsy or go on to have a diagnosis of epilepsy. In those investigated further, EEG and MRI
abnormalities were specific to epilepsy. Children who have generalised epilepsy and status epilepticus are more likely to be on polytherapy. Overall, these are valuable prognostic factors for emergency and long-term care plans of convulsive status epilepticus.

Keywords:
Status Epilepticus

EPNS21-472 Oral or poster
Epilepsy: Medical & Surgical Treatment

Delineating the epilepsy phenotype of the 16p11.2 microdeletion

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Objective: 16p11.2 microdeletions are associated with a range of neurodevelopmental disorders and are a common reason for referral to clinical genetics. This microdeletion includes PRRT2, a negative modulator of sodium channels. Loss of function variants in PRRT2 result in carbamazepine-responsive self-limited infantile seizures and PKD. In this retrospective systematic case review we aimed to assess the epilepsy phenotype of 16p11.2 microdeletion syndrome including response to carbamazepine.

Methods: 62 patients had a 16p11.2 microdeletion identified by microarray. A structured case review was undertaken, focusing on epilepsy and developmental features.

Results: In the overall cohort, the microdeletion was de novo in 11 (17.7%) and maternally inherited in 7 (11.3%); in 44 (71%) inheritance was unknown. 14 of 62 patients experienced at least 1 seizure episode. 4 (28.6%) presented with early infantile-onset epilepsy and 2 (14.3%) with catamenial epilepsy. Seizures were self-limiting in 5 (35.7%). Median age of seizure onset was 0.92 years and median age of offset was 1.33 years. EEG was performed in 9 patients, 5 (55.6%) were normal, 3 (33.3%) revealed focal abnormalities, with 1 also displaying migrating ictal activity, and 1 generalised abnormalities with photosensitivity. Anti-epileptic medications (AEMs) were prescribed in 7 (50%). A range of AEMs including lamotrigine, levetiracetam and sodium valproate led to seizure reduction but not seizure freedom. Carbamazepine was prescribed for 3 patients (42.9%) who all became seizure free. 46 (74.2%) patients had developmental delay.

Conclusions: Although numbers are small, response to carbamazepine was excellent. This may reflect its mechanism of action via sodium channel blockade. Carbamazepine should be considered for first line AED treatment in 16p11.2 deletion. The phenotypic delineation in this study is helpful for epilepsy management, developmental surveillance and genetic counselling.

Keywords:
16p11.2, epilepsy, carbamazepine, PRRT2, paediatric

EPNS21-550 Oral or poster
Neurodevelopmental

MITOCHONDRIAL DYSFUNCTION IN RETT SYNDROME: STUDY OF A CLASSIC NEURODEVELOPMENTAL DISEASE FROM THE PRISM OF SYNAPTIC METABOLISM TO FIND NEW TREATMENT OPTIONS.

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Objective: Although Rett syndrome has traditionally been studied as a disorder of neurotransmission and neuronal maturation, in recent years attention is being paid to bioenergetic function in the study. We have focused our research on two questions: the analysis of mitochondrial homeostasis in Rett models and whether it can be modulated for therapeutic purposes.

Methods: We have profiled mitochondrial dysfunction in terms of ATP measurement, reactive oxygen species (flow cytometry), evaluation of the mitochondrial network (immunocytochemistry and confocal microscopy) or expression of different markers. These have been performed both in patients fibroblasts and in mice model of Rett syndrome. In addition, in the latter we have been able to assess the effect of treatment on their behavior and activity, by means of the NORT, Plus Maze and Rotarod tests.

Results: We report defective bioenergetics and altered mitochondrial dynamics and ROS production in patient fibroblasts. Interestingly, when we treated fibroblasts with a PPARg agonist, ATP production capacity increased and ROS generation decreased. We then moved forward to analyze mitochondrial function and its targeting in animal models. We observed a dysfunction already in presymptomatic mice, suggesting that mitochondria plays a role in the development and progression of the phenotype. Treatment of symptomatic mice with the aforementioned agonist resulted in behavioral improvement and amelioration of mitochondrial dysfunction (especially in terms of ATP production and lipid peroxidation).

Conclusions: Our results reaffirm mitochondria as an effective target for the treatment of Rett syndrome and support a clinical trial with the aforementioned PPARg agonist. Furthermore, we highlight mitochondrial dysfunction even before the onset of symptoms, highlighting the importance of therapeutic windows in neurodevelopmental diseases. The study of classical diseases through the prism of synaptic metabolism may result in the definition of new therapeutic opportunities.

Keywords:
Mitochondria, Rett syndrome, Synaptic metabolism, therapy

EPNS21-333 Oral or poster
Epilepsy: Diagnosis and Investigations

The spectrum of gain of function SCN1A disorders: novel phenotypes, disease mechanisms and response to sodium channel blocking therapies

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Objective: Brain SCN1A loss-of-function mutations cause Dravet syndrome and genetic epilepsy with febrile seizures plus (GEFS+). Gain-of-function (GOF) SCN1A variants are associated with familial hemiplegic migraine type 3 (FHM3). Novel SCN1A phenotypes have been described, including early infantile developmental and epileptic encephalopathy (EIDEE) with movement disorder (MD) and more recently neonatal presentations with arthrogryposis. We describe a clinical, genetic and functional evaluation of affected individuals.

Methods: Patients were ascertained via an international network using structured clinical questionnaires and from the literature. We compared sodium channels containing wild-type versus variant NaV1.1 subunits using whole-cell voltage clamp electrophysiological recordings.

Results: 45 patients were included harbouring 33 different variants, 15 of which were biophysically characterised and 18 underwent in-silico functional prediction. The most severely affected infants (n=13) presented with congenital arthrogryposis, epilepsy onset within 3 days of life, tonic seizures and apnoeas, accompanied by MD, profound intellectual disability and significant mortality. Twenty patients presented later, between 2 weeks and 3 months, with early infantile DEE and MD, and one patient presented after 3 months with DEE only. Eleven patients presented with FHM3. Associated SCN1A variants appear to cluster in regions of channel inactivation and biophysical recordings show evidence of GOF properties. Clinically, 15 out of 18 (83%) GOF variants were associated with a response to sodium channel blocker treatment.

Conclusions: SCN1A GOF mutations underlie a disease spectrum ranging from the previously undescribed neonatal DEE with MD and arthrogryposis (NDEEMA) to EIDEE with or without MD and FHM3. Our study expands the spectrum of GOF SCN1A-related phenotypes, recognises key clinical features, provides insights into the underlying disease mechanisms and identifies potentially efficacious therapies.

Keywords:
SCN1A, Epilepsy, Gain-of-function

EPNS21-573 Oral or poster
Epilepsy: Medical & Surgical Treatment

Predictive factors of seizure reduction due to ketogenic diet therapy in childhood epilepsy

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Objective: To identify children with epilepsy showing a seizure reduction to ketogenic diet therapy (KDT) and to find predictors for its effectiveness.

Methods: We analysed data from our single-center prospective longitudinal database on childhood epilepsy treated with KDT. Outcome measures included seizure reduction (in %) and seizure reduction > 50% at 3 months. Predictive factors studied were: age at KDT start, epilepsy duration before KDT, gender, known etiology, epilepsy syndrome, number of seizure types, presence of focal seizures, presence of generalised tonic clonic seizures, serum levels of beta-hydroxybutyrate (BHB) before and after KDT start, and number of antiseizure drugs (ASD) before start. A final regression model included 4 factors.

Results: The final analysis was performed on 183 patients. At 3 months, absolute seizure reduction was median 67%. Relevant correlations coefficients to seizure reduction at 3 months in percent were observed for: number of ASD before start (- 1.63; p = 0.027), BHB at dismissal (after 1 week of KDT) (0.156; p = 0.061), BHB after 3 months (- 0.414; p = 0.000), fat/ non-fat ratio at 3 months (0.195; p = 0.010), and age-appropriate neurological development before start (- 0.210; p = 0.004). Regression analysis revealed that age-appropriate neurological development, higher BHB at 3 months, shorter duration before KDT, lower ratio and lower number of ASD positively predicted outcome (p=0.04). A best model included epilepsy syndrome and higher BHB at dismissal (p=0.006).

Conclusions: We were able to identify age-appropriate development at start, shorter duration of epilepsy, lower number of ASD, epilepsy syndrome and a higher BHB level at dismissal as predictive factors. However, a reliable individual prediction model before starting KDT has to be validated in a larger patient cohort.

Keywords:
ketogenic diet, childhood epilepsy, effectiveness, seizure freedom, prediction model

EPNS21-649 Oral or poster
Epilepsy: Medical & Surgical Treatment

Electric Source Imaging on Ictal Conventional Scalp EEG Delineates Seizure Onset and Predicts Surgical Outcome in Children with Epilepsy

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Objective: Delineation of the seizure onset zone(SOZ) is required in children with drug resistant epilepsy(DRE) undergoing surgery. Intracranial EEG(iEEG) serves as the gold standard for this but presents limitations due to its invasiveness. We examine the clinical utility of virtual implantation based on electrical source imaging(ESI) performed on ictal scalp EEG for mapping the SOZ. We hypothesize that ESI virtual implantation can delineate the SOZ and guide the placement of iEEG electrodes.

Methods: We retrospectively analyzed ictal scalp EEG (19 channels) from 35 children who underwent iEEG monitoring and epilepsy surgery. We dichotomized surgical outcome into seizure-free(SF) and non-seizure-free(NSF). We identified ictal onsets recorded with scalp EEG. Using ESI, we estimated virtual sensors at brain locations that matched the iEEG implantation. We described the seizure onset patterns of virtual EEG and compared them with iEEG. We estimated the agreement between virtual and iEEG SOZ-electrodes and built receiver operating characteristic curves(ROC) to test whether it predicted outcome.

Results: Twenty-one patients(60%) were seizure free after surgery. We identified three seizure onset patterns: low-voltage fast activity:37.1%, rhythmic activity: 34.3%, and burst of spike-and-waves:29.6%. Moderate agreement between virtual and iEEG SOZ patterns was found (kappa=0.45, $p<0.001$). Virtual SOZ agreement with clinically defined SOZ was higher in seizure-free compared to non seizure-free patients (67.5% vs37%,p=0.01). Anatomical concordance of virtual SOZ with iEEG SOZ predicted seizure freedom (AUC=0.73; sensitivity=57.1%; specificity=78.6%; accuracy=65.7%).

Conclusions: Virtual implantation based on ictal recordings with scalp EEG can delineate the SOZ and predict surgical outcome. Non-invasively mapping the SOZ using virtual intracranial EEG sensors may augment epilepsy surgery planning, tailor the intracranial EEG implantation, and predict surgical outcome in children with DRE undergoing epilepsy surgery.

Keywords:
Epilepsy Surgery, Seizure Onset Zone, Electrical Source Imaging, Conventional EEG, Virtual Implantation

EPNS21-679 Oral or poster
Epilepsy: Medical & Surgical Treatment

Comparison of two real-life cohorts of infantile spasm syndrome receiving sequential versus combined vigabatrin and oral steroid

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Objective: Treatments of infantile spasm syndrome (ISS) have been extensively studied. But there is no international consensus on the best option. O'Callaghan reported in 2017 that the combination of oral steroids and vigabatrin gave a better response that oral steroids aline whatever the etiology

Methods: We compared two cohorts of patients with ISS: a first multicenter, retrospective cohort of 40 children treated mostly in the first line with vigabatrin and then steroids (2015-2016) and a second prospective monocenter cohort of 50 children treated with a combination vigabatrin and prednisolone (since 2017).

Results: Our two cohorts were comparable in terms of patient characteristics at diagnosis. In the retrospective cohort, 11 patients were spasm free after the first line of treatment (27.5%), 11 additional after the second line (38%) i.e. 55% of patients were spasm free after the first and second lines of treatment (i.e. in about 2 to 4 weeks after the diagnosis of infantile spasms). In the prospective cohort, 34 patients (68%) were free of spasms after the first line of treatment (vigabatrin and prednisolone) at the latest at D14 of diagnosis. In this prospective cohort, 70% of patients were still spasm free by June 2021

Conclusions: Combination of vigabatrin and oral steroids seems to result in an earlier spasm-freedom than sequential treatment. Several studies have established that a delay in treatment increases the risk of cognitive impairment and non-response to antiseizure medicationS. While it is not yet clear that combined treatment changes the overall cognitive impact of ISS, the impact at the individual level may be beneficial as recently suggested in the long-term study by O'Callaghan

Keywords:
Infantile spasm syndrome; steroids; West syndrome

EPNS21-712 Oral or poster
Epilepsy: Medical & Surgical Treatment

Determinants of seizure outcome after epilepsy surgery in patients with presumed nonlesional epilepsy: a European multicenter cohort study

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Objective: We aimed to assess determinants of postoperative seizure outcome in MRI-negative focal epilepsy patients in whom no histopathological diagnosis could be established.

Methods: Observational multicenter cohort study of pathology-negative patients who were derived from the European Epilepsy Brain Bank and underwent epilepsy surgery between 2000-2012 in 34 epilepsy surgery centers within Europe. We collected data on clinical and (pre-) surgical characteristics, post-operative outcome and treatment regimen in all patients.

Results: We included 571 patients in whom no histopathological lesion was microscopically identified. Of those, 217 patients (38.0%) were confirmed as 'truly' non-lesional following systematic review of MRI results. In 354 patients (62.0%), a likely epileptogenic pathology was visible on MRI but a representative brain tissue specimen for microscopic inspection not made available. One hundred three of 217 non-lesional patients (47.4%) were seizure free (Engel I) 1 year after surgery. Temporal lobe surgery significantly more often led to seizure-freedom (58.1%) compared surgery in the extratemporal regions (23.1%), with lowest seizure-freedom rates in parietal lobe resections (12.5%). Mean epilepsy duration was significantly shorter in seizure-free patients (15.87 yr ± 9.93) compared to those with recurrent seizures postsurgically (18.32 yr ± 10.70).

Conclusions: In almost half of truly non-lesional patients, seizure-freedom was achieved after surgery. Outcome was less often favorable in extratemporal epilepsy, longer duration of disease, and nonconcordant invasive monitoring findings. This cohort of patients with a electroclinical identified focus will be a promising group for advanced molecular-genetic analysis of brain tissue specimens in order to identify new brain somatic epilepsy genes or epilepsy-associated molecular pathways.

Keywords:
epilepsy surgery, non-lesional, outcome

EPNS21-2008 Oral or poster
Neurodevelopmental

Donepezil as precision therapy in KCNQ2/KCNQ3 gain-of-function encephalopathy

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Objective: The KCNQ2/KCNQ3 genes encode for the voltage-gated-K-channel underlying the neuronal M-current. Loss-of-function variants cause neonatal epilepsy, treatable with M-current openers. Gain-of-function (GOF) variants present with later onset epilepsy and developmental disability, and could be amenable to M-current blockers, but such therapies are not available. We researched if the cholinergic drug Donepezil suppress M-currents and improve symptoms.

Methods: 1/In vitro study: The effect of 1 µM donepezil on the amplitude of the M-current was measured in excitatory and inhibitory neurons of primary cultured hippocampal cells [14-16 d in-vitro]. To identify GABAergic neurons, we infected hippocampal cultures with a recombinant virus derived from an AAV-viral vector driving the expression of the fluorescent protein mCherry under the control of the specific GABAergic hDlx promoter. The M-current was measured by the standard deactivation protocol (holding at 0 mV and deactivation at -60 mV) in the whole-cell configuration of the patch-clamp technique. The M-current was determined by the amplitude of the tail. 2/Exploratory study: Three patients bearing GOF variants- KCNQ2(p. Arg144Gly), KCNQ3(p.Arg227Gln, p.Arg230Cys) will be administered donepezil 5mg/d for 6 months. Outcome measures will be seizure frequency, epileptiform activity on sleep-EEG and neuropsychological tests (ABAS-II, CDI, CARS-2).

Results: 1/ Application of 1 µM donepezil produced within 3-5 min a significant inhibition of 67% of the M-current amplitude of excitatory neurons (2.4±0.46 vs.0.89±0.15pA/pF, $p<0.01$). In inhibitory neurons, application of 1 µM donepezil produced a lesser inhibition of 59% of the M-current amplitude (1.39±0.43 vs. 0.57±0.21, $p=0.053$), which did not reach statistical significance. 2/ We expect donepezil to improve cognitive outcome measures by 20% and reduce seizure frequency by 50%.

Conclusions: The repurposed drug Donepezil would serve as precision treatment for GOF variant KCNQ2/KCNQ3 encephalopathy.

Keywords:
targeted therapy; precision medicine; KCNQ2 encephalopathy; KCNQ3 encephalopathy; gain of function

EPNS21-2020 Oral or poster
Miscellaneous Topics

Predictors of Complicated Disease Course and Outcomes in Pediatric Patients with Idiopathic Intracranial Hypertension

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Objective: To identify predictors for complicated disease course, clinical and visual outcomes in pediatric patients with IIH.

Methods: Clinical, ophthalmological, and imaging data of patients diagnosed with IIH between 2003-2021 were retrospectively collected. The diagnosis of IIH was retrospectively confirmed using the revised criteria for IIH. Visual outcome was defined as poor if optic atrophy (OA)or optic neuropathy (ON) were found at the last follow-up. The need for more than one drug, treatment dependence or disease relapse, or surgical intervention were considered as a complicated disease course. An unfavorable clinical outcome was defined when there was documentation of chronic headache at the last follow-up.

Results: Out of 97 patients (mean age 11.1±4.16 years), 16 subjects (18%) had poor visual outcome. Twenty-eight patients (29%) had an unfavorable clinical outcome. Forty-two patients (43%) had a complicated disease course. Female gender (P=.02), visual field defect (VFD) at presentation (P=.02), retinal nerve fiber layer (RNFL) thickness >130m after treatment initiation (P=.03), overweight/obesity (p=.05), higher opening pressure (p=.01), evidence of polycystic ovary syndrome (p=.02), and higher triglyceride levels (p=.03) were associated with a complicated disease course. Risk factors for poor visual outcome were female gender (P<.001), VFD at presentation (P< .001), RNFL thickness >130 m (P=.05), overweight/obesity (P=.05), disease relapse (P<.001) and ON or OA at presentation (P=.04). Patients with unfavorable clinical outcome tended to have lower opening pressure (p<.001), lower rates of papilledema (p=.03) and lower rates of radiographic biomarkers suggestive of increased intracranial pressure (p=.01).

Conclusions: We identify predictive factors for a complicated disease trajectory and poor clinical and visual outcomes in pediatric patients with IIH. Identifying patients at risk is essential for an optimal medical care that may improve long-term outcomes.

Keywords:
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EPNS21-2046 Oral or poster
Movement Disorders

Early intervention with deep brain stimulation (DBS) for children with epsilon-sarcoglycan myoclonus dystonia (SGCE-MD)

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Objective: SGCE-MD is considered a benign condition in children, and patients usually receive DBS in adulthood after many years of disease duration.
We aim to evaluate the efficacy and safety of Globus Pallidus Internus DBS (GPi-DBS) in early stages of disease course.

Methods: 8 children with drug-resistant SGCE-MD and moderate-to-severe impairment on fine and/or gross motor function were evaluated for DBS. Bilateral directional electrodes were inserted in the GPi using Leksell®Vantage stereotactic guide. Electrodes were connected to Vercise Genus rechargeable generator. Accuracy of stimulating electrode placement was determined by CT/MRI fusion using Brainlab Elements Stereotaxy software. Patients were evaluated prospectively using Burke-Fahn-Marsden (BFM) and Unified Myoclonus (UMRS) rating scales. Task-specific dystonia was assessed using Writer's cramp rating scale (WCRS) and the newly developed Gait dystonia rating scale (GDRS).

Results: DBS was performed at [mean±SD] 13±3 years, after 10±1.5 years of disease onset. The error for electrode placement was X-axis 0.46±0.38, Y-axis 0.73±0.53 and Z-axis 0.32±0.41. After 23[6-60] months of follow-up, stimulation parameters were 2.6[1.9-3.5] milliamps, 60[60-80] millisec, 130[120-200] hertz. We observed an improvement on: UMRS[74%, p=0.018], BFM-motor[78%, p=0.017], WCRS[72%; p=0.027], GDRS[83%; p=0.041]. Oral medication was removed in all cases. Five cases were diagnosed with obsessive-compulsive disorder, generalised anxiety disorder, adaptive-depressive disorder and ADHD on pre-DBS assessment. DBS had a positive impact on psychiatric features. In two patients, atrophic scar and scalp wound infection were satisfactorily treated.

Conclusions: GPi-DBS in children with SGCE-MD was safe and effective. It significantly improved fine and gross motor skills, such as handwriting and gait, preventing motor sequela. Longitudinal studies are necessary to demonstrate if early intervention also improves long-term prognosis.

Keywords:
myoclonus dystonia ; SGCE ; DBS; MD

EPNS21-2053 Oral or poster
Movement Disorders

CACNA1A Variant- Related Pediatric Epilepsy. An International Multicenter Retrospective Study

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Objective: CACNA1A related disorders are channelopathies and present with 2 main phenotypes:persistent movement abnormality(usually cerebellar ataxia)and paroxysmal epileptic and non-epileptic events.

Methods: The study is retrospective and multicenter.Clinical,electro-radiological and genetic data of 30 patients with childhood onset epilepsy and CACNA1A variants were analyzed.

Results: Age of seizure onset ranged from 4 months to 7 years,with 47% before age 2. 66% of patients had de novo variants. Pathogenic variants were found in 29%,Likely pathogenic in 22%,VUS in 32%.
63% displayed GDD before seizure onset. 33% had first a febrile seizure.GTCS was most common (30%).Effective medications were valporal,levetiracetam, benzodiazepines.56% developed prolonged episodes of unconsciousness:5 patients -status epilepticus,12 patients- coma,4 patients both.70% developed paroxysmal non-epileptic events,most commonly Episodic Ataxia and Migraine.Cerebellar features were frequent.Seizure control was achieved in 63% of patients.Intellectual difficulties found in 73%,autism in 33%. 4% patients were non-ambulant.Brain MRI findings in 28 patients were cerebellar (42%) and cerebral (7%) atrophy.Progressive course observed 46%,non-progressive- 23%; 30% of patients showed improvement.
We did not find correlations between disease severity,age of seizure onset,type of inheritance,and frequency of prolonged loss of consciousness.
Comparing patients with epilepsy from our current study and patients without epilepsy from our previous study on infantile onset CACNA1A revealed a higher incidence of febrile seizures, autism,coma events in patients with seizures.

Conclusions: CACNA1A-related pediatric epilepsy is a developmental and epileptic encephalopathy.Patients develop cognitive difficulties regardless of seizure control.Seizure in patients with CACNA1A variants is a risk factor for autism.Febrile seizures in patients with CACNA1A are a risk factor for epilepsy.

Keywords:
CACNA1A, PEDIATRIC, EPILEPSY

EPNS21-2072 Oral or poster
Metabolic Disorders

Mitochondrial diseases mimicking autoimmune diseases of the CNS

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Objective: To alert treating physicians dealing with neuroimmunological diseases such as autoimmune encephalitis (AE) or acquired demyelinating syndromes (ADS) that neurological symptoms and imaging features can indistinguishable from mitochondrial diseases (MD) in particular at disease onset.

Methods: METHODS: Retrospective analysis of the clinical, laboratory and neuroimaging features of five patients who presented with signs of a neuroimmunological disease but had all pathological mutations in genes related to mitochondrial energy metabolism.

Results: All five patients presented with an acute neurological episode between 4 to 30 years of age fulfilling either the criteria for a probable AE or ADS. In one child cerebrospinal fluid (CSF) studies revealed a mildly elevated cell count, three had elevated CSF lactate, none had oligoclonal bands (OCBs). MRI findings were compatible with neuroimmunological diseases in all patients. All patients improved rapidly with intravenous steroids or immunoglobulins. Four patients had one or more relapses. Three patients showed worsening of their neurological symptoms with subsequent episodes and one patient died. Relapses in conjunction with new and progressive neurological symptoms, led to additional work-up which finally resulted in different genetic diagnosis of MD in all patients (MT-TL1, MT-ND5, APOA1-BP, HPDL, POLG).

Conclusions: We would like to draw attention to this subset of patients with MD mimicking neuroimmunological diseases. Absence of CSF pleocytosis, elevated CSF lactate and progressive, relapsing course should trigger further (genetic) investigations in search of a MD even in patients with good response initially to immunomodulating therapies.

Keywords:
mitochondrial diseases, MRI, CSF, children, autoimmune encephalitis

EPNS21-2082 Oral or poster
Neuromuscular

Infantile onset neuronopathy and peripheral neuropathy, related with SPTLC2 intronic variant.

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Objective: To describe a patient with infantile-onset neuronopathy, severe polyneuropathy and a rapidly progressive course.

Methods: At five months, the patient presented with progressive paralytic hypotonia, loss of motor milestones and signs of denervation, mimicking spinal muscular atrophy (SMA), albeit with negative molecular testing. Clinical deterioration with tracheostomy and mechanical ventilatory support with nasogastric tube feeding occurred at nine months with minimal voluntary movement, mainly at fingertips. In addition, there were signs of dysautonomia with sweating, unexplained tachycardia, and hypertension. Cognitive function, oculomotion and alertness were preserved.

Results: SMN1 gene screening for deletions and point mutations was negative. Array-CGH and Whole Exome Sequencing (WES) revealed no pathogenic mutations relevant to the phenotype. The metabolic screening was suggestive of increased urinary methylmalonic acid. EMG was consistent with severe motor-sensory polyneuropathy. The sural nerve biopsy revealed severe myelin deficiency with demyelinated fibers and preserved axons.
The combination of neuronopathy and dysautonomic polyneuropathy raised the suspicion of a complex phenotype of Hereditary Sensory Autonomic Neuropathy (HSAN) with neuronopathy as an early onset Amyotrophic Lateral Sclerosis (ALS). Whole Genome Sequencing (WGS) analysis revealed an intronic SPTLC2 gene mutation causing a sphingolipid/ceramide metabolism defect due to Serine Palmitoyl Transferase enzyme deficiency. In order to prove the pathogenicity of the mutation, functional studies were performed showing a marked accumulation of total 1-deoxySA-ceramides and 1-deoxySO-ceramides in the patient's fibroblasts. Ceramide accumulation has also been described in non-q deletion SMA patients with Progressive Myoclonic Epilepsy (SMA-PME) due to ASAH1 mutations.

Conclusions: A new early-onset phenotype of SMA-like and HSAN1 is described, presenting in infancy with severe and progressive course.

Keywords:
SPTLC2, SMA-like, HSAN1, polyneuropathy

EPNS21-119 Oral or poster
Neuro rehabilitation

Lower extremity kinematics during gait in adolescents with multiple sclerosis

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Objective: The purpose of this study was to examine the lower extremity joint angle motion during level walking in adolescents with MS compared to healthy age-gender-matched teenagers.

Methods: The study design was cross-sectional. We evaluated retrospective data collected from the Multiple Sclerosis Center, Sheba Medical Center, Tel Hashomer, Israel's computerized database, from all adolescents with MS who undergone a full gait analysis test from January 2012 through August 2021. Gait testing took place at the Sheba Gait Analysis Laboratory with a 10-camera Vicon system. Reflective markers were strapped on the participant's pelvis and lower limbs to calculate Joint angle motion during gait, specifically of the hip, knee and ankle. Participants performed all tasks barefoot during self-selected walking speed across a 6-meter pathway. In order to determine normality of joint angles during gait in the MS group, we compared our results to reference data from normal teenagers.

Results: The total sample included 27 adolescents with MS (12 girls, 15 boys). Mean disease duration was 20.4 (S.D=24.9) months and mean age 15.2 (S.D=1.2) years. The median expanded disability status scale (EDSS) score was 1.5 indicating minimal disability. Adolescents with MS walked slower compared to age-matched healthy controls. Furthermore, according to the normalized joint angle motion parameters, adolescents with MS walked with decreased knee flexion during swing, increased knee extension during mid-stance, decreased hip extension during terminal stance and decreased plantar flexion during pre-swing compared to the values in the healthy adolescents.

Conclusions: The current study presents, for the first time, joint angle motion parameters in gait of adolescents with MS. Our findings indicate that although this this unique population is defined as minimally disabled, they experience gait modifications in key lower extremity joints compared with healthy teenagers.

Keywords:
Multiple sclerosis, Gait, Adolescents

EPNS21-2033 Oral or poster
Neuro rehabilitation

Robot-assisted gait training on walking abilities and cerebral connectivity in children with hemiplegic cerebral palsy

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Objective: To determine whether robot-assisted gait training with the G-EO® system better improves walking abilities and cerebral connectivity compared to classical physiotherapy in children with hemiplegic cerebral palsy.

Methods: Forty children aged 4 to 18 years with hemiplegic cerebral palsy were randomly allocated for age and GMFCS score in a French monocentric study to a ten 20-minute robot-assisted gait training sessions using the G-EO® system, five days a week (group 1, n=20) or to six 30-minute physiotherapy sessions, three days a week (group 2, n=20), for two consecutive weeks, during a period from September 2020 to December 2021. Functional clinical and cerebral MRI outcomes before and one month after treatment were compared in pre and post-treatment between the two groups. The primary outcome was gait speed on a Gait-Rite® system. The secondary outcomes included the 6-minute walk test distance, functional abilities using GMFM-88, global improvement using the PGI questionnaire, functional and structural cerebral connectivity on resting state functional MRI and diffusion tensor imaging.

Results: The gait speed, the 6-minute walk test distance and functional cerebral connectivity in the sensory-motor pathway in both hemispheres were improved in the robot-assisted gait therapy group compared to the physiotherapy group after rehabilitation, while DTI parameters in the cortico-spinal tracts did not change in both groups. The Pediatric Global Improvement was also higher in the robot-assisted gait therapy group.

Conclusions: A short term benefit of a two week robot-assisted gait training on gait speed and functional cerebral connectivity was found in children with hemiplegic cerebral palsy compared to a classical rhythm of physiotherapy. These findings are a first step to clarify and objectify the interest and impact of these new therapeutic options for rehabilitation in cerebral palsy.

Keywords:
robot-assisted gait training; cerebral palsy, brain connectivity, functional MRI, DTI

EPNS21-2040 Oral or poster
Fetal and Neonatal Neurology

Medullary Tegmental Cap Dysplasia: A Novel Brainstem Malformation - Fetal and Postnatal Presentation

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Objective: Medullary tegmental cap dysplasia (MTCD) is an extremely rare brainstem malformation, first mentioned by Barkovich et al. in their classification of midbrain-hindbrain malformations from 2009. An anomalous mass protruding from the posterior medullary surface is the hallmark of this syndrome. There is only one case-report that shows the neuroimaging features. We collected three fetal and five post-natal patients. The aim of this study is to describe the neuroimaging, clinical, autopsy and genetic findings defining this novel syndrome.

Methods: This is a multicenter international retrospective study. We reviewed the patients' medical records, prenatal ultrasounds, MR scans, genetic findings and autopsy results of our 7 patients, and an additional patient from the literature.

Results: Eight unrelated patients were included; three fetuses and four children. In all cases an anomalous mass protruding from the posterior medullary surface was observed. Additional imaging features were: rotated position of the medulla, small and flat pons, hypoplastic cerebellar hemispheres with disorganized foliation, hypoplastic vermis, and callosal agenesis/ partial agenesis. Post-mortem analysis in two patients revealed that the mass contained mature ganglion cells consistent with a hamartoma in one patient, and tracts of the anterior pons, in the other.

Conclusions: This is the first study to delineate a series of eight patients with the new syndrome of medullary tegmental cap dysplasia. Due to the variations in the clinical, imaging and the autopsy findings, we can conclude that there is no single etiology or pathophysiology. We suggest that the common pathophysiology might be impaired ciliary function, leading to abnormal axonal midline crossing.

Keywords:
Medullary tegmental cap dysplasia; Axonal guidance; Ciliopathy; Joubert-Boltshauser syndrome; Anterior Mesencephalic Cap Dysplasia; Pontine tegmental Cap dysplasia

EPNS21-2052 Oral or poster
Movement Disorders

Sleep and circadian rythme disorders in children with Alternating Hemiplegia of Childhood (AHC): preliminary results of the HEPNOS-circa study.

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Objective: The resolution of paroxysmal events upon sleep is a core feature in AHC. Recent data support that AHC patients suffer from sleep disorders. At the same time, many other features of the disease, (specific triggers, medications, epilepsy, neurodevelopmental & neuropsychiatric disorders) are known predisposing factors for sleep and circadian cycle disorders. Circadian rythme disruption has been shown in animal models with ATP1A3 mutations. The HEPNOs-circa study aims to evaluate this landscape using a variety of sleep assessement methods.

Methods: We prospectively included 21 AHC patients after informed consent [mean age 15,41 years (min 1,77 years, max 39,91 years), male 61,9%]. We analyzed sleep-related questionnaires (n=18), actigraphy(n=10), polysomnography (n=14) and urinary melatonine cycle (n=15) along with clinical details from patients' medical records. SPSS 27.0 was used for statistical analysis.

Results: According to questionnaires, 52,9% of patients with AHC have a morning circadian phenotype; only 11,11% have recognised a sleep disorder (parasomnia). However, 28,6% were under regular melatonine treatment and PSG was suggestive for a sleep pathology in 85,7% of patients (obstructive apneas=5, central apneas=2, altered sleep architecture=3, upper airway resistance syndrome=2). Low melatonine urinary secretion was found in 46,7% of patients. Actograms non-parametric circadian rhythm comparisons with healthy population have shown
a delay of 2 hours in L5 (onset of the least active 5 h) in children and a high intra-daily variability (IV) (0.80, p= 0.04) in adults.

Conclusions: The preliminary results of our study show alterations of the rest-activity cycle in AHC, in particular a delayed cycle in children and a higher fragmentation in adults. We have also shown a low melatonine secretion and a high percentage of pathological PSG findings. Given the limited number of subjects, these premiminary results should be taken with caution and need to be confirmed on a larger population.

Keywords:
sleep disorders, Alternating Hemiplegia of Childhood, circadian rythme, polysomnography, actigraphy, melatonin

EPNS21-323 Oral or poster
Neurodevelopmental

Eladocagene Exuparvovec Improves Body Weight and Reduces Respiratory Infections in Patients With Aromatic L-Amino Acid Decarboxylase Deficiency

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Objective: Aromatic L-amino acid decarboxylase (AADC) deficiency is caused by mutations in the dopa decarboxylase gene leading to reduced AADC enzyme activity. Patients with AADC deficiency often have feeding, swallowing, and gastrointestinal problems, which may contribute to low body weight. Upper respiratory tract infections (URTIs) and pneumonia are major causes of morbidity in these patients. Eladocagene exuparvovec is a recombinant adeno-associated viral vector serotype 2 carrying the coding sequence for the human AADC gene.

Methods: Eladocagene exuparvovec was administered via bilateral infusion into the putamen of 28 children with AADC deficiency in 3 clinical trials (AADC-CU/1601 [8 patients, completed], AADC-010 [10 patients, completed], and AADC-011 [10 patients at 26 Feb 2020 cutoff date, ongoing]). Patients received 1.8 × 1011 vg (n=21) or 2.4 × 1011 vg (n=7; AADC-011)]. Body weight was measured at baseline and at 12-month follow-up and compared with age- and gender-matched values for children without AADC deficiency.1 Rate of URTI/pneumonia was measured annually for 5 years after therapy.

Results: At baseline, most patients (83.3%, 20/24) had a body weight ≤ 3rd percentile. At 12 months, 95.9% maintained or gained weight relative to age- and gender-matched children without AADC deficiency; 42% (10/24) shifted to a higher percentile, and 54% (13/24) maintained the same percentile as at baseline. The annual rate of URTI/pneumonia decreased from 2.41 at 1 year after treatment to 0.31 at 5 years after treatment.

Conclusions: These results demonstrate the efficacy of eladocagene exuparvovec in improving body weight and reducing respiratory infections in patients with AADC deficiency.

Keywords:
AADC deficiency; gene therapy; rare disease

EPNS21-477 Oral or poster
Neurodevelopmental

Eladocagene Exuparvovec Gene Therapy Improves Motor Development in Patients With Aromatic L-Amino Acid Decarboxylase Deficiency

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Objective: Aromatic L-amino acid decarboxylase (AADC) deficiency is caused by mutations in the dopa decarboxylase gene leading to reduced AADC enzyme activity; it is characterized by motor impairments and inability to attain developmental milestones. Eladocagene exuparvovec (PTC-AADC) is a recombinant adeno-associated viral vector serotype 2 carrying the coding sequence for human AADC.

Methods: PTC-AADC was infused bilaterally in the putamena of 28 children with AADC deficiency in 3 clinical trials (AADC-CU/1601 [8 patients, completed], AADC-010 [10 patients, completed], and AADC-011 [10 patients at 26 February 2020 cutoff, ongoing]). Patients received a total of 1.8 × 1011 vg (n=21) or 2.4 × 1011 vg (n=7; AADC-011)] and were assessed for the motor milestone attainment using the Peabody Developmental Motor Scale, 2nd edition (PDMS-2) and Alberta Infant Motor Scale (AIMS). PDMS-2 contains subscales for interrelated motor abilities and AIMS contains subscales for elements of movement in different positions

Results: All patients treated with PTC-AADC had clinically meaningful increases in total PDMS-2 and total AIMS scores, which were maintained or improved over time, up to 60 months (LS mean change from baseline [SE] 15.0 [8.54] and 27.5 [2.62] respectively, at 60 months, the last measured timepoint). Similar increases were noted for PDMS-2 and AIMS subscores. Clinically meaningful increases from baseline in PDMS-2 total scores were seen as early as 3 months post-treatment and extended to at least 60 months.

Conclusions: The data indicate that PTC-AADC can provide a durable, positive impact on motor development in patients with AADC deficiency.

Keywords:
AADC deficiency; gene therapy; rare disease

EPNS21-121 Oral or poster
Epilepsy: Miscellaneous

A 10-year follow-up on cognition and comorbidities in SCN1A positive Dravet syndrome

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Objective: Dravet syndrome (DS) is a drug-resistant, severe developmental and epileptic encephalopathy caused by a mutation of the SCN1A gene. This 10-year follow-up study investigated the long-term outcomes in DS and aimed to identify seizure outcomes, survival data, and specifically developmental outcome and cognition.

Methods: As a prospective follow-up study from a 2009 study involving the same participants, 141 clinicians were contacted of which 140 responded. 7 patients died, 10 were lost to follow up and 10 were excluded for non-DS phenotypes. 113 participants were contacted and asked to re-complete the Epilepsy & Learning Disabilities Quality of Life questionnaire. Furthermore, a detailed demographic questionnaire, the Adaptive Behavioural Assessment System - Third Edition (ABAS-3) and the Sleep Disturbances Scale for Children were asked to be completed. Genetic information was available for each case. Questionnaires were scored and compared to previous/standardised data.

Results: 68 patient's parents (60%) responded to the questionnaires. Seizure severity remained unchanged at follow-up. 34% indicated not having had a formal discussion about sudden unexpected death in epilepsy.
Several comorbidities were present: Autism was diagnosed in 63%, behavioural problems were reported in 81% and 80% suffered from mobility problems.
The developmental quotient was significantly lower compared with the previous study ($p<0.001$) and over 91% of affected individuals now had a severe or profound learning disability compared to 25% 10 years ago. Both practical and conceptual domains of the ABAS-3 had been severely impacted with 71% scoring the lowest score. Sleep was normal in only 10%, with the most affected factor being in disorders of initiating and maintaining sleep.

Conclusions: This study highlights the ongoing cognitive difficulties and comorbidities patients with DS face. Early interventions may benefit patients to avert the observed severe developmental and cognitive disability.

Keywords:
Dravet syndrome, SCN1A, Epilepsy

EPNS21-277 Oral or poster
Epilepsy: Diagnosis and Investigations

IMPACT OF WHOLE GENOME ANALYSIS ON DIAGNOSTIC DELAY IN CHILDREN WITH PROBABLE GENOMIC EPILEPTIC ENCEPHALOPATHIES

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Objective: Neurogenetic disorders present diagnostic challenges. Next-generation sequencing has strengthened and shortened diagnostic pathways. We assessed the impact of simultaneous whole genome sequencing and microarray (WGS+M) as a primary diagnostic method on time / resource utilization in children with epileptic encephalopathies.

Methods: The Next Generation Children's Project (NGC) investigated the yield of WGS+ M with result delivered within 4 weeks of consent. A subgroup of 83 children were referred to the project by the paediatric neurology team (PNT). Group A was referred to PNT prior to and Group B was referred after the availability of rapid WGS via NGC. Children were enrolled when other investigations had not yielded a diagnosis, there was a likely genomic disorder and parents consented to trio testing. Referral dates to PNT ranged from 7 years prior to the NGC study start (2011-2018, Group A) to 3 years after (2018-2020, Group B).

Results: In 21 children the genomic cause of the epilepsy was identified (10 children from Group A). Five became eligible for targeted therapy (e.g. SCN1A). Group A underwent an average of 7.8 investigations (46% of local protocol), while Group B underwent an average of 5.6 (33%). Unpaired t-test p-value was 0.104 (n.s.). One child was excluded from analysis as previous investigation results were not available.

Conclusions: Children with rapid WGS+M earlier in the diagnostic pathway underwent fewer investigations. With larger numbers, the difference in groups may have reached statistical significance. Rapid WGS +M reduced time-to-diagnosis (results within four weeks of consent). Genomic diagnoses increased opportunities for early interventions, reducing uncertainty-related caregiver stress and enabled appropriate diagnosis-specific family counselling. Trio WGS+M with results three weeks after consent should be included in first line investigations for probable genomic epileptic encephalopathies.

Keywords:
Epilepsy, Genomic diagnoses, whole genome sequencing

EPNS21-385 Oral or poster
Epilepsy: Medical & Surgical Treatment

Using a Time-to-Event Analysis to Measure Treatment Effect of Fenfluramine (FINTEPLA) on Seizure-Free Days: Post-Hoc Analysis of Two Phase 3 Studies in Dravet Syndrome

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Objective: Apply a post-hoc time-to-event (TTE) analysis to data from 2 phase 3 trials of fenfluramine (FFA) in Dravet syndrome (DS) to evaluate time required post randomization for each patient to experience the same number of seizures experienced during baseline (Study 1, N=119; Study 3, N=143; NCT02682927, NCT02826863).

Methods: Patients aged 2 to 18 years were randomized to placebo or add-on FFA (0.7 mg/kg/day or 0.2 mg/kg/day). TTE was defined as time required during the treatment period to experience the same number of seizures during the 6-week baseline. Kaplan-Meier TTE curves were statistically analyzed by log-rank test. ANCOVA and Wilcoxon rank sum test were performed for longest duration of convulsive seizure-free days per 28 days.

Results: Proportionately more patients in the FFA groups never reached baseline seizure count relative to placebo in both studies (fenfluramine 0.7 mg/kg/day, 60%-65%; FFA 0.2 mg/kg/day, 31%-39%; placebo, 6%-13%). In both studies, median TTE was longer in the FFA groups than placebo (FFA 0.7 mg/kg/day, 13-14 weeks; 0.2 mg/kg/day, 10-11 weeks; placebo, 6-7 weeks; $P<0.001$ vs placebo in both dose groups and both studies). Median longest duration of convulsive seizure-free days was greater in the FFA groups than placebo (fenfluramine 0.7 mg/kg/day, 25.0 and 30.0 days; 0.2 mg/kg/day, 15.0 and 18.5 days; placebo, 9.5 and 10.0 days; $P<0.05$ for all dose groups in both studies vs placebo).

Conclusions: TTE analysis of 2 independently conducted phase 3 studies in patients with Dravet syndrome demonstrated comparable results, with a median TTE longer than placebo of 13-14 weeks in the FFA 0.7 mg/kg/day group and 10-11 weeks in the FFA 0.2 mg/kg/day group compared with 6-7 weeks in placebo. These data support the efficacy of fenfluramine in increasing windows of seizure freedom in patients with Dravet syndrome and support further research into using TTE as an efficacy endpoint in clinical studies.

Funding: Zogenix

Keywords:
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EPNS21-456 Oral or poster
Epilepsy: Diagnosis and Investigations

Diffusion tensor imaging, functional MRI and quantitative EEG signatures of cognition and behaviour in children and adolescents with pharmaco-responsive non-lesional epilepsy

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Objective: To determine diffusion tensor imaging (DTI), functional MRI (fMRI) brain and quantitative electroencephalogram (qEEG) correlates of cognition and behaviour in children and adolescents with pharmaco-responsive non-lesional epilepsy (PRNLE)

Methods: Fifty PRNLE cases, aged 6-17 years, presenting to a tertiary care teaching hospital were evaluated for cognition {Wechsler Intelligence Scale for Children (WISC-IV)}, executive function {Stroop test (ST)} and behaviour {Childhood Behaviour Checklist (CBCL)}. All underwent DTI and fMRI whereas 31 underwent qEEG. The WISC-IV and CBCL parameters were compared with age-matched, 31 normal historical controls. Coefficient of correlation was calculated for DTI, qEEG and fMRI parameters with WISC-IV, ST and CBCL scores ($p<0.05$ significant).

Results: Mean age of the cases was 146.2±34.1 months (66% males and 60% focal epilepsy). Compared to controls, mean full scale intelligence quotient, verbal comprehension index and perceptual reasoning index scores were significantly less and proportion of children with abnormal total CBCL, social, attention and aggression scores were significantly more in the cases.
The significant correlations were
DTI: fractional anisotropy (FA) of right inferior frontooccipital fasciculus with CBCL anxiety and bilateral cingulate fibres with ST scores (-ve); FA of right external capsule with CBCL and uncinate fasciculus with ST and WISC-IV scores (+ve)
Task fMRI: Differential activation of insular cortex, lingual gyrus and cingulate fibres in unimpaired compared to impaired ST group

qEEG: resting beta and alpha powers with inattention and total CBCL scores (+ve) respectively and WISC-IV scores (-ve); task reaction times with gamma (-ve), delta and beta (+ve) powers.

Conclusions: The impairments in cognition, EF and behavior in PRNLE bear signatures on DTI, qEEG and fMRI in the form of abnormalities in axonal integrity of white matter association fibres, composition of background brain frequencies and functions of inhibition pathways.

Keywords:
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EPNS21-484 Oral or poster
Epilepsy: Medical & Surgical Treatment

Early magnetic resonance markers of the epileptogenic zone in children with tuberous sclerosis

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Objective: The study analyses the value of early (before 8 months of age) magnetic resonance (MR) in localizing the epileptogenic zone in patients with tuberous sclerosis complex (TSC). We hypothesize that MR of unmyelinated brains can serve as a valuable auxiliary marker in determining the epileptogenic zone (EZ).

Methods: Patients with the definite clinical/genetic diagnosis of TSC who underwent resective or disconnective epilepsy surgery in Motol Epilepsy Center, Prague have been included. The inclusion criteria included the availability of good quality MR images before the age of 8 months, which has been acquired after the epilepsy onset. We evaluated the localization of hypointense lesions on the T2 sequence in unmyelinated brain, including the largest one, and those with prominent signs of cortical dysplasia - on both the first and presurgical MR examination. We have also assessed the evolution of T2 hypointensities and whether these lesions have been a part of the resection.

Results: In 11 patients with TSC and the development of epilepsy at 60 ± 83 days, 28 lesions were identified by the initial brain MR, (27 tubers, T2 hypointense in 26 of them). Twelve tubers have been included in the EZ. With one exception, all lesions designated as EZ have been identifiable on the first MR. All T2 hypointense lesions have developed dysplastic signs at later MR scans, the most frequent being cortical thickening. All lesions with transmantle sign have been resected.

Conclusions: T2 hypointense tubers on the initial MR present with dysplastic signs and are often marked as a part of the epileptogenic zone. Because of the later increase in the tuber load, assessing initial examination may largely reduce the number of candidate lesions. We emphasize the diagnostic benefit of early MR imaging with dedicated protocols during the epilepsy surgery evaluation. Validation in a larger cohort is needed.

Keywords:
epilepsy surgery, tuberous sclerosis complex, magnetic resonance

EPNS21-547 Oral or poster
Epilepsy: Medical & Surgical Treatment

Successful resective epilepsy surgery is possible in children with opercular-insular epilepsy: Results of a large unicentric cohort

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Objective: Delineation of epileptogenic zone in opercular-insular region represents a challenging diagnostic task in pre-surgical diagnostic evaluation. Surgical resection of insular cortex carries major surgical risks related to its location in a close proximity to perisylvian blood vessels laterally and pyramidal tract and basal ganglia medially.

Methods: We analysed pre- and post-surgical data of 29 paediatric patients with drug-resistant epilepsy who underwent pre-surgical evaluation in Motol Epilepsy Center followed by surgical resection of the presumed epileptogenic zone in opercular-insular region between 2010 and 2021.

Results: The most frequent aetiology was focal cortical dysplasia (FCD, n=22), followed by long-term epilepsy-associated tumors (LEAT, n=5) and tuberous sclerosis (TSC, n=2). Patients' seizure semiology and electrophysiological findings varied intra- and inter-individually, and all warranted the use of multimodal imaging with post-processing tools. Twenty patients underwent SEEG monitoring followed immediately by surgical resection. In most patients, intra-operative visual detection of implanted oblique SEEG electrodes, along with electrical stimulation mapping significantly helped guide the resection. In 17/29 patients, the EZ was located in the left hemisphere. One year post-surgery, seizure-free status (ILAE 1) was achieved in 21 patients; in 4 patients, seizure frequency decreased >50% (ILAE 4), one patient has <1 year of follow-up. Postoperative complications included transient hemiparesis (n=7), mutism (n=3), anomic aphasia (n=2), persisting mild hemiparesis (n=2), and transient severe brain oedema (n=1).

Conclusions: Epilepsy surgery in opercular-insular region warrants multimodal diagnostic approach. Despite the diagnostic and surgical challenges, the patients could achieve excellent outcomes.

Keywords:
epilepsy surgery, opercular-insular epilepsy, multimodal imaging, SEEG

EPNS21-210 Poster only
Neuromuscular

RAINBOWFISH: Preliminary efficacy and safety data in risdiplam-treated infants with presymptomatic SMA

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Objective: Risdiplam (EVRYSDI®) is a centrally and peripherally distributed, oral survival of motor neuron 2 (*SMN2*) pre-mRNA splicing modifier that has been approved by the European Commission for the treatment of patients aged ≥ 2 months, with a clinical diagnosis of Type 1, 2 or 3 SMA or with 1-4 *SMN2* copies. The objectives of this study are to investigate the efficacy, safety and pharmacokinetics (PK)/pharmacodynamics of risdiplam in infants with genetically diagnosed presymptomatic spinal muscular atrophy (SMA).

Methods: RAINBOWFISH (NCT03779334) is an open-label, single-arm, multicentre study actively enrolling infants from birth-6 weeks of age at first dose, regardless of *SMN2* copy number. The primary analysis will be conducted at Month 12 in infants with two SMN2 copies and a compound muscle action potential (CMAP) amplitude of ≥ 1.5mV at baseline.
The primary endpoint is the proportion of infants sitting without support for ≥ 5 seconds (Item 22 of the Gross Motor Scale of the Bayley Scales of Infant and Toddler Development, Third Edition). Secondary endpoints include the development of clinically manifested SMA; survival and permanent ventilation; achievement of motor milestones; motor function; growth measures; nutritional status; CMAP; PK; and safety monitoring.

Results: As of the data cut-off (20 February 2021), the median age at first dose was 28.5 days (range: 16-40 days) for the first 12 enrolled infants. No treatment-related serious adverse events were reported in infants treated for up to 18.1 months. Efficacy data from infants receiving risdiplam for ≥ 12 months demonstrated that these infants reached a Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders score of ≥ 60 and maintained swallowing and feeding abilities.

Conclusions: RAINBOWFISH is ongoing worldwide and is providing valuable information about outcomes following presymptomatic administration of risdiplam, which will help to determine the dose for infants aged <2 months.

Keywords:
Spinal muscular atrophy, risdiplam, clinical trial

EPNS21-215 Poster only
Neuromuscular

JEWELFISH: Safety, pharmacodynamic and exploratory efficacy data in non-naïve patients with spinal muscular atrophy (SMA) receiving treatment with risdiplam

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Objective: Risdiplam (EVRYSDI®) is a centrally and peripherally distributed, oral survival of motor neuron 2 (*SMN2*) pre-mRNA splicing modifier that has been approved by the European Commission for the treatment of patients aged ≥ 2 months, with a clinical diagnosis of Type 1, 2 or 3 SMA or with 1-4 *SMN2* copies. The objectives of this study are to determine the safety, tolerability and pharmacokinetic/pharmacodynamic (PD) relationship of risdiplam in non-naïve patients with spinal muscular atrophy (SMA).

Methods: JEWELFISH (NCT03032172) is a multicentre, open-label study of daily risdiplam in non-naïve patients with SMA (inclusion criteria aged 6 months to 60 years at enrolment) who previously received RG7800 (RO6885247), nusinersen (SPINRAZA®), olesoxime or onasemnogene abeparvovec (ZOLGENSMA®).

Results: The enrolled population (N=174) included a broad range of ages (1-60 years), SMA types (1-3), *SMN2* copy numbers (1-4) and motor function (non-sitters/sitters/walkers). Safety data are available from 173 patients: one patient withdrew from the study at baseline. Of 173 patients, 13 previously received RG7800, 76 received nusinersen, 70 received olesoxime and 14 received onasemnogene abeparvovec. Risdiplam treatment led to a rapid and sustained, >2-fold increase in SMN protein levels compared with baseline (data cut-off: 1 June 2020), which was consistent with PD data from the SUNFISH study of treatment-naïve patients with Types 2/3 SMA. No drug-related safety findings leading to withdrawal were reported for any patient in JEWELFISH (data cut-off: 31 July 2020). The safety profile was consistent with the safety profile observed in treatment-naïve patients.
We present 12-month safety, PD and exploratory efficacy data from JEWELFISH (data cut-off: 29 January 2021).

Conclusions: JEWELFISH is ongoing at sites across Europe and the US and will provide important data on the safety, PD and exploratory efficacy of risdiplam in a broad population of non-naïve patients with SMA.

Keywords:
Spinal muscular atrophy, risdiplam, clinical trial

EPNS21-219 Oral or poster
Neuromuscular

FIREFISH Parts 1 and 2: Safety and efficacy of risdiplam in Type 1 spinal muscular atrophy

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Objective: Risdiplam is a centrally and peripherally distributed, oral survival of motor neuron 2 (*SMN2*) pre-mRNA splicing modifier that has been approved by the European Commission for the treatment of patients aged ≥ 2 months, with a clinical diagnosis of Type 1, 2 or 3 SMA or with 1-4 *SMN2* copies. The objective of these analyses is to determine the longer-term safety and efficacy of risdiplam (EVRYSDI®) in patients with Type 1 spinal muscular atrophy (SMA).

Methods: FIREFISH (NCT02913482) is a multicentre, open-label, two-part study of risdiplam in infants with Type 1 SMA and two *SMN2* gene copies (inclusion criteria 1-7 months old at enrolment). Part 1 assesses safety, tolerability and pharmacokinetics/pharmacodynamics of different risdiplam doses (low-dose cohort, n=4; high-dose cohort, n=17). Pivotal Part 2 (N=41) assesses safety and efficacy of risdiplam at the dose selected from Part 1.

Results: The primary endpoint in FIREFISH Part 2 was met, with 29% (12/41) of infants able to sit without support for ≥ 5 seconds at Month 12, as measured by the Gross Motor Scale of the Bayley Scales of Infant and Toddler Development, Third Edition (Item 22; P<0.0001, performance criterion=5%).

Pooled safety and efficacy data were available from 58 patients who received risdiplam treatment for ≥ 24 months (Part 1 [high-dose cohort, n=17] and Part 2 [N=41]). As of the cut-off date (12 November 2020), there were no treatment-related adverse events leading to withdrawal. At Month 24, 84% of patients were alive and did not require permanent ventilation. Patients continued to show improvements in motor function and achieved motor milestones not observed in the natural history of Type 1 SMA. Here we present longer-term pooled safety and efficacy data from patients who have received risdiplam treatment for ≥ 3 years.

Conclusions: FIREFISH Parts 1 and 2 are ongoing globally and are providing long-term safety and efficacy data of risdiplam in infants with Type 1 SMA.

Keywords:
Spinal muscular atrophy, risdiplam, clinical trial

EPNS21-246
Neuromuscular

Poster only

Phase 1/2a Trial of SRP-9001 in Patients with Duchenne Muscular Dystrophy: 3-Year Safety and Functional Outcomes

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Objective: The investigational gene transfer therapy rAAVrh74.MHCK7.micro-dystrophin (SRP-9001) is being developed to achieve targeted skeletal and cardiac muscle expression of a shortened functional micro-dystrophin protein. This Phase 1/2a, single-dose, open-label clinical trial (NCT03375164) evaluates the safety of systemic gene transfer of SRP-9001 in patients with Duchenne muscular dystrophy (DMD).

Methods: Four ambulatory patients with DMD (4-7 years old) were enrolled. Patients were given an intravenous infusion of SRP-9001 at a dose of $2.0x10^{14}$ vg/kg (supercoiled qPCR, linear plasmid standard equivalent of $1.33x10^{14}$ vg/kg) and prednisone (1 mg/kg/day) 1 day pre- to 30 days post-gene delivery. The primary outcome measure is safety. The secondary outcome measures include micro-dystrophin expression quantified by immunofluorescence and western blot in pre- and post-treatment (Week 12 post-infusion) muscle biopsy. Key efficacy outcome measures include change in the North Star Ambulatory Assessment (NSAA) and timed function tests (100m, 4-Stair Climb, and Time to Rise).

Results: Three-year data demonstrated that SRP-9001 was linked to an acceptable safety profile. Treatment-related adverse events (AEs) were mild to moderate, occurred mostly in the first 90 days of treatment, and all resolved. No serious AEs, study discontinuations, or AEs associated with clinical complement activation were reported. All patients demonstrated a clinically meaningful improvement on NSAA (mean change [standard deviation] from baseline to Year 3: +7.5 points [3.42]). Patients treated with SRP-9001 generally maintained muscle strength (Time to Rise and 4-Stair Climb) and showed improvement in ambulation ability (100m) from baseline to Year 3.

Conclusions: The observed safety profile and the enduring response following gene transfer provide proof-of-concept for the continuation of clinical trials assessing SRP-9001 using single-dose gene transfer therapy in patients with DMD.

Keywords:
Duchenne muscular dystrophy, gene therapy, clinical trials, gene transfer

EPNS21-504
Neuromuscular

Poster only

The DMD Hub: a UK network enabling trials in Duchenne muscular dystrophy

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Objective: The DMD Hub, initiated in 2015, is an innovative collaboration between Duchenne UK, and two leading UK neuromuscular centres of excellence, the John Walton Muscular Dystrophy Research Centre in Newcastle and Great Ormond Street Hospital in London. The initial objective was to expand capacity for DMD trials in the UK.

Methods: With investment exceeding £3.2million, the DMD Hub has funded 30 key posts at 11 sites across the UK, facilitated the sharing of expertise and successfully developed a network of trial-ready centres to take on interventional trials in DMD.

Results: The increased number of trial sites has directly increased the number of trials taken on by UK sites and offered additional opportunities for over 300 patients to participate in clinical research.

Training (workshops and online modules), secondments and support networks have been successfully set-up and are enabling the sharing of knowledge and promoting best practice.
The PI network enables sponsors to consult with potential UK investigators to assess trail feasibility and anticipate capacity issues
The nurse and clinical trial coordinator networks help monitor the upcoming trials and facilitate recruitment

The DMD Hub website (dmdhub.org) is a key resource for industry, clinicians and patients. It hosts the Clinical Trial Finder, which comprehensively lists all DMD clinical trials at the sites. The Central Contact list, currently being developed, will further facilitate patient recruitment in a fair and equitable way.

Conclusions: The DMD Hub has helped implement significant changes to the UK clinical trial environment for patients with DMD, hospitals and pharmaceutical companies, and the model is currently being rolled out in other countries and disease areas.

Priorities currently include addressing challenges associated with delivering DMD gene therapy trials in the UK, addressing bottlenecks in clinical trial set up and improving procedures for fair and equitable recruitment to trials.

Keywords:
Duchenne Muscular Dystrophy, Collaborations, Network, Training and Education

EPNS21-671 Poster only
Neuromuscular

King-Denborough syndrome revisited - novel patients and emerging genotype-phenotype correlations

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Objective: King-Denborough syndrome (KDS) is a rare but distinct myopathy due to mutations in the skeletal muscle ryanodine receptor (RYR1) gene. The aim of this study was to analyse a cohort of patients with a clinical diagnosis of KDS and to establish genotype-phenotype correlations for this rare syndrome.

Methods: Patients were included as part of a retrospective multicentre study based on the presence of at least one RYR1 variant in the context of a congenital myopathy with at least 3 of the following 4 features: short stature, skeletal deformities, facial dysmorphism and/or malignant hyperthermia (MH) susceptibility.

Results: We identified 12 patients from 7 participating neuromuscular centres, 8 males and 4 females. All 12 patients met the clinical criteria for a diagnosis of KDS and at least 4 had suffered an MH reaction. Muscle biopsy appearance was heterogeneous, ranging from a core myopathy to more non-specific histopathological findings. Four patients had 2 RYR1 variants in trans compatible with recessive inheritance. In the remaining 8 patients only 1 RYR1 variant was identified, with apparent de novo occurrence in 4 patients. Interestingly, based on the predicted crystallographic structure of the RyR1 protein, the vast majority of RYR1 variants identified localized to RyR1 residues 2206 and 2787 (p.Thr2206Arg, p.Thr2206Met, p.Arg2241*, p.Glu2371Lys, p.Arg2452Trp, p.Arg2508His, p.Ser2776Phe, p.Thr2787Ser), a region contained within the bridging solenoid domain (aa2145-3613) implicated in RyR1 channel gating.

Conclusions: This is the largest cohort of KDS patients reported to date. Our study will contribute to better delineate the clinic-pathological features of this rare syndrome and aid its recognition. Emerging genotype-phenotype correlations support the unique position of KDS within the emerging spectrum of RYR1-related disorders and may aid the pathophysiological understanding of this rare syndrome.

Keywords:
King-Denborough Syndrome, RYR1, Malignant hyperthermia, MH, congenital myopathy

EPNS21-2045 Oral or poster
Metabolic Disorders

FBX-101, an Intravenous AAV Gene Replacement Therapy given after Infusion of Hematopoietic Stem Cells, corrects disease manifestations in Krabbe Disease

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Objective: Krabbe disease (KD) is a devastating neurodegenerative disease caused by a deficiency of galactosylceramidase (GALC) enzyme leading to cytotoxic build-up of psychosine. Myelin-producing cells are particularly sensitive to psychosine, resulting in rapid demyelination of the central (CNS)and peripheral nervous system (PNS). Infantile KD usually results in death by age 2. There is currently no cure for KD. The standard of care for patients with presymptomatic or minimally symptomatic KD (diagnosed by newborn screening or family history) is hematopoietic stem cell transplantation (HSCT) which significantly improves long-term outcomes but most patients develop progressive peripheral nerve disease.

FBX-101 is an AAV gene therapy systemically delivered by intravenous administration goals of correcting the PNS and increase GALC expression in patients with KD that received HSCT.

Methods: The complementary HSCT/AAV approach was evaluated for safety and efficacy studies in murine and canine models of KD as well as in a long-term rat GLP toxicology study. A conditioning regimen similar to those used in humans was developed for immunosuppression and allogeneic HSCT in murine and canine models of KD as well as the wild type rat.

Results: At the molecular level, biodistribution studies demonstrate significant transduction and correction of enzyme expression and normalization of the CNS and PNS disease. At the functional level, this treatment significantly extended the lifespan of treated animals, with safety being demonstrated in a long-term rodent GLP toxicology study.

Conclusions: The administration of FBX-101 following infusion of unrelated HSCT donor cells, in immune suppressed animal models is a safe and highly effective approach to address the CNS and PNS manifestations of KD. FBX-101 entered the clinical trials in 2021.ClinicalTrials.gov identifier: NCT04693598.

Keywords:
Krabbe, Neurodegenerative, HSCT, AAV; Gene Therapy; Metabolic Disorders, Newborn Screening

EPNS21-361
Genetics

Oral or poster

A recurrent, homozygous EMC10 frameshift variant is associated with a syndrome of developmental delay with variable seizures and dysmorphic features

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Objective: The endoplasmic reticulum membrane complex (EMC) is a highly conserved, multifunctional 10-protein complex related to membrane protein biology. In seven families, we identified 13 individuals with highly overlapping phenotypes who harbor a single identical homozygous frameshift variant in EMC10.

Methods: Using exome, genome, and Sanger sequencing, a recurrent frameshift EMC10 variant was identified in affected individuals in an international cohort of consanguineous families. Multiple families were independently identified and connected via Matchmaker Exchange and internal databases. We assessed the effect of the frameshift variant on EMC10 RNA and protein expression and evaluated EMC10 expression in normal human brain tissue using immunohistochemistry.

Results: A homozygous variant EMC10 c.287delG (Refseq NM_206538.3, p.Gly96Alafs*9) segregated with affected individuals in each family, who exhibited a phenotypic spectrum of intellectual disability (ID) and global developmental delay (GDD), variable seizures and variable dysmorphic features (elongated face, curly hair, cubitus valgus, and arachnodactyly). The variant arose on two founder haplotypes and results in significantly reduced EMC10 RNA expression and an unstable truncated EMC10 protein.

Conclusions: We propose that a homozygous loss-of-function variant in EMC10 causes a novel syndromic neurodevelopmental phenotype. Remarkably, the recurrent variant is likely the result of a hypermutable site and arose on distinct founder haplotypes

Keywords:
homozygous loss-of-function variant in EMC10

EPNS21-382 Oral or poster
Genetics

R14 Rapid Trio Exome Sequencing for Acutely Unwell Children at the Royal London Hospital

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Objective: This study is a retrospective service evaluation and analysis of all cases referred for rapid trio exome sequencing since the introduction of the R14 service at the Royal London Hospital from Oct'19 - Jul'21. We review its diagnostic utility and impact on re-directing clinical management

Methods: Clinical notes for all referred patients were reviewed retrospectively; data was collated and analysed for presenting symptoms, family history, investigations, subsequent changes to clinical management after trio exome results, and the patient outcomes

Results: 18 unrelated cases (9 NICU, 9 PICU) were referred for testing following clinical assessment by paediatric neurology and discussion with clinical geneticists. The diagnostic rate was 67% (12/18), significantly higher than the centrally reported rate of 26.8%. This genetic diagnosis directly influenced clinical management in 11/12 cases (92%): specific treatment (medication) was commenced in 2 patients (17%), specialist care with symptom management plans and surveillance were initiated for 3 patients (25%) and re-direction to palliative care was sought for 6 patients (50%). All patients received the final report within the 21-day national TAT target. 50% (9/18) of referred cases had consanguineous parents; 100% of positive neonatal cases had consanguinity

Conclusions: With a high diagnostic yield of 67% in our patient group, the R14 service has proven to be a valuable tool for rapidly resolving the diagnostic odyssey for these acutely unwell children and improving their care in our unit. It has enabled precision medicine interventions, surveillance investigations, and informed palliative care discussions and re-direction of care. Given the high rate of consanguinity and the greater incidence of autosomal recessive conditions in our patient population, clinicians should have increased clinical suspicion of a monogenic disorder in acutely unwell children and become more familiar with this technology to utilise as a primary investigation

Keywords:
Neonatal, Intensive Care, Neurology, Genetics, Genetic Disorders, Audit

EPNS21-464 Oral or poster
Genetics

Mutations in HOPS-complex genes VPS16 and VPS41 cause early-onset movement disorders

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Objective: Most people with probable genetic dystonia never receive a specific diagnosis. This implies that multiple causative genes have yet to be recognised. Through identifying these, we aimed to improve the prospects of diagnosis for people with dystonia.

Methods: Weighted burden analysis was performed on whole-exome sequencing data from 138 individuals with generalised dystonia believed to be genetic. Once a gene (VPS16) was identified, additional cases were sought in international databases of people with movement disorders. Variants in functionally-related genes were then also sought. Electron microscopy was undertaken on patient-derived lymphocytes and fibroblasts.

Results: Statistical analysis implicated a significant excess burden of VPS16 variants in the dystonic cohort. A total of 19 individuals from 15 families with loss-of-function variants in VPS16 were identified. They experienced early-onset progressive dystonia, predominantly upper limb, cervical, bulbar and orofacial. Several had neurodevelopmental and/or neuropsychiatric comorbidities. VPS16 encodes a subunit of the homotypic fusion and vacuole protein sorting (HOPS) complex, essential for autophagosomes-lysosome fusion. We also identified a child with a homozygous splicing variant in a gene encoding another HOPS subunit, VPS41: he presented with neurodevelopmental impairment, dystonia, ataxia and cerebellar atrophy. Seven other families have since been reported and the condition is now designated autosomal recessive spinocerebellar ataxia 29. Electron microscopy showed vacuolar abnormalities suggesting impaired lysosomal fusion in cells from patients with both VPS16 and VPS41-related conditions.

Conclusions: VPS16 and VPS41 are two novel causes of genetic dystonia, both related to disruption of the HOPS complex and thereby lysosomal function. Further links of the aetiological chain remain to be elucidated. The name "HOPS-associated neurological disorders" (HOPSANDs) has been proposed.

Keywords:
VPS16; VPS41; HOPSANDs; HOPS complex; dystonia; lysosome

EPNS21-519 Oral or poster
Genetics

Epilepsy course and developmental trajectories in STXBP1-DEE

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Objective: The clinical manifestations in STXBP1 developmental and epileptic encephalopathy (DEE) vary in severity and outcome, and the genotypic spectrum is diverse. We aimed to trace the neurodevelopmental trajectories in individuals with STXBP1-DEE and dissect the relationship between neurodevelopment and epilepsy.

Methods: Retrospective standardized clinical data were collected. A composite neurodevelopmental score system compared the developmental trajectories in STXBP1-DEE.

Results: 48 patients with de novo STXBP1 variants and a history of epilepsy were included. Seventeen individuals (35%) were seizure-free at the time of inclusion, 13 of whom (76%) achieved remission within the first year of life. 22 individuals (46%) presented with signs of developmental impairment and/or neurological abnormalities before epilepsy onset. Age at seizure onset correlated with severity of developmental outcome and the developmental milestones achieved, with a later seizure onset associated with a more favorable developmental outcome. In contrast, age at seizure remission and epilepsy duration did not impact neurodevelopmental outcomes. Overall, we did not observe a clear genotype-phenotype correlation but monozygotic twins with de novo STXBP1 mutation showed similar phenotype and parallel disease course.

Conclusions: The epilepsy course in STXBP1-DEE presents with two main trajectories, with either early seizure remission or drug-resistant epilepsy, and a range of neurodevelopmental outcomes from mild to profound intellectual disability. Age at seizure onset is the only epilepsy-related feature associated with neurodevelopment outcome. These findings can inform future dedicated natural history studies and trial design.

Keywords:
STXBP1, neurodevelopment, epilepsy, DEE, genetics

EPNS21-619 Poster only
Genetics

GENETICS OF EARLY INFANTILE EPILEPSIES:A SPANISH SERIE

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Objective: To determine the diagnostic rentability of genetic studies in infants begining their seizures before age 4.

Methods: This is a retrospective (from 2016 to 2021) unicenter study of 331 patients aged 0-15 years old, whose epilepsy had started before the age of 4. We identified and phenotyped every patient and recall the data of genetic testing consisting in epilepsy gene panel (7500 genes) by Next-Generation Sequencing technic and/or microarray. Clinical epilepsy diagnosis included Developmental and Epileptic Encephalopathy (DEE), early onset focal or generalized epilepsies

Results: Overall, we identified pathogenic genetic variants or chromosomal abnormalities in 42% of patients (139/331). The most frequent genes affected were: SCN1A, PCDH19, KCNQ2, STXBP1, CACNA1A, GBR3,GRIN2A, MECP2,and SCN2A. Followed by SLC2A1,CDKL5,CHD2. We found also pathogenic mutations in rare genes as FARS2, WWOX, EEF1A2, CRBN, KCNB1, FGF12, KCNMA1, AUTS2 and MAP2K1. The more severe was the phenotype the more rare was the gene mutated.

Conclusions: Our data argue for the consideration of early genetic testing in every child with early infantile epilepsy onset specically with concomitant neurodevelopment stagnation or deterioration.
The studies must be exhaustive and in case of negativity proceed to a Whole Exome Sequencing (WES)

Keywords:
Next Generation Sequencing, Early Onset Infantile Epilepsy, Developmental Epileptic Encephalopathy

EPNS21-2029 Oral or poster
Epilepsy: Miscellaneous

The ENVISION Study, an International, Prospective Natural History Study in Young Children with SCN1A+ Dravet Syndrome

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Objective: Dravet Syndrome (DS) is the prototypic developmental and epileptic encephalopathy characterized by drug-resistant seizures and developmental impairment. There are limited prospective long-term data describing the full range of phenotypic features and evolution, and the impact of DS in young children. ENVISION is a comprehensive observational study aimed at prospectively evaluating the course and impact of disease in young children living with SCN1A+ DS and families. Data collected during 1½ year of study will be presented.

Methods: Ongoing international, multicenter, longitudinal, prospective study of children with DS with a confirmed SCN1A pathogenic or likely pathogenic variant, aged 6 months to 5 years at study entry. Participants are assessed remotely every 3 months (6 in-person) for 24 months to evaluate the longitudinal progression of various endpoints using an electronic seizure diary and validated tools, including Bayley-III, Vineland-III, and PedsQL.

Results: As of 5Nov2021, 45 children have been enrolled (mean age 31 months). Nearly 40% of participants were younger than 2 years at enrollment (19/45) and over 70% have truncating variants (32/45). Despite multiple antiseizure medications (median 3; range 1-6), median monthly countable seizure frequency (MCSF) increases with age. High MCSF heterogeneity was observed (range 0-2647 seizures per 28 days at 3-month visit). Regardless of variant type, participants showed substantially decreased neurocognitive abilities by age 3 years; children aged 4-5 years show skills comparable to neurotypical children at age 2 years. Gross/fine motor skills are impaired in children with DS younger than 3 years of age. Quality of life is impaired and worsens with age, functional abilities are affected as early as 2 years of age.

Conclusions: Initial ENVISION data demonstrate the trajectory and timing by which children with DS deviate from neurotypical peers and highlight the early therapeutic window for disease-modifying therapies to provide maximum benefit.

Keywords:
Dravet syndrome, ENVISION study, developmental and epileptic encephalopathy (DEE), Natural history, longitudinal study, observational study, international study

EPNS21-211 Oral or poster
Epilepsy: Miscellaneous

Routine investigations in children with drug-resistant epilepsy on a ketogenic diet: Compliance with local guidelines and clinical significance of results

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Objective: The efficacy of the ketogenic diet for seizure control in children with drug-resistant epilepsy is well established. Consensus guidelines recommend children are monitored with regular investigations. Fulfilment of these recommendations / the frequency of clinically significant abnormal results is little reported. We aimed to evaluate the compliance and results of testing in children with drug-resistant epilepsy on a ketogenic diet.

Methods: We performed a retrospective cohort study of 19 consecutive patients with drug-resistant epilepsy, aged 4 months to 15 years old, started on a ketogenic diet before March 2018. Routine tests completed over 2 years of the diet were compared with local hospital guidelines. Patient data was analysed for abnormal results.

Results: According to local guidelines, each child should have 41 tests completed over the 2-year period. Within the cohort, 403 of 779 expected tests were carried out (52%). 31% of reported results were abnormal. Documentation of the impact of these results on patient care was unclear in all patients.

Conclusions: Compliance with local guidelines on regular testing for children on a ketogenic diet is low. When testing was conducted, 31% results fell outside normal ranges, but the significance of these and action taken were unclear/ not documented. These results were shared with the local paediatric neurology team. We are devising a new protocol with fewer tests, aiming to increase compliance, save resources and improve tolerability. Documentation needs to improve as abnormal results could have had impacts that were not documented.

Keywords:
drug-resistant epilepsy, ketogenic diet

EPNS21-235 Oral or poster
Epilepsy: Diagnosis and Investigations

Epileptic networks of patients with hypothalamic hamartoma on surface EEG

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Objective: To investigate ictal and interictal epileptic networks of patients with Hypothalamic Hamartoma (HH) in detail, using surface EEG data from long-term (>24h) video-EEG-monitorings (VEEGs). We hypothesized that different seizure types access different networks that can be measured by EEG, and that these networks would be influenced by the patients' history of disease and anatomical features of the hamartoma.

Methods: We studied the VEEGs of 34 patients (age 1-55) with epilepsy due to HH and without prior brain surgery. Interictal epileptic discharges (IEDs) and seizures were visually analyzed with regard to onset zone (IEDs: maximum) and propagation of the EEG pattern. The data was condensed to reflect the main regions of the brain and visualized and analyzed using the Matplotlib-library for Python and R.

Results: We evaluated 325 ictal events and 83 foci of IEDs. IEDs most commonly had their maximum in the temporal (53%) and frontal lobe (33.8%), propagations occurred mostly unilaterally frontal-temporal. EEG patterns of all seizure types occurred mostly frontal and temporal. Focal aware seizures lacked EEG correlate in about half of the cases and observed patterns were more diffuse, while focal impaired awareness seizures showed clear, ipsilaterally accentuated fronto-temporal seizure patterns. Networks showed significant differences depending on the attachment side of the hamartoma. For instance, ictal patterns occurred significantly more often on the ipsilateral side ($p<0.01$, Chi2-Test). Ictal networks of patients with generalized IEDs showed prominent fronto-temporal propagations on one or both sides.

Conclusions: EEG can be used to investigate epileptic networks in patients with HH and our observations emphasize the importance of fronto-temporal tracts for the genesis and dissemination of the symptoms. Networks differed depending on the attachment side of the hamartoma, and in future, a deepened understanding of the surface EEG of these patients may also help with surgical therapy planning.

Keywords:
hypothalamic hamartoma, epileptic networks, VEEG, seizure pattern, networks, IEDs, surface EEG

EPNS21-369 Oral or poster
Epilepsy: Medical & Surgical Treatment

FINTEPLA (Fenfluramine) Treatment Dose is Associated with Improvement in Everyday Executive Functioning in Preschool Children with Dravet Syndrome: Analyses From Two Pooled Phase 3 Clinical Studies

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Objective: To evaluate dose effect of fenfluramine (FFA) on everyday executive function (EF) in 2 pooled phase 3 studies of preschool children with Dravet syndrome (DS).

Methods: Children with DS received placebo or FFA (0.2, 0.4, or 0.7mg/kg/day) in 1 of 2 phase 3 studies. EF was evaluated at baseline and Week 14-15 for children aged 2-4 years with parent ratings on the Behavior Rating Inventory of EF-Preschool (BRIEF®-P); raw scores were transformed to T-scores and summarized in Inhibitory Self-Control Index (ISCI); Flexibility Index (FI); Emergent Metacognition Index (EMI); and Global Executive Composite (GEC). Clinically meaningful improvement was defined using RCI≥90%; worsening, RCI≥80% certainty. The association between treatment groups and likelihood of clinically meaningful change in BRIEF®-P indexes/composite T-scores was evaluated using Somers' D; post hoc analyses were calculated by Fisher's Exact tests (2-sided p≤0.05).

Results: Data were analyzed for 61 children (placebo, n=22; FFA 0.2mg/kg/day, n=15; 0.4mg/kg/day, n=10; 0.7mg/kg/day, n=14; median age, 3 years; 54% male). Median baseline T-scores were clinically elevated (T≥65) for ISCI, EMI, and GEC (T=68, 75, and 71, respectively). No treatment was associated with significant worsening in any BRIEF®-P indexes/composite T-score (p>0.05). There was a significant association between treatment groups and clinically meaningful improvement in ISCI, FI, GEC (p ≤0.01), and EMI (p≤0.04). FFA 0.7mg/kg/day showed a greater likelihood of improvement than placebo in ISCI, FI, and GEC (p<0.01), and than FFA 0.2mg/kg/day in ISCI (p≤0.05) and EMI (p≤0.04).

Conclusions: In this DS population with high baseline EF impairment, FFA treatment for 14-15 weeks improved EF, suggesting that patients treated with 0.7mg/kg/day FFA are more likely to experience clinically meaningful improvements in EF relative to placebo and 0.2mg/kg/day FFA. Larger studies are warranted to characterize dose-response relationships.

Funding: Zogenix

Keywords:
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EPNS21-521 Oral or poster
Epilepsy: Miscellaneous

Families driven drug development and clinical trials: a pilot study in Dravet Syndrome to delineate what really matters

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Objective: We aimed to identify the caregivers' opinion on the outcome measures that matters in clinical trials in individuals with DS and their correlation with the age of the individual with DS.

Methods: We conducted a prospective international study with convenience sample based on a 11-closed questions survey developed with three European patients' advocacy groups (PAG) for DS (France, Italy and Germany). The items were about seizures and daily life outcomes that a clinical trial should target according to family opinion. Items were scored from 1 (not important at all) to 5 (highly important). Statistical analyses were performed to evaluate country (ANOVA and khi2 tests) and age effect (Spearman's test).

Results: Hundred and fifty-three caregivers answered the survey (68%: France, 28%: Germany and 24%: Italy; affected individuals' characteristics: 86 males, age: 11.4 [25th -75th percentile:7-20.4] years). Demographic characteristics were not significantly different between countries. Families ranked as important almost all the items proposed. However, most of the items related to daily life had the highest rank in all 3 countries compared to items about seizures (p=0.02). Positive correlation between age and age at diagnosis (p=0.26, p=0.02) and negative correlations between age and targeting seizure duration and between age (p=-0.25, p=0.005) and targeting the need of referral to hospital (p=-0.26, p=0.005) were identified.

Conclusions: This study emphasized the DS families' expectations from therapies beyond seizure efficacy. These data can help to adapt patients-centered outcome measures in future clinical and real-life trials in DS.

Keywords:
Dravet syndrome; caregiver; clinical trial

EPNS21-615 Poster only
Epilepsy: Medical & Surgical Treatment

Use of VGB in infantile spasms: experience of a tertiary center for epilepsies through an open source data warehouse

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Objective: To report the use of vigabatrin (VGB) for infantile spasms in a tertiary center for rare epilepsy in the last 20 years.

Methods: This is a monocentric cohort study including patients followed in a tertiary center for rare epilepsy between 2000 and 2020. Participants were recruited through an open source data warehouse oriented toward clinical narrative reports. This software uses UMLS Metathesaurus to recognize phenotype concepts inside narrative medical reports. Descriptive statistics included mean ± standard deviation for normal data, and median [25th-75th percentile] for non-normal data.

Results: 176 Patients were included (84 females, age at epilepsy onset: 5.51 [3.02-7.74] months, age at spasm onset: 5.93 [4.11-8.49] months and age at last follow-up: 4.6[2.9-7.4] years). Another type of seizure preceded the onset of spasms in 31 individuals (17.6% of the cohort) by 4.03 [1.1-6.62] months. VGB was initiated as first medication in 140 individuals (79.5%). Median delay from spasms onset to the initiation of VGB was 16 [5-39.25] days. A complete disappearance of spasms and hypsarrhythmia for at least two months was obtained in 105 (60%), while 33 (18.9%) showed a partial response, and 37 (21.1%) were non responders. Twenty-four individuals (21.2% of responders) showed a relapse of spasms during treatment with VGB at 5[3-12] months of its initiation. Of the 81 remaining, in 46, VGB was withdrawn during follow-up after complete spasms disappearance (n=37, 80.4%) at 28 [19-53] months of its introduction, in 6 VGB was replaced by another ASM due to the onset of new seizure type (13%), 3 stopped VGB for other reasons (6.5%). Four individuals had spasms relapse within 6 months after VGB withdrawal (n=4; 8,7%).

Conclusions: Relapse of infantile spasms during VGB treatment can be challenging. Relapses after VGB withdrawal are less frequent but should be carefully weighted by the clinician and followed up.

Keywords:
West syndrome, developmental epileptic encephalopathy, relapse, outcome

EPNS21-158 Oral or poster
Epilepsy: Diagnosis and Investigations

Preliminary Study About A Significant and Treatable Cause of Epileptic Encephalopathy: GRIN2D Mutation

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Objective: Glutamate is the main excitatory neurotransmitter of the central nervous system and has a key role in basic neuronal functions and central nervous system processes, such as learning, memory, and synaptic plasticity. Four independent genes (GRIN2A, GRIN2B, GRIN2C, and GRIN2D) encode GluN2A-D subunits of NMDA receptors. NMDAR mutations are associated with various neurologic diseases, including schizophrenia, intellectual disabilities, autism, epilepsy, and attention-deficit/hyperactivity disorder. Epileptic encephalopathies manifest with intractable seizures and neurodevelopmental disabilities and have monogenic disorders as part of the various etiologies. Revealing genetic etiologies and specific disease mechanisms make personalized therapeutic regimens possible. The GRIN2D gene mutation causes severe forms of epileptic encephalopathy. NMDAR antagonists and magnesium sulfate could be useful as adjunctive therapy to control seizures in individuals with GRIN2D encephalopathy. The aim of this study was to describe the clinical features and treatment options of GRIN2D encephalopathy.

Methods: Patients followed up with epileptic encephalopathy in our pediatric neurology clinic were investigated for genetic etiology using next-generation sequencing (NGS)-based tests. Patients with the GRIN2D mutation were overviewed for clinical and genetic characteristics.

Results: A total of 53 patients were screened and GRIN2D mutations (c.3684_3685insGA, c.3248_3254del, c.1579G>T, c.47_49del) were detected in four patients. Occipital epileptic activity was frequently detected among our patients. Three patients received memantine treatment for intractable epilepsy and remained seizure-free.

Conclusions: GRIN2D encephalopathy is a treatable epileptic encephalopathy, and its recognition is important in terms of outcomes. Occipital epilepsy is generally benign, but developmental and epileptic encephalopathies such as GRIN2D encephalopathy should be considered in the presence of concomitant developmental delay.

Keywords:
developmental delay; epileptic encephalopathy; GRIN2D; memantine; NMDA

EPNS21-172 Oral or poster
Epilepsy: Miscellaneous

Corpus Callosum Thickness: A Biomarker For Prognosis Of Rolandic Epilepsy?

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Objective: Although rolandic epilepsy is known to be a benign condition it is important to predict poor prognostic factors of patients with inadequate control of seizures. Corpus callosum thickness reflects the volume of the hemispheres and responds to changes through direct effects or through wallerian degeneration. The aim of this study is to investigate the existence of a possible linkage between the thickness of corpus callosum (CC) and the prognosis of rolandic epilepsy.

Methods: We measured certain CC thickness in 68 patients and 42 healthy controls between 4-12 years using in vivo magnetic resonance imaging. Patients were divided into two groups: good prognosis group, which represented patients with optimal seizure control and poor prognosis group consisting of patients with more than 2 seizures within 6 months. We compared the two groups in relation to the clinical (duration of epilepsy, frequency and number of seizures, response to treatment) and EEG features. Students' t test, two-way ANOVA and Spearman test were used for statistical analysis.

Results: The thickness of the genu, isthmus and splenium was significantly lower in the poor prognosis group than the healthy controls based on the posthoc analysis ($p=0.023$, $p<0.001$ and $p=0.008$). The isthmus and splenium were significantly thinner in patients with poor prognosis than those with good prognosis ($p=0.005$ and $p<0.001$). The thickness of the genu was positively correlated with the age at onset of the seizure in patients with poor prognosis. The total number of seizures was also negatively correlated with the thickness of the body, isthmus and splenium.

Conclusions: Our study highlights notable differences in spesific areas of CC in rolandic epilepsy patients. Isthmus and splenium thickness is seem to be related with seizure reccurence and poor prognosis. Future studies are required to light on the importance of commissural fibers connecting homotopic cortical regions.

Keywords:
corpus callosum thickness, rolandic epilepsy, biomarker

EPNS21-177 Oral or poster
Epilepsy: Miscellaneous

Sleep in children with refractory epilepsy: preliminary results of an ongoing prospective EEG study

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Objective: Sleep disorders are prevalent in children with epilepsy. We aim to better understand the impact of refractory epilepsy on sleep architecture. As secondary objective we are looking for an interictal epileptic discharge index during sleep which correlates with intellectual disability, controlling for etiology and comorbidities.

Methods: We present an ongoing prospective case-control study comparing sleep quality of children with different types and severity of epilepsy and healthy controls. Data from sleep EEG with EOG and chin EMG measurements and questionnaire results are analyzed.

Results: To date, we included 35 patients with epilepsy with a mean age of 11.05 years, 40% were female. Eighteen have drug refractory epilepsy as defined by the ILAE, 17 have well controlled epilepsy. 8 controls without epilepsy were included, mean age 8.38 years, 62.5% female. Hypnogram data up until now are available for 13 drug resistant patients, 10 well controlled patients and 8 healthy controls. Mean rapid eye movement (REM) sleep percentage was significantly lower in the refractory epilepsy group ($p = 0.012$) compared to well controlled epilepsy patients, as was sleep efficiency (percentage ratio between total sleep time and time in bed) and wake after sleep onset. Preliminary results of the modified sleep behavior questionnaire were available in 28 out of 35 patients. A composite sleep index higher than 4, suggestive of a severe sleep disorder, was present in 42.9% of refractory versus 14.3% of well controlled epilepsy patients, however no significance level was reached ($p = 0.209$).

Conclusions: Preliminary results suggest lower REM sleep and increased sleep fragmentation in patients with refractory epilepsy compared to well controlled epilepsy patients. Continuation of the trial will be necessary to confirm these findings, as well as to validate sleep biomarkers correlated to intellectual disability.

Keywords:
drug resistant epilepsy, refractory epilepsy, children, sleep, EEG

EPNS21-300 Poster only
Epilepsy: Miscellaneous

Is there a relationship between socioeconomic factors and prevalence, adherence and outcome in childhood epilepsy? A systematic scoping review

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Objective: Socioeconomic factors play a role in the outcome of chronic diseases in childhood. Epilepsy is the most common chronic neurological disease in childhood. The relationship between socioeconomic factors and prevalence, adherence and outcome in children with epilepsy has not, to our knowledge, been systematically reviewed and therefore the aim of our study.

Methods: Searches were conducted in PubMed, Embase and Cochrane databases from the first documented publications until 31th May 2020. The keywords included socioeconomic status, epilepsy, anticonvulsant, children and systematic review.

Results: The search generated 4687 abstracts. Twenty six articles were included in the final analysis after the screening process. We found 1 paper regarding prevalence, 12 regarding adherence and 13 regarding outcome and their relationship to socioeconomic factors.
Socioeconomic factors of caregivers impacted school performance, seizure freedom, quality of life and risk of unemployment in adulthood. Lower socioeconomic status was associated with non-adherence. Epilepsy may be more prevalent in children living in lower socioeconomic neighborhoods.

Conclusions: In conclusion, we found that socioeconomic factors of the caregiver, especially their level of education, annual income and marital status, had a significant impact on adherence to anticonvulsants and the global outcome in children with epilepsy. Our review also shows that children belonging to a lower socioeconomic group are at risk of having poorer outcomes regarding adherence and hence remission, quality of life and academic achievement. We need to recognize this aspect and integrate it in the overall management of these children.

Keywords:
: Socioeconomic status, epilepsy, anticonvulsant, children, systematic review

EPNS21-406 Oral or poster
Epilepsy: Diagnosis and Investigations

A Window in the Brain: Applying data science to quantitatively detect seizures with minimal-density EEG montage

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Objective: Gold-standard multi-channels electroencephalogram (EEG) seizure detection is not deliverable as a round-the-clock service in paediatric intensive care units (PICU). We are the first to demonstrate quantitative seizure detection is possible using 8-channels EEG montage. It is unknown if this type of seizure detection is possible with the 4-channels configuration that PICU team can reliably apply. We aim to deliver an innovative seizure detection algorithm that can accurately detect seizures using only 4-channels.

Methods: Retrospective data analysis of fully anonymised routinely generated clinical multi-channel EEG was performed. Forty randomly selected recordings were processed automatically using the BrainsView seizure detection software using 8- and 4-channels (C3, C4, P3, P4) of the 64-channels EEG to demonstrate the software's baseline performance. We refined the BrainsView seizure detection software by adding an extra feature extraction method (cross-channel amplitude coherence i.e. CA) to the existing phase synchrony (PS) calculation. The automated seizure detection analysis was repeated using the revised BrainsView algorithm for both 8-channels and 4-channels of EEG to detect seizures. Seizures identified using the original (PS only) and revised (Combined PS + CA) seizure detection algorithms were then compared with the gold-standard neurologist identified seizure markings on the EEG to determine their seizure detection performance.

Results: Enhanced seizure detection on both the 8- and 4-channels EEG montage were achieved using the combined PS and CA feature extraction method. Sensitivity and specificity for the revised algorithm on seizure detection for 8- and 4-channels were 70.4% and 82.2%, and 70.1% and 83.4%, respectively.

Conclusions: Quantitative ictal activity can be captured with as few as 4 EEG channels using our innovative seizure detection algorithm. A larger-scale validation study is required to ascertain its performance before facilitating clinical translation.

Keywords:
PhaseSynchrony AutomatedSeizureDetection NonlinearMethods

EPNS21-89 Oral or poster
Epilepsy: Medical & Surgical Treatment

Long-term treatment with intracerebroventricular cerliponase alfa for children with CLN2 disease: Safety and efficacy after >5 years

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Objective: Objectives: A primary open-label study showed that intracerebroventricular (ICV) infusion of 300 mg cerliponase alfa (rhTPP1) every 2 weeks for 48 weeks slowed deterioration in motor and language function in children with CLN2 disease. This extension study (NCT02485899) assessed long-term safety and efficacy of cerliponase alfa over an additional 240 weeks.

Methods: Methods: Subjects who completed the primary study continued receiving 300 mg cerliponase alfa biweekly for up to 240 weeks in the open-label extension. Cumulative data from both studies were used to evaluate long-term safety and efficacy. The primary efficacy endpoint was time to unreversed 2-point decline or score 0 in the motor-language (ML) domains of the CLN2 rating score, comparing treated subjects with natural history (NH) controls.

Results: Results: A total of 24 subjects (9 male, 15 female) were treated with cerliponase alfa in the primary study. Mean (SD) age at enrollment was 4.9 (1.3) years; mean (SD) ML score was 3.5 (1.2) at 300 mg dose baseline. 23 subjects enrolled in the extension and received 300 mg cerliponase alfa for a mean (range) of 272 (162-300) weeks. Treated subjects were significantly less likely than NH controls to experience an unreversed 2-point decline in ML score or score 0 (HR, 0.14; 95% CI: 0.06, 0.33; $p<0.0001$). The mean (SD) rate of decline in ML score was 0.38 (0.50) points/48 weeks for treated subjects compared with 2.13 (0.95) points/48 weeks for NH controls; mean difference (95% CI): 1.75 (1.39, 2.11) points/48 weeks ($p < 0.0001$). All subjects experienced ≥1 adverse event (AE); 21 (88%) experienced a serious AE. There were no deaths and no study discontinuations due to an AE. The most common drug-related AEs were pyrexia (46%), hypersensitivity (42%) and seizures (38%); device-related AEs were observed in 20 subjects (83%).

Conclusions: Conclusions: ICV-administered cerliponase alfa for children with CLN2 disease has an acceptable safety profile and sustained treatment effect over >5 years.

Keywords:
CLN2 disease, epilepsy, cerliponase alfa

EPNS21-275
Basic Science

Poster only

Cosyntropin modulates microglia morphology and cytokine expression following experimental traumatic brain injury in mice

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Objective: Traumatic brain injury (TBI) is a significant public health concern and a leading cause of death and disability. TBI initiates a cascade of cellular changes culminating in a robust inflammatory response including increased cytokine expression and microglia activation. Following injury, microglia undergo rapid and robust morphological changes taking on a more amoeboid shape with a reduction, thickening and shortening of their ramifications. Melanocortins (MCs) are a family of peptides endogenously derived from pro-opiomelanocortin precursors and include compounds such as adrenocorticotropic hormone (ACTH) and alpha-melanocyte stimulating hormone (alpha-MSH), both of which have been shown to reduce inflammation.

Methods: Using an adult mouse model of TBI, we hypothesized that Cosyntropin (CoSyn), a long-acting synthetic ACTH analog, would reduce the early neuroinflammatory response following TBI and reduce the inflammation-induced morphological changes in microglia. We used multiplex ELISA to quantify cytokine expression and ImageJ+FracLac to assess morphological changes in microglia. We used ANOVA to compare saline, saline+TBI, saline-CoSyn, and TBI-CoSyn treatment groups after injury.

Results: We found significant changes ($p < 0.05$) in microglia morphology including: fractal order, lacunarity, cell area and cell perimeter ($n = 5$-7). We also saw significant reduction in IL-6 and TNF-alpha in CoSyn treated animals post TBI ($n = 4$). We also evaluated memory through the Morris water maze. Mice treated with CoSyn following injury demonstrated reduced latency to platform during early training days compared to saline-treated mice.

Conclusions: Cosyntropin reduces neuroinflammation in cortex, decreases the pro-inflammatory phenotype of microglia and improves memory suggesting a beneficial alteration of inflammation following TBI

Keywords:
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EPNS21-288 Poster only
Genetics

Unilateral nodular heterotopia - the clinical and genetic spectrum in a population of pediatric Romanian patients

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Objective: Gray matter heterotopia (GMH) is a rare cortical malformation characterized by abnormal neuronal migration. Among GMH, the unilateral nodular forms present particular challenges regarding genetic testing and genotype-phenotype correlations. In this study we present the results of clinical and genetic investigation in 11 patients with unilateral nodular GMH.

Methods: General clinical examination, neurologic, psychiatric/psychologic evaluations and MRI were performed for all the children. Array based comparative genomic hybridization was used for all patients.

Results: Most of the patients (10 cases) were referred for epilepsy with or without intellectual disability (ID). 9 patients had unilateral nodular GMH with anterior localization, two patients, with posterior localization. Eight cases had isolated GMH; in three patients the unilateral nodular GMH was associated with other structural defects.
Clinical features included focal epileptic seizures (ten patients), mild ID (two patients), and behavioral problems (three cases). Two genomic imbalances with potential clinical significance were identified, 22q11.2 duplication and 7q35 deletion including CNTNAP2 gene. The duplication on 22q11.2 overlaps the critical region for 22q11.2 duplication syndrome; there are no previous reports of heterotopia associated with 22q11.2 duplication. Homozygous or compound heterozygous mutations of CNTNAP2 are associated with Cortical Dysplasia-Focal Epilepsy Syndrome. The contribution of these two CNVs to heterotopia pathogenesis worth further analysis.

Conclusions: Our study brings new data on the clinical and genetic features of unilateral nodular GMH. Genetic investigations could be useful in these patients, but a phenotype-genotype correlation is difficult to establish in some cases.

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Keywords:
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EPNS21-442
Basic Science

Oral or poster

Recombinant human erythropoietin modifies AMPA-R dysregulation and excitotoxicity in the hypoxic developing mouse brain

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Objective: Hypoxia-induced glutamate excitotoxicity during acute seizure activity activates prolonged apoptosis in the neonatal brain. Recently, we demonstrated that neuronal excitotoxicity is related to dysregulation of the AMPA-R subunit GluR2 and ADAR2 resulting in intracellular Ca2+ accumulation. We aimed to analyze in-vivo effects of recombinant human erythropoietin (rhEPO) on the permeability of AMPA-R and ADAR2-edited GluR2 mRNA in the developing mouse brain as a possible target of neuroprotection.

Methods: P7-mice were exposed to acute systemic hypoxia (FiO2 of 8% for 6 h) using a Hypoxic Workstation INVIVO2400 (Ruskinn Life Sciences) and treated with rhEPO (2500, 5000 IU/kg). After 1 and 7d of regeneration, cerebral AMPA-R and ADAR2 gene expression was quantified by real time RT-PCR. Degree of apoptosis was analyzed by TUNEL staining in the hippocampus (HC) and subventricular zone (SVZ).

Results: RhEPO modulated cerebral mRNA expression of the AMPA-R subunits as well as of ADAR2: Compared to vehicle-treated controls, rhEPO enhanced the expression of GluR1, GluR2, GluR3, and GluR4 mRNA levels in a dose-dependent manner by 152% ($p=0.019$), 176% ($p=0.003$), 142% ($p=0.006$), and 278% ($p<0.0001$), and increased the percentage of GluR2 mRNA of the AMPA-R pool by 129% ($p=0.048$). The effect persisted and became even more pronounced after 7d. Simultaneously, rhEPO significantly increased ADAR2 mRNA concentrations by 172% ($p=0.021$) after 1d of regeneration compared to controls. A decreased number of TUNEL positive cells was detected in the HC and SVZ in response to rhEPO.

Conclusions: Considering functional role of RNA-edited GluR2 for Ca2+-permeability of AMPA-R for glutamate excitotoxicity, increased expression of GluR2 and ADAR2 may explain region specific anti-apoptotic effects of rhEPO. Modulation of AMPA-R Ca2+-permeability might be a promising target for age-specific prevention of excitotoxic injury of the developing brain.

Keywords:
EPO, excitotoxicity, AMPA, ADAR, GluR2, Gria2, neuroprotection

EPNS21-501 Oral or poster
Genetics

Neuroradiological features of Pallister-Killian syndrome: a study of 21 children

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Objective: Pallister-Killian syndrome (PKS) is a rare genetic disorder caused by mosaic tetrasomy of 12p. This study aims to systematically investigate the neuroradiological features of PKS and identify the possible existence of a typical pattern. Moreover, to find any correlations with clinical and demographic variables.

Methods: This retrospective observational study was conducted on 21 individuals (10Males/11Females; age range 1 month-17 years old). Instrumental and clinical-anamnestic data were collected. Brain MRIs were blindly reviewed by an experienced pediatric neuroradiologist. Descriptive statistical methods, chi-square test, and Spearman's Rho test were used; $p<0.05$ was set. The local ethics committee approved the study and consents were obtained.

Results: Brain abnormalities were observed in all 21 individuals. Corpus callosum abnormalities were found in 15/21 (75%): 3 had callosal hypoplasia; 7 had global hypoplasia with hypoplastic splenium; 3 had only hypoplastic splenium, and 2 a thin corpus callosum. Cerebral atrophy was found in 17/21 (81%) and ventriculomegaly in 14/21 (67%). Other frequent features were the enlargement of the cisterna magna in 13/21 (70%), and polymicrogyria 11/21 (63%). Notably, polymicrogyria was located in the perisylvian area in all 11 cases and was bilateral in 10/11. The presence of polymicrogyria was significantly associated with the presence of epilepsy (p=0,048).

Conclusions: We observed that brain abnormalities are very common in PKS and occur much more frequently than previously reported. In particular, bilateral perisylvian polymicrogyria, described in only 4% of patients reported in the literature, was one of the main features in our population and it was correlated with the presence of epilepsy.
Our findings can provide an additional tool for early diagnosis and management.
Further studies to investigate the possible correlations with both genotype and phenotype may help to increasingly define the etiopathogenesis of the neurologic phenotype of this syndrome.

Keywords:
PKS, polymicrogyria, callosal hypoplasia, brain malformations, rare disease.

EPNS21-703 Oral or poster
Genetics

Neonatal hypotonia - the clue for early diagnosis of Prader-Willi syndrome

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Objective: Prader-Willi syndrome (PWS) is a rare genetic disorder characterized by different clinical features depending on age. Early diagnosis and interventions could influence prognosis. The aim of the study is to highlight clinical findings in neonatal period that could indicate PWS.

Methods: Retrospective study which included review of the medical records of all children in a tertiary pediatric center with genetically confirmed diagnosis of PWS who visited our institution from July 2017 to September 2021.

Results: Twenty-one children (10 males) with PWS symptoms and hypermethylation findings within 15q11q13 were included in this study. In 4/21 children, PWS was diagnosed during the neonatal period, while the remaining 17/21 children were genetically diagnosed at an older age (from 36 days to 13.5 years). For 2 children (age 1.6 and 4.8 years) detailed medical perinatal and clinical data were missing. Comparing the frequency of clinical characteristics present in the first weeks of life between children diagnosed in the neonatal period and children older than 28 days, we did not identify significant differences. All patients from both groups presented with neonatal hypotonia and cryptorchism, while feeding difficulties were present in 75% and 73.3% patients respectively. Facial dysmorphic features (dolichocephaly, almond-shape eyes, micromandible, and thin and downturned mouth) have been noticed more frequently in the neonatal group (86,7% vs 73,3%). To clarify the etiology of the disorder, in 13/15 patients (86,4%) a thorough clinical investigation, including neuroimaging (7), electromyoneurography (3), metabolic testing (7) and exome sequencing (3) was performed.

Conclusions: Neonatal hypotonia, especially in association with feeding difficulties, cryptorchism and dysmorphic facial features must be indication for genetic investigation for PWS. Late diagnosis leads to unnecessary investigations and delays in early interventions that could change the natural history of PWS.

Keywords:
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EPNS21-72
Basic Science

Oral or poster

Lipidomics reveals an altered CSF profile in patients with Rett Syndrome (RS)

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Objective: Rett syndrome (RS) is defined as a rare disease with a prevalence of 1:15000 and caused by mutations of the methyl-CpG binding protein 2 (MECP2). It is one of the most common causes of genetic mental retardation in girls, characterized by normal infantile psychomotor development, followed by severe neurologic regression. RS lacks a specific biomarker but altered cholesterol and lipid metabolism has been found in a KO-mouse model as well as in RS patient. The aim of this study was to investigate the cerebrospinal fluid (CSF) and plasma of a RS study group in order to analyze for metabolomics and lipidomics perturbations.

Methods: We employed both targeted and untargeted LC-MS/MS metabolomics and lipidomics to investigate the CSF and plasma composition of patients with RS for biochemical variations compared to healthy controls. Data obtained by UHPLC-MS/MS underwent lipid identification with the Lipid Data Analyzer (LDA) software, followed by statistical univariate and multivariate analysis with R (version 4.1.1) and the lipidr package.

Results: In all 7 CSF samples collected from RS patients lipidomics revealed decreased cholesterol levels compared to controls (n=20). Plasma cholesterol levels were at normal range in all 13 RS patients compared to 18 control samples. Levels of various phospholipid (PL) and sphingomyelin (SM) species were also decreased in the CSF of RS patients. Plasma samples showed reduced levels of PL, whereas triglyceride (TG) species were increased compared to healthy controls. Metabolomics data multivariate analysis did neither show a separation of the two groups (controls versus patients), nor metabolites responsible for differences within the groups.

Conclusions: This study showed alterations in the CSF lipidomics but not in the metabolomics profile in patients with RS. Future (functional) studies are going to validate selected lipid species as CSF biomarker for RS and to clarify whether these results reflect unspecific or specific effects of MeCP2 related neurodegeneration.

Keywords:
Rare diseases, metabolomics, lipidomics, Rett syndrome, cholesterol

EPNS21-103 Oral or poster
Movement Disorders

Prevalence of spasticity-related pain in children/adolescents with cerebral palsy

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Objective: Chronic pain is one of the most common complaints accompanying cerebral palsy (CP), but it is under-recognized and under-treated. This analysis determined the prevalence and intensity of spasticity-related pain (SRP) in children/adolescents (C/As) with CP using baseline data from three prospective trials in the incobotulinumtoxinA international paediatric phase 3 study program.

Methods: Baseline data from the TIM, TIMO and XARA trials were pooled. In all three studies, SRP was assessed in C/As aged 2-17 years with lower limb (LL) and/or upper limb (UL) spasticity (Gross Motor Function Classification System Expanded and Revised [GMFCS-E&R] level I-V; Ashworth Scale score >=2) using the Questionnaire on Pain caused by Spasticity (QPS); both self-reports (direct or via interviewer) and parent/caregiver (P/C) observer reports were included. A C/A was considered to have SRP if any QPS key item score was rated >0 at baseline. Individual QPS modules were descriptively analysed.

Results: At baseline, 331 and 155 C/As and 841 and 444 P/Cs completed at least one item of the relevant LL and UL QPS module, respectively. The presence of LL or UL SRP with at least one activity at baseline was respectively reported by 81.9% and 69.7% of C/As and observed by 85.9% and 77.7% of P/Cs. For both LL and UL SRP, intensity and frequency were higher with more demanding activities, irrespective of who completed the QPS. P/Cs indicated that SRP altered many of their child's behaviours, such as activity level, posture, mood, facial expression, eating, sleeping and interactions with others.

Conclusions: This pooled analysis of self-reported and P/C-observed QPS data indicates that a substantial proportion of C/As with CP and LL and/or UL spasticity experience SRP, and that pain is associated with more demanding activities. The high SRP prevalence along with its negative consequences emphasizes the need for effective, early and long-term pain management in C/As with CP.

Keywords:
Prevalence, Muscle Spasticity, Movement Disorders, Paediatric, Cerebral Palsy, Pain

EPNS21-106 Poster only
Movement Disorders

EARLY-ONSET ATAXIA ASSOCIATED WITH MUTATIONS IN THE ITPR1 GENE: PEDIATRIC COHORT - CLINICAL, RADIOLOGICAL AND GENETIC CHARACTERIZATION

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Objective: Some missense mutations in ITPR1 are responsible of an infantile-onset non-progressive cerebellar ataxia, called spinocerebellar ataxia type 29. The aim of this study is to characterize the clinical, neuroimaging and genetic features in patients with ITPR variants, in order to define more specifically this condition, with diagnostic and prognosis consequences.

Methods: Genetic, clinical and neuroimaging features of 8 pediatric patients with ITPR variants from unrelated families were assessed. Medical reports were reviwed and personal examination of the cohort was performed. MRI studies were assessed together with a neuroradiologist.

Results: The symptoms at onset were hypotonia (8/8) and ocular movement disorders (6/8). Psychomotor delay and signs of cerebellar dysfunction were present in the first years in all patients. The SARA scale (6/8 patients, age range 6-11 years), showed a total score range between 17-26. Brain MRI showed global cerebellum atrophy in all cases, and hyperintensity of the cerebellar cortex (6/8). Psychometric tests (4/8) showed an IQ score ranging 45-68. Genetic test showed de novo heterozygous ITPR1 missense variants, 2/5 not previously described.

Conclusions: This study extends the clinical, radiological, and genetic knowledge of this condition in a pediatric cohort. The early-onset ataxia, together with hypotonia, gross motor delay and cognitive impairment represented the main features. The oculomotor abnormalities were an early sign in our cohort. The cerebellar atrophy associated with a cortical cerebellar hyperintensity was frequent in the patients reported. All together suggest that some dominant mutations in ITPR1 gene cause an early-onset, non-progressive ataxia with a recognizable pattern.

Keywords:
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EPNS21-314 Oral or poster
Movement Disorders

Diagnosing ATP1A3-related Disorders. Are our clinical criteria sufficient?

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Objective: ATP1A3 comprises an expanding spectrum of neurological disorders. Due to phenotypic variability and lack of functional assay, evaluating variant pathogenicity can be challenging. We report the clinical features of a cohort of patients with pathogenic/likely pathogenic ATP1A3 variants and perform a literature review of all ATP1A3 variants associated with human disease, in order to better define the phenotypic and genotypic spectrum.

Methods: Patients with ATP1A3 variants were identified within the Deciphering Developmental Disorders (DDD) study, with additional cases contributed by national and international collaborators. Referring clinicians completed a standardised clinical questionnaire. A PubMed search was undertaken for all publications containing "ATP1A3" from 2004 to 2021.

Results: 24 patients with a neurological phenotype, were found to carry 21 different ATP1A3 variants. Patients usually experienced 2-3 different types of paroxysmal events. All patients had cognitive impairment. Other common neurological features included microcephaly (7;29%), ataxia (13;54%), dystonia (10;42%) and hypotonia (7;29%). Neuropsychiatric diagnoses were reported in 16(66.6%) patients. Most patients did not fit proposed clinical criteria for common ATP1A3 phenotypes. 1108 patients carrying 168 different ATP1A3 variants were identified using the literature search. Common variants are associated with well-defined phenotypes, while rare variants often result in criteria non-conforming phenotypes, as demonstrated in our study. Pathogenic/likely pathogenic missense variants had significantly higher CADD scores (26.5 (SD: 2.04) vs 7.7 (SD: 5.27), $p < 3.49e-85$) and clustered within 6 regions of constraint.

Conclusions: Rather than using the proposed diagnostic criteria, an ATP1A3-related condition should be suspected by the combination of paroxysmal events, hyperkinesia, neuropsychiatric symptoms and cognitive impairment. CADD score and variant location can also aid diagnosis.

Keywords:
ATP1A3, hyperkinetic movement disorder, paroxysmal events, Alternating Hemiplegia of Childhood, Rapid-Onset Dystonia Parkinsonism, CAPOS

EPNS21-380 Poster only
Movement Disorders

MOVEMENT DISORDERS IN MCT8 DEFICIENCY

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Objective: AHDS is a rare genetic leukoencephalopathy caused by a defect of thyroid hormone transport to central nervous system, characterized by a complex neurological presentation,. Movement disorders (MDs) have been frequently reported in this condition, but not systematically studied so far.

Methods: We included patients with proven AHDS through an international multicenter collaboration. Each patient was video-recorded during a routine outpatient visit according to a predefined protocol. Each patient was evaluated for the presence or absence of a MD and the type of MD (hypokinetic or hyperkinetic, namely dystonia, chorea, athetosis, ballism, myoclonus, tremor and tics). The type of MD was blindly scored by two child neurologists experts in inherited white matter diseases and in MD. When more than one type of MD was present we scored each but we noted which was the predominant one. Dystonia was scored using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS)Interrater reliability was tested by kappa statistic (kappa with linear weighting [kw])

Results: 27 AHDS male patients were included. Mean age at evaluation was 9.3 years (range 0.9-18.5). In our series, we observed three types of MDs: dystonia, hypokinesia, and paroxysmal MD. Hypokinesia was present in 25/27 patients and it was the predominant MD in 19. It was often associated with hypomimia and global hypotonia. Dystonia was observed in 25/27 patients, however, in a minority of cases (5) it was the predominant. In eleven patients, exaggerated startle reactions and/or other paroxysmal non-epileptic events during diaper change were observed.

Conclusions: Our study demonstrated that MDs are frequent in AHDS, possibly related to the important role of thyroid hormones in brain development and functioning of normal dopaminergic circuits. Hypokinesia was frequently observed in our cohort and was the most severe MDs. According to literature, dystonia was common, but usually mild to moderate in severity.

Keywords:
hypokinesia; dystonia, MCT8

EPNS21-531 Poster only
Movement Disorders

Role of the cerebellum in pathogenesis of mirror movements: an fMRI study

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Objective: congenital mirror movements (MM) are a rare genetic disorder characterized by involuntary movements of one side of the body that mirror voluntary movements of the contralateral side. Previous evidence suggests that MM arise from both abnormal interhemispheric connections between motor cortices and aberrant corticospinal tract decussation. However, other mechanisms may contribute to MM. Particularly, the role of cerebellum has not been investigated yet.

Methods: 18 congenital MM patients and 22 healthy subjects (HS) underwent a session of task functional MRI performing three motor tasks consisting of sequential finger movements (unimanual-dominant hand, unimanual-non-dominant hand and bimanual task). Imaging data were post-processed in SPM12. Functional laterality indices for the cerebellum and the precentral region were calculated by the LI-tool and compared by Kruskal-Wallis test. Cerebellar functional activation during the three tasks was compared between CMM and HS by T-test for independent samples.

Results: Compared to HS, patients showed a lesser lateralized functional activity during both unimanual tasks in the cerebellum (dominant hand: $p=0.005$; non-dominant hand: $p=0.027$) and in the precentral region (dominant hand: $p<0.001$; non-dominant hand: $p=0.013$). During dominant hand task, patients showed a significant activation of the contralateral cerebellar lobules I-V. No significant difference during the non-dominant hand task and the bimanual task was detected.

Conclusions: our results suggest a loss of cerebellar functional asymmetry during unimanual tasks in MM, reproducing the effect observed in the motor cortex. The abnormal activation of the contralateral cerebellum only during the dominant hand task suggests that different degrees of lateralization of cerebellar activity underlie the movements of the two hands. In summary, the cerebellum is included in the MM network, probably because of an abnormal delivery of the motor command from motor cortex to both cerebellar hemispheres.

Keywords:
Mirror Movements; Cerebellum; movement disorders; Neurodevelopment

EPNS21-668 Oral or poster
Epilepsy: Miscellaneous

Epilepsy in Sturge-Weber Syndrome: analysis of a multicentre cohort

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Objective: Sturge-Weber Syndrome (SWS) is a congenital neurocutaneous syndrome characterized by the presence of facial capillary malformations that can be associated to leptomeningeal vascular malformation and glaucoma. It is classified in SWS type I if there are both cutaneous and neurological involvement, type II if only the port wine stain is present and type III, the rarest, when there is isolated cerebral involvement. Epilepsy is a frequent neurological complication often with an onset before 1 year of age. We aimed to evaluate epileptological characteristics in a large cohort of SWS patients and indications to epilepsy surgery.

Methods: this national multicentre cohort included patients with Sturge Weber Syndrome and epilepsy. Our findings were compared with cohorts reported in the literature.

Results: we collected 100 patients (54 males, age at last follow-up mean 12 years, median 10 years, range 0-38) with SWS and epilepsy, 24 patients were type III. Mean age at first seizure was 19.8 months (median 10). Bilateral brain involvement was present in 14% of the patients. Age at first seizure < or = 10 months was statistically related with the presence of intellectual disability (p = <0.0001) and behavioural/psychiatric disorders (p = 0.005) at last follow-up. Drug resistance was frequent in our cohort (40.8% of patients). Twenty patients were surgically treated with a seizure free outcome in 11 cases (Engel class I). Indications for epilepsy surgery (p= 0.009) and drug resistance (p = <0.0001) were more frequent in patients who experienced status epilepticus.

Conclusions: epilepsy in Sturge Weber Syndrome has frequently an early onset with occurrence in infancy of status epilepticus and cluster of seizures. Many patients develop drug-resistance and intellectual disability. Epilepsy surgery may represent a valid therapeutic option in selected cases although it is still rarely considered.

Keywords:
Sturge-Weber Syndrome, epilepsy, epilepsy surgery, developmental outcome

EPNS21-191 Oral or poster
Inflammatory Disease of the CNS

Incidence of paediatric multiple sclerosis and other acquired demyelinating syndromes: 10-year follow-up surveillance study

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Objective: To describe a 10-year follow-up of children (<16y) with acquired demyelinating syndromes (ADS) from a UK-wide prospective surveillance study.

Methods: Diagnoses were retrieved from the patients' records via the patients' paediatric or adult neurologist using a questionnaire. Demyelinating phenotypes at follow-up were classified by an expert review panel.

Results: Twenty-four out of 125 (19.2%) children (64 males, 61 females; median age 10.0yrs, range 1.3-15.9), identified in the original study, were diagnosed with multiple sclerosis (incidence of 2.04/million children/year); 23 of 24 fulfilled 2017 McDonald criteria at onset. Aquaporin-4-antibody neuromyelitis optica spectrum disorders were diagnosed in three (2.4%, 0.26/million children/year), and relapsing myelin oligodendrocyte glycoprotein antibody-associated disease in five (4%, 0.43/million children/year). Three out of 125 seronegative patients without multiple sclerosis relapsed and 85 of 125 (68%) remained monophasic over 10 years. Five of 125 patients (4%) originally diagnosed with ADS were reclassified during follow-up: three children diagnosed initially with acute disseminated encephalomyelitis were subsequently diagnosed with acute necrotising encephalopathy (RAN-binding protein 2 mutation), primary haemophagocytic lymphohistiocytosis (Munc 13-4 gene inversion), and anti-N-methyl-D-aspartate receptor encephalitis. One child initially diagnosed with optic neuritis was later diagnosed with vitamin B12 deficiency, and one presenting with transverse myelitis was subsequently diagnosed with Sjögren syndrome.

Conclusions: The majority of ADS presentations in children are monophasic, even at 10-year follow-up. Given the implications for treatment strategies, multiple sclerosis and central nervous system autoantibody mimics warrant extensive investigation.

Keywords:
paediatric multiple sclerosis, acquired demyelinating syndromes, MOGAD, NMOSD, epidemiology

EPNS21-415 Oral or poster
Inflammatory Disease of the CNS

Increased neurofilament light chain concentration in serum and CSF in children and adolescents with Guillain-Barré syndrome

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Objective: Guillain-Barré syndrome (GBS) is an acute inflammatory polyradiculoneuropathy characterized by progressive, symmetrically ascending motor weakness, absent or reduced tendon reflexes, neuropathic pain, and autonomic dysfunction. Neurofilament light chain (NfL) concentrations in serum and CSF are a potential biomarker supporting the prognostic assessment of adult patients with a variety of neurological disorders like GBS and multiple sclerosis. So far, its potential has not been evaluated for pediatric patients with GBS.

Methods: We retrospectively evaluated baseline serum and CSF NfL in pediatric patients with GBS and pediatric healthy controls using Simoa technology and planned to analyze its correlation with disease severity and prognosis.

Results: We included 21 serum and 10 CSF baseline samples of 19 pediatric patients with GBS variants (15 AIDP, 2 AMAN, 1 AMSAN, 1 MFS; 13 males) and a median age of 11 years. Median serum NfL concentration was 143.7 pg/ml, median CSF NfL concentration 1075 pg/ml. In the healthy control group (median age 12 years; 15 males) the median serum NfL concentration was 3.6 pg/ml and by that significantly lower.

Conclusions: Serum NfL is increased in pediatric GBS patients as anticipated and might be useful as prognostic biomarker. Further analysis of the presented patient cohort is still pending and on its way.

Keywords:
Guillain-Barré syndrome, NfL, neurofilament light chain, CSF biomarker, serum biomarker

EPNS21-537 Oral or poster
Inflammatory Disease of the CNS

Obesity and sex hormones in pediatric onset multiple sclerosis

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Objective: To clarify the involvement of adipokines and sex hormones in pediatric onset multiple sclerosis (POMS) patients and to investigate their immunological profile.

Methods: Leptin, adiponectin, and FABP4 levels were quantified by enzyme-linked immunosorbent assay (ELISA) in 44 POMS patients (18 boys, 6 overweight, 2 obese children and 26 girls, 6 overweight, 3 obese children), with a sample at diagnosis and for 15 patients, a follow-up sample. Control patients were 16 children (7 boys, 1 overweight and 9 girls, 2 overweight) hospitalized in pediatric neurology, without neuroinflammation. Immunophenotyping and hormone (dihydrotestosterone, estrogens) assays were performed by flow cytometry and mass spectrometry, respectively, for 60 of the samples.

Results: Leptin and adiponectin levels were higher in POMS patients versus controls, mainly in non-obese patients. Leptin and FABP4 levels were higher in females and inversely for adiponectin. There was a trend in POMS patients toward a higher proportion of NK cells, and lower of active testosterone (DHT).

Conclusions: The depletion in DHT in boys, the increase in NK cells and in adipokines are the basis for opening the field of therapeutics (testosterone, targeted therapies on NK and adipokines?) to POMS. Larger scale studies are needed to confirm these findings.

Keywords:
obesity, sex hormones, NK cells, adipokines, pediatric onset multiple sclerosis

EPNS21-639 Oral or poster
Inflammatory Disease of the CNS

Central nervous system manifestations of LRBA deficiency

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Objective: LPS-responsive beige-like anchor protein (LRBA) deficiency is a primary immunodeficiency disease (PID) characterized by a regulatory T-cell defect resulting in immune dysregulation and autoimmunity. We present two siblings born to consanguineous parents of North African origin with LRBA deficiency and central nervous system (CNS) manifestations, and compared our findings with available literature.

Methods: The younger brother presented with enteropathy at age 1.5 years, and subsequently developed Evans syndrome and diabetes mellitus. These autoimmune manifestations led to the genetic diagnosis of LRBA deficiency through whole exome sequencing with PID gene panel. At 11 years old he had two tonic-clonic seizures. MRI of the brain showed multiple FLAIR-hyperintense lesions and a T2-hyperintense lesion of the cervical medulla.

His sister presented with immune cytopenia at age 9 years, and developed diffuse lymphadenopathy and interstitial lung disease. Genetic testing confirmed the same mutation as her brother. At age 13 years, in a work-up of new lung lesions, a brain MRI showed multiple T2/FLAIR-hyperintense lesions. She received an allogeneic hematopoietic stem cell transplantation (allo-HSCT) 3 months later. Follow-up MRI showed regression of these lesions.

We performed a PubMed literature review to compare our findings to those previously published.

Results: Neurological disease is documented in 12-23% of patients with LRBA deficiency. Manifestations range from cerebral granulomas to transverse myelitis but detailed descriptions of neurological and imaging phenotypes are lacking.

Conclusions: PID such as LRBA deficiency should be part of the differential diagnosis in patients with inflammatory brain lesions. We strongly advocate for a more detailed description of CNS manifestations in patients with LRBA deficiency, when possible with MRI footage. This will aid clinical decision making with respect to both anti-infectious and anti-inflammatory therapy and in considering the indication for allo-HSCT.

Keywords:
LRBA, primary immunodeficiency disease, PID

EPNS21-682 Poster only
Inflammatory Disease of the CNS

United Kingdom experience of COVID-19 in children treated with immunomodulatory therapies for demyelinating disorders

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Objective: Paediatric neurologists are concerned about the risk of COVID-19 in children with demyelinating disorders receiving immunomodulatory treatment. To evaluate this we collected data via the UK Childhood Neuro-Inflammatory Disorders (UK-CNID) network of the British Paediatric Neurology Association (BPNA).

Methods: Survey of paediatric neurologists managing UK patients with a demyelinating disorder [Multiple sclerosis (MS); Neuromyelitis Optica Spectrum Disorder (NMOSD) and Myelin Oligodendrocyte Glycoprotein Antibody Disease (MOGAD)] on immunomodulatory therapy with SARS-CoV-2 infection confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) on nasopharyngeal swabs between March 2020 and September 2021.

Results: Of 151 UK children (MS 98, MOGAD 37, NMOSD 16), twenty-two (4 male:18 female) with a median age of 16 (range 6-19 years) had a positive PCR for SARS-CoV-2. Sixteen had MS and six had MOGAD. Ten were white; seven were Asian or South Asian; one was mixed Caucasian/south-Asian; one was North African; three were Black (two Afro-Caribbean; one Black African). Two were asymptomatic; two required brief hospital admissions for respiratory symptoms; eighteen had mild symptoms including fever, cough, and headache. MOGAD patients were receiving; combination of oral prednisolone and intravenous immunoglobulin (n=2), prednisolone (n=2), and azathioprine (n=2). MS patients were on the following immunomodulation: ocrelizumab (n=7); natalizumab (n=2); teriflunomide (n=1); dimethyl fumarate(n=2); fingolimod (n=1); interferon-beta (n=1); glatiramer acetate (n=1); prednisolone(n=1).

Conclusions: Compared to adult patients, who often have underlying co-morbidities and advanced neurological disabilities, we have identified that children treated for demyelinating disorders appear to have a milder COVID-19 course. Whilst the number of children treated for demyelinating disorders that developed COVID-19 is low, the outcomes described should provide reassurance to neurologists, patients and families.

Keywords:
COVID-19, demyelination, Multiple sclerosis, MOGAD, MOG, NMOSD

EPNS21-184 Oral or poster
Epilepsy: Medical & Surgical Treatment

N-of-1 trial Recommendations for Precision Treatments in Monogenic Epilepsies

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Objective: Up to a quarter of severe childhood epilepsies result from single-gene mutations. This discovery has laid the groundwork for precision medicine targeting the underlying genetic etiology in these epilepsies. While several centers offer precision treatments to individual patients, a common therapeutic or monitoring approach is lacking and clinical trials are hampered by interpatient heterogeneity and low disease prevalence. N-of-1 trials address this problem by considering individual patients as the sole unit of observation in establishing the efficacy or side-effect profiles of different interventions.

Methods: A retrospective study including patients with monogenic epilepsies who have been treated with precision therapies will be performed in collaboration with the European Reference Network for rare and complex epilepsies, EpiCARE. This registry will help define patient populations that could benefit from precision treatments and assist in the design of future efficacy studies. Based on the results of this survey, an n-of-1 ethical and methodological framework tailored to different monogenic epilepsy phenotypes and treatment characteristics will be developed.

Results: This abstract concerns the study setup. The expected result of this project will be a methodological framework for the use of tailored n-of-1 trial approaches. This will include a set of eligibility criteria, treatment regimens, as well as, pre-defined baseline and outcome measurements. Implementation of this framework will harmonize data collection for monogenic epilepsies and allow pooling of safety and efficacy data of precision treatments.

Conclusions: The results of this project will provide a basis for the choice of appropriate trial designs for precision therapies in monogenic epilepsies in order to provide high-quality evidence for treatment recommendations.

Keywords:
monogenic epilepsy, precision treatment, re-purposed therapy, single-patient trials, n-of-1 trials

EPNS21-2044 Oral or poster
Neuromuscular

Startle responses in Duchenne muscular dystrophy: a novel biomarker of brain dystrophin deficiency

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Objective: Duchenne muscular dystrophy (DMD) is characterised by loss of dystrophin in muscle, as well as a variable degree of central nervous system (CNS) co-morbidities. A DMD mouse model (mdx) exhibits exaggerated startle responses to threat, which normalise with postnatal dystrophin-restoration therapies. A pathological startle response is not a recognised feature of DMD and its characterisation has implications for improved clinical management and translational research. The aim was to investigate if abnormal startle responses are present in young males with DMD compared to controls using a fear-conditioning task.

Methods: Fifty-six males aged 7-12 years (31 affected boys, mean age 9.7±1.8 years; 25 controls, mean age 9.6±1.4 years), viewed trials of two neutral visual stimuli; one 'safe' cue presented alone, and one 'threat' cue paired with an aversive noise to enable conditioning of physiological startle responses (skin conductance response, SCR, and heart rate, HR). Retention of conditioned physiological responses was tested by presenting both cues without the aversive noise in an 'Extinction' phase. Outcomes were unconditioned SCR and change in HR to the initial 'threat' and acquisition and retention of conditioned responses. Neuropsychological measures and genotype associations were also obtained.

Results: The mean unconditioned SCR was greater in the DMD group than Controls (mean difference 3.0µS, 95%CI (1.0, 5.1); P=.004), associated with a significant threat-induced bradycardia only in the patient group (mean difference -8.7bpm, 95%CI (-16.9, -0.51); P=.04).

Conclusions: This study provides the first evidence that boys with DMD show similar increased unconditioned startle responses to threat to the mdx mouse. Our study provides new insights into the neurobiology underlying the complex neuropsychiatric co-morbidities in DMD and defines an objective measure of this CNS phenotype, which will be valuable for future CNS-targeted dystrophin-restoration studies.

Keywords:
Duchenne Muscular Dystrophy; Dystrophin; Brain; Fear conditioning; Anxiety

EPNS21-2049 Oral or poster
Genetics

MitoPhen: A human phenotype ontology-based tool to identify mitochondrial DNA disease

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Objective: To build a manually curated database of mitochondrial DNA (mtDNA) disease phenotypes and genotypes, using the human phenotype ontology (HPO).
To use this database to identify patients with mtDNA disease in large rare disease sequencing projects.

Methods: We independently reclassified mtDNA variants from MITOMAP and ClinVar through online literature review of pathogenicity criteria.
The literature on each pathogenic variant was manually curated to provide individual-level phenotype-genotype data in a relational database called MitoPhen.
Phenotype similarity scores were performed between probands in MitoPhen and patients with confirmed mtDNA diseases and individuals with a non-mitochondrial nuclear genetic disorder enrolled in the NIHR BioResource Rare Diseases study and the Solve-RD research project.

Results: 89 mtDNA variants (4 indels, 85 single nucleotide variants), fulfilled criteria for pathogenicity. 676 publications were used to populate MitoPhen. We curated data from 6688 individuals, 3696 (55%) were recorded as clinically affected. 1349 (20%) are affected patients with Paediatric-onset disease. The mean number of terms per proband is 11.4.
Using mean phenotype similarity scores computed through MitoPhen, we were able to show that patients with mtDNA disease could be distinguished from non-mitochondrial rare diseases (including other neurodevelopmental disorders). There was no statistically significant difference between phenotype similarity scores computed for adult-onset and paediatric-onset mtDNA disease patients.

Conclusions: Current variant annotation pipelines in rare disease sequencing projects are supplemented by HPO analyses, however a reference phenotype dataset for mtDNA disease does not exist.
MitoPhen, found at www.mitophen.org, provides the first manually curated database for mtDNA disease that could be used to discover mtDNA diagnoses in large sequencing projects. Further work is needed to enrich the database with rare pathogenic variants.

Keywords:
Mitochondrial disease, MtDNA, Rare disease, Variant, Pipeline

EPNS21-2064 Oral or poster
Genetics

Childhood onset chorea: an overview of genetic etiologies in a series of 85 patients

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Objective: Chorea is a kyperkinetic movement disorder (MD), the third most frequent MD in children, after tics and dystonia. It is characterized by random, continuous and brief involuntary movements. Onset may be acute or early with chronic evolution. Regarding the etiologies, chorea is either acquired or genetic. Autosomal dominant NKX2-1 related chorea is the most frequent cause in children, in which the MD may be associated with hypothyroidism or pulmonary disorders. More recently, other genes have been identified (ADCY5, GNAO1, etc..).
Objective: To assess the genetic epidemiology of childhood onset chorea.

Methods: We reviewed the clinical history of 85 patients with early onset chorea (<2y), initially referred for NKX2-1 analysis (2011-2019). Patients with a confirmed clinical diagnosis of chorea, absent or mild ID, and negative NKX2-1 screening, were analysed using first a NGS targeted panel (104 MD genes), and then exome or genome sequencing.

Results: After clinical review, 75 patients were included. 34 were related to NKX2-1 pathogenic variants or deletions. 3 had a clinical diagnosis of kernicterus or choreiform tics. Panel analysis allowed the identification of causal variants in 45% non-NKX2-1 patients (16/38), and exome/genome sequencing in 4. ATM, ADCY5 and GNAO1 were the most frequent genes after NKX2-1. A surprising diagnosis of glutaric aciduria was made in a 70-year-old patient emphasing the need to carefully look at the MRI. Chorea was a milder phenotype or onset presentation of known pathologies related to KMT2B, GNB1 (mosaicism), PDE10A, or GRIA3 for example.

Conclusions: We identified a genetic cause in 72% patients of the series, NKX2-1 being the major gene (45%). NGS panel was a performant tool, allowing also diagnosis of mosaicism and deletions, simpler than exome analysis. Etiological diagnosis of chorea is important for genetic counseling, etiological treatment if available, and management of possible associated complications like cancer (NKX2-1, ATM).

Keywords:
Chorea, genetic, movement disorders, NKX2-1, NGS panel

EPNS21-2070 Oral or poster
Neuromuscular

Carriers in XL-MTM: a spectrum extending from asymptomatic carriers to severely affected patients - Results of an international questionnaire study

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Objective: The mode of inheritance of X-linked myotubular myopathy (XL-MTM) is currently considered recessive and the proportion of manifesting carriers is assumed low.
We aimed to characterize the spectrum of clinical signs and symptoms in a cohort of female XL-MTM carriers, including prevalence, genetic features and associated disease burden.

Methods: We performed a cross-sectional online questionnaire study among XL-MTM carriers, recruiting from patient associations, medical centres and registries in the United Kingdom, Germany and the Netherlands. We used a custom-made questionnaire, the Checklist Individual Strength (CIS), the Frenchay Activities Index (FAI), the SF-12 Health Survey and the McGill Pain Questionnaire (MPQ). Carriers were classified as manifesting or non-manifesting, based on self-reported ambulation and muscle weakness.

Results: The prevalence of manifesting carriers in this study population (n=76) was 51%, subdivided into mild (independent ambulation, 39%), moderate (assisted ambulation, 9%) and severe (wheelchair-dependent, 3%) phenotypes. In addition to muscle weakness, manifesting carriers often reported fatigue (70%) and exercise intolerance (49%). Manifesting carriers scored higher on the overall CIS ($p=0.001$), the fatigue sub-scale ($p<0.001$) and least severe pain sub-scale ($p=0.005$) than non-manifesting carriers. They scored lower on the FAI ($p=0.005$) and the physical component of the SF-12 Health survey ($p<0.001$).

Conclusions: The prevalence of manifesting female XL-MTM carriers may be higher than currently assumed, most having a mild phenotype and a wide variety of symptoms. Manifesting carriers are significantly affected by fatigue, limitations of daily activities, pain and reduced quality of life. The large percentage of manifesting carriers may indicate that inheritance of this X-linked disorder is not strictly recessive and symptomatic carriers are to be considered. Our findings should raise awareness and offer useful information for health care providers and clinical trials.

Keywords:
centronuclear myopathy, myotubular myopathy, XL-MTM, female carrier

EPNS21-2073 Oral or poster
Movement Disorders

KMT2B variants associated with freezing of gait and altered DAT Scan in deep brain stimulation treated patients

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Objective: Mutations in KMT2B gene were identified in individuals with pediatric-onset complex dystonia. We report on KMT2B variants associated with freezing of gait (FOG) and altered DAT Scan in deep brain stimulation (DBS) treated patients.

Methods: A group with DYT-KMT2B due to loss-of-function variants and refractory dystonia to medications (including L-dopa) received internal globes pallidums DBS. Patients underwent brain SPECT for 123Ioflupane (DaTScan) imaging.

Results: Five patients (4 female) presented with severe, persistent, complex generalized dystonia including laryngeal dystonia. The mean age at dystonia onset was 3.6 years and median age at DBS implant 23 years. They were followed post-DBS for a median of 14.5 years. The five maintained significant benefit from DBS, except for laryngeal dystonia and gait
FOG was documented in all, occurring from 14-43 years of age (1-15.5 years after GPi-DBS). DaTscan was abnormal in 4/5 patients undertaken from 2.5 years before, to 24 years after DBS insertion. Prior to DBS, dystonia was unresponsive to L-dopa in all subjects, as was FOG post-DBS in 2/5. Only 1/5 has maintained independent gait at last follow-up, despite 4/5 having recovered autonomous gait at steady state under DBS.
In this DYT-KMT2B group, FOG occurred from an early post-operative presentation at one year, to more than 15 years after DBS insertion. All patients had protein-truncating variants. To date, FOG has not been reported in patients with missense variants. Our finding of bilateral short putamen on DaTscan is suggestive of striatal dopaminergic denervation in DYT-KMT2B.

Conclusions: The potential risk of hypokinetic gait disorders in DYT-KMT2B should be considered in patients undergoing GPi-DBS, which warrants strict monitoring of the motor phenomenology post-procedure. Serial DaT SPECT imaging may aid identification of striatal dopaminergic denervation in DYT-KMT2B. As for other dystonias, the relationship between DYT-KMT2B, FOG and DBS intervention remains yet to be fully elucidated.

Keywords:
KMT2B, freezing of gait, DaTscan, deep brain stimulation

EPNS21-341 Poster only
Epilepsy: Medical & Surgical Treatment

Epilepsy surgery in patients with Sturge-Weber Syndrome: a Tertiary Center experience.

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Objective: Epilepsy surgery is an established treatment option for children with pharmacoresistant focal epilepsy. We report clinical data and seizure outcomes of children with Sturge-Weber Syndrome (SWS) undergoing epilepsy surgery.

Methods: We retrospectively reviewed a cohort of patients with a diagnosis of SWS undergoing epilepsy surgery between September 2008 and October 2020. We collected patient demographics, clinical details, type of surgery and the post-surgical outcome at the last follow-up.

Results: 13 patients (8 males) with an year-long minimum follow-up were identified: 4/13 (30.8%) children showed type III SWS, while 9/13 (69.2%) were affected by type I SWS. Klippel Trenaunay syndrome affected 3/13(23.1%). Mean age at seizure onset was 10.2 months (range 1-21). Most common was seizure onset in the first 12 months of life (9/13, 69.2%) and presentation with focal motor seizures with or without secondary generalization (11/13, 84.6%). Epileptic spasms were seen in 3/13(23.1%), while oro-alimentary automatisms in other 3 cases and hypotonia in 1/13 (7.7%). A history of status epilepticus was reported in 11/13 (84.6%). Pre-surgery developmental impairment was present in 8/13 (61.5%). Surgical procedures performed at mean age 7.0 years (range 2-30) were: hemispherotomy or hemispherectomy in 4/13 (30.8%), a less extensive focal resection or disconnection in 9/13 (69.2%). Postoperative complications requiring surgical management occurred in 1/13 (7.7%) due to hydrocephalus. Median post-surgical follow-up was 5.7 years (range 1-13). The seizure outcomes at last follow-up were Engel I class in 10/13 (76.9%) (9 cases IA, 1 case IC), Engel III class in 2/13 (15.4%) and Engel IV class in 1/13 (7.7%). After surgery, none of them experienced further cognitive decline.

Conclusions: In this case series of patients with SWS, the majority had a good seizure outcome (Engel class I) following epilepsy surgery.

Keywords:
Sturge-Weber syndrome, epilepsy surgery, outcome

EPNS21-143 Oral or poster
Genetics

Gene variant effects across sodium channelopathies predict function and guide precision therapy

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Objective: Variants in the voltage-gated sodium channel family (SCNs) lead to epilepsy, neurodevelopmental disorders, cardiac arrhythmias, skeletal muscle channelopathies and peripheral neuropathies. As functional effects of variants can guide therapy, we investigated whether similarities in biophysical properties between different SCN-gene paralogs can predict function and inform precision treatment.

Methods: We performed a systematic literature search identifying functionally assessed variants within all genes in the SCN-family until 28 April 2021. We included missense variants that had been electrophysiologically characterised in whole-cell patch-clamp recordings. We performed an alignment of linear protein sequences of all sodium channel genes and correlated variants by their overall functional effect.

Results: Of 951 identified records, 437 variants met our inclusion criteria. 146 variants were epilepsy-associated (SCN1/2/3/8A), 83 had a neuromuscular phenotype (SCN4/9/10/11A), 148 had a cardiac phenotype (SCN5/10A) and 60 (14%) were assumed benign. We detected 39 pairs of missense variants with an identical disease-associated variant in a different SCN-gene. Missense variants in each pair (35/39 = 92%) produced similar functional effects. Pathogenic missense variants clustered in specific functional domains, whereas population variants were more frequent across non conserved domains (odds ratio = 16.4; 95% CI = 9.9 to 29.1; P<0.001). Pore-loop regions were frequently associated with loss-of-function variants, inactivation sites were associated with gain-of-function (odds ratio = 33.8, 95% CI = 12.4 to 93.7; P<0.001) and variants in voltage-sensing regions comprised a range of gain- and loss-of-function effects.

Conclusions: Our findings suggest that functional characterisation of variants in one SCN-gene can predict channel function across different SCN-genes where experimental data are unavailable. Knowledge of the underlying channel function can aid variant analysis and guide precision therapy.

Keywords:
SCN1A; SCN2A; SCN4A; SCN5A; SCN8A

EPNS21-2035 Oral or poster
Neuromuscular

Motor unit changes in children with symptomatic spinal muscular atrophy treated with nusinersen

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Objective: To elucidate the motor unit response to intrathecal nusinersen in children with symptomatic spinal muscular atrophy (SMA) using a novel motor unit number estimation technique.

Methods: MScanFit MUNE studies were sequentially undertaken from the abductor pollicis brevis muscle after stimulation of the median nerve in a prospective cohort of symptomatic children with SMA, undergoing intrathecal treatment with nusinersen at a single neuromuscular centre from June 2017 to August 2019. Electrophysiological measures included compound muscle action potential (CMAP), motor unit number estimation (MUNE), motor unit number contributing to 50%-100% of CMAP (N50) and measures of collateral reinnervation including largest single motor unit potential (LSMUP) and amplitude of the smallest unit contributing to N50 (A50).

Results: Twenty children (median age 99 months, range 4-193) were followed for a median of 13.8 (4-33.5) months. Therapeutic intervention was an independent and significant contributor to an increase in CMAP ($p = 0.005$), MUNE ($p = 0.001$) and N50 ($p = 0.04$). The magnitude of this electrophysiological response was increased in children with shorter disease durations ($p<0.05$). Electrophysiological changes delineated children who were functionally stable from those who attained clinically significant gains in motor function.

Conclusions: Nusinersen therapy facilitated functional innervation in SMA through recovery of smaller motor units. Delineation of biomechanisms of therapeutic response may be the first step in identifying potential novel targets for disease modification in this and other motor neuropathies. MScanFit MUNE techniques may have a broader role in establishing biomarkers of therapeutic response in similar adult-onset diseases.

Keywords:
motor unit number estimation, spinal muscular atrophy, nusinersen, biomarker

EPNS21-440 Poster only
Genetics

Clinical spectrum familial IQSEC2 pathogenic sequence variant

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Objective: Describe the clinical spectrum of a pathogenic variant of *IQSEC2* in four affected maternal half-siblings.

Methods: In this retrospective, descriptive, observational study we report four siblings with the c.3433C>T pathogenic variant in *IQSEC2* gene causing the premature stop signal p.Arg1145Ter. The index case was analyzed by whole exome sequencing. Rest of them were studied by Sanger sequencing. We recollected the clinical data by analyzing the medical reports. We also describe the clinical manifestations of the mother, obligate carrier.

Results: Four patients with *IQSEC2* mutation were identified, 3 males and 1 female. The mother refused to perform genetic testing. The c.3433C>T pathological variant led to premature truncation.
Global delay development was present in all cases before the onset of epilepsy. The mean of the seizure onset was 15 months (range 2-25). Seizure types were mostly generalized (tonic, absence, tonic-clonic). EEG recordings showed background slowing in most of them. Boys had more epileptiform activity and refractory epilepsy than female. All siblings were nonverbal. Motor impairment was more severe in males, they couldn't walk independently. Mother's neurodevelopment was normal, but psychiatric symptoms started at 13 years old (borderline personality disorder was diagnosed later) and onset generalized epilepsy at 15.

Conclusions: Although previous studies reported truncating variants were mostly de novo, supposedly because they are worse tolerated in female carriers, it is not the pattern in our family. As literature described, males and females are both affected, although with worse outcomes for males. Moreover, given the phenotypic variability between mother and daughter and that this gene escapes X-inactivation, we hypothesize a possible somatic mosaicism in the mother, although epigenetic factors or another expression regulatory mechanisms could be alternative explanations of the clinical differences between them.

Keywords:
IQSEC2, affected females, escape X-inactivation, developmental and epileptic encephalopathy

EPNS21-491 Oral or poster
Genetics

Genetic evaluation of older children with Learning Disability and Epilepsy

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Objective:
To undertake an evaluation of genetic testing in children and young people with learning disability and epilepsy and establish the benefits of revisiting investigations with currently available genetic tests.
The prevalence of epilepsy in those with mild to moderate LD is 15% and severe to profound LD is 30% to 50%.
Several aetiological pathways contribute to the co- occurrence of these two conditions. Advances in the field of genetics are contributing to identifying further common denominators.
The ILAE classification of epilepsies includes aetiology, emphasizing the need to determine the cause.
Large population based studies have been conducted to understand the genetic aetiologies for early onset epilepsies and developmental disorders, but studies that include older children with LD, who later develop epilepsy and have undergone genetic testing to unify their diagnosis are limited.

Methods: Traditional tests for children who presented with developmental difficulties were karyotype and Fragile X test. This was superseded by array CGH. Further testing was not always explored despite advances in genetics even when they developed co-morbid conditions such as epilepsy.
Epilepsy gene panel testing was made available in Wales in 2018. Since then we have been undertaking genetic re-evaluations of our patients with unexplained epilepsy and LD and requesting an epilepsy gene panel.

Results: The diagnostic yield from testing 20 children has been 20%. Mutations such as GRIN2A, SLC6A1 and SCN1A were found in patients with long standing epilepsy and LD. The result came as a relief to the families; provided insight into child's diagnosis, facilitated genetic counselling, guided treatment and aided further assessments for wider family.

Conclusions: This has radically changed our practice and it is vital that clinicians revisit the history and investigations in older children with learning disability and co-occurring epilepsy to explore if they would benefit from the currently available genetic tests.

Keywords:
Genetics, epilepsy, learning disability

EPNS21-568 Oral or poster
Genetics

Non-coding MLC1 variants causing megalencephalic leukoencephalopathy with subcortical cysts

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Objective: Reaching a genetic diagnosis in a patient with classical megalencephalic leukoencephalopathy with subcortical cysts (MLC) phenotype and negative whole exome sequencing.

Methods: 7 year-old boy, first seen for evaluation of macrocephaly at age 9 months. Development was age-appropriate and the neurological exam did not disclose abnormalities except for head circumference of 51,5 cm (+4 SD). Brain MRI showed diffuse cerebral and brainstem white matter T1 hypointensity and T2 hyperintensity, as well as anterior bitemporal subcortical cysts. Trusight One Sequencing panel (TSO, Illumina), WES, WGS and functional validation were sequentially performed.

Results: NGS studies (TSO, WES) in 2015-2016 did not reveal pathogenic variants in MLC1, GLIALCAM or other genes relevant for patient's phenotype. Whole genome sequencing was then performed and scrutiny of MLC1 intronic regions uncovered the compound heterozygous candidate variants NM_139202 c.597+37C>G and c.-195T>C (5'UTR). Segregation analysis of the variants was consistent with a recessive mode of inheritance. A minigene splicing assay showed that the c.597+37C>G variant alters the splicing and creates two novel major isoforms that include 159 or 168 bp of intron 7, leading to in-frame insertions of 53 or 56 amino acids and likely the disruption of one of the MLC1 transmembrane domains. The c.-195T>C is evolutionarily conserved and up to six diferent algorithms of in silico predictors indicate a damaging effect on the protein. The patient continues to show normal global development, macrocephaly and fine and gross motor clumsiness on exam. A brother born in 2021 after genetic counselling and prenatal diagnosis of non-carrier status does not show any MLC signs.

Conclusions: As proved by WGS analysis in our patient, phenotype-driven analysis of genomic data is crucial for diagnosis. MLC can be caused by deep intronic splice variants, thus opening the way to variant-specific therapies such as antisense oligonucleotide-mediated splice modulation.

Keywords:
MLC1, splicing, intronic variant

EPNS21-673 Oral or poster
Genetics

A novel missense variant resulting in autosomal recessive IFNAR2 deficiency

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Objective: Type I interferons (IFN-I) play a critical role in human antiviral immunity, as demonstrated by exceptionally rare inborn errors of IFNAR1 or IFNAR2.

We investigated a boy from the Arctic circle presenting with meningoencephalitis following live-attenuated viral vaccination.

Methods: We here present experimental studies on Peripheral Plood Mononuclear Cells (PBMC) and fibroblasts from the boy. We found novel missense IFNAR2 variant, S53P, and experimentally demonstrate its causal relationship to AR IFNAR2 deficiency

Results: Whole exome sequencing identified homozygous single nucleotide variant in IFNAR2, predicted to produce a missense substitution of proline for serine at position 53 (c.157T>C, p.Ser53Pro).
The substitution yielded expression of a less abundant, aberrantly N-glycosylated IFNAR2 protein that was not expressed at the cell-surface. Cells bearing S53P in the homozygous state lacked responses to recombinant IFN-I and displayed heightened vulnerability to multiple viruses - a phenotype rescued by wild-type IFNAR2 complementation.

Although absent from reference databases, further analysis identified this variant at a minor allele frequency (MAF) of 0.024-0.034 in over 5000 Inuit genomes.

Conclusions: The clinical phenotype highlights several emergent phenotypic characteristics of AR IFNAR deficiency, namely susceptibility to life-threatening complications of live attenuated vaccines and hyperinflammation. Further, our study extends the clinical phenotype of AR IFNAR2 deficiency to include evidence of vulnerability to naturally acquired viruses, including HSV1, and highlights the clinical importance of pursuing functional studies of missense variants of uncertain significance.

The distribution of this variant across the circumpolar region suggests the possibility of a founder mutation.

This novel cause of AR IFNAR2 deficiency reinforces the essential role of IFN-I in control of live-attenuated viral vaccine(s) and may have public health significance for this population.

Keywords:
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EPNS21-223 Oral or poster
Metabolic Disorders

Age and sex distribution in patients in a registry for Vanishing White Matter

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Objective: Vanishing White Matter (VWM) is a leukodystrophy, characterized by chronic neurologic deterioration and stress-provoked episodic decline. The age of onset (AoO) ranges from infancy to adulthood. Early onset is associated with mostly motor dysfunction, severe disease course and early demise, whereas adult onset is associated with mostly cognitive problems, slow decline and long survival. We set up a registry to study the natural clinical course of VWM in more detail.

Methods: Genetically confirmed VWM patients were included in a registry. We collected information with customized and standardized questionnaires. Patients were stratified based on the AoO: group 1 (<1 year), 2 (1-<2 y), 3 (2-<4 y), 4 (4-<8 y), 5 (8-< 18 y), and 6 (>18 y). Descriptive statistics were used to present demographic data.

Results: A total of 383 patients (47% male (M)) were included, and divided in group 1 (12%, 60% M), 2 (16%, 53% M), 3 (28%, 43% M), 4 (20%, 53% M), 5 (10%, 47% M), and 6 (13%, 27% M). AoO varied from 0 to 55 years. 129 patients were deceased, of whom 81% had an AoO <4 years. Of the remaining 249 patients, the median current ages for each group were: 12.4 y (75% M), 15.2 y (49% M), 17.3 y (41% M), 22.7 y (55% M), 31.1 y (50% M), 54.8 y (28% M). Overall, 66% of living patients are currently older than 18 years (42% M).

Conclusions: Our data confirm the wide age distribution in VWM. As onset in childhood is most common, VWM is generally considered a pediatric disorder. However, a large proportion of the patients reaches adulthood and most surviving patients are adult. Patients with adult onset are more commonly female. These data underscore the need to consider adult VWM patients for therapeutic trials. The VWM Registry can aid in making informed decisions when designing trials and for preselecting eligible patients.

Keywords:
leukodystrophy, vanishing white matter, natural history, registry

EPNS21-245 Oral or poster
Metabolic Disorders

Natural MRI history in Vanishing White Matter

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Objective: Vanishing white matter (VWM) is a leukodystrophy, characterized by chronic neurological decline and stress-provoked episodes of rapid, partially transient decline. Earlier onset is associated with faster progression. Radiological hallmarks are rarefaction and cystic decay of the cerebral white matter (WM). Information on clinical-radiological correlation is lacking.

Methods: We retrospectively scored MRI scans of genetically confirmed VWM patients. Patient records were reviewed for information, such as age at onset and episodic decline. The ventricle-to-skull ratio was measured to estimate brain atrophy. Cerebral WM was visually scored on FLAIR images as normal, hyperintense, rarefied or cystic in percentage of the total volume and converted into a WM decay score. Cerebral WM was also segmented into normal-appearing, FLAIR-hyperintense, and rarefied or cystic WM (FLAIR-hypointense). Cerebellum, brainstem, thalamus and basal ganglia were scored as normal or T2-hyperintense.

Results: 485 scans of 277 patients were available. Cerebral WM was always abnormal, even in presymptomatic patients. Earlier onset was related to higher rarefied or cystic WM volume [$F(5)=13.3$; $P<.001$], higher WM decay score [$F(5)=4.68$; $P<.001$], and faster progression of the WM decay score [$b=-1.6$, $t(109)=-3.9$; $P<.001$]. Later onset was associated with more cerebral atrophy [$F(5) = 8.42$; $P < .001$]. Cerebral WM never improved over time.
Patients with acute episodes more often had diffuse T2-hyperintensities in the brainstem, thalamus and/or basal ganglia. These appeared with acute decline and mostly resolved over time.

Conclusions: Cerebral WM abnormalities never improve and likely reflect the chronic aspect of VWM. Signal abnormalities in brainstem, thalamus and basal ganglia appear with rapid decline and mostly resolve; they likely reflect the acute episodes. These insights are essential for proper interpretation of MRI findings. Insight in the natural MRI history is crucial in upcoming trials.

Keywords:
Leukodystrophy, MRI, Vanishing white matter

EPNS21-283 Oral or poster
Metabolic Disorders

A nation-wide study of neuroimaging findings in pyruvate dehydrogenase complex (PDHc) deficiency-novel presentations

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Objective: Pyruvate dehydrogenase complex (PDHc) deficiency is a major cause of primary lactic acidosis in children. This nationwide population-based study sought to systematically describe the neuroradiological spectrum of the disease and its development over time.

Methods: The patients were recruited from a nation-wide population-based study. All patients with a genetically confirmed diagnosis that had been investigated with an MRI of the brain were included. The MRI investigations were re-evaluated by a child neuroradiologist, and a pediatric neurologist, using a standardized evaluation form.

Results: MRI investigations had been performed in 34 patients. Prenatal developmental lesions were most often presented as corpus callosum abnormalities while prenatal clastic lesions were more frequently presented as ventriculomegaly and intraventricular membranes. Leigh-like lesions with predominant involvement of globus pallidus were present in 12, while leukoencephalopathy was present in six and stroke-like lesions in three individuals. A combination of prenatal developmental and clastic lesions was present in 15 individuals. In addition, one male with PDHA1 also had postnatal clastic lesions.

Conclusions: The most frequent findings in our study were agenesis or hypoplasia of corpus callosum, ventriculomegaly or Leigh-like lesions. In addition, we identified a broader spectrum of MRI changes that include leukoencephalopathy and stroke-like lesions. Furthermore, the presence of lesions on MRI that have occurred during different phases of brain development should suggest the possibility of PDHc deficiency.

Keywords:
pyruvate dehydrogenase complex deficiency, magnetic resonance imaging, stroke-like lesions, leukoencephalopathy, Leigh-like lesions

EPNS21-557
Metabolic Disorders

Oral or poster

A new era in the treatment of neuropediatric disorders: n-of-1 trials. The usefulness of personalized medicine in the diagnosis and management of the disease.

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Objective: To study in a personalized way a selection of patients to either advance and conclude on their diagnosis or propose a personalized treatment strategy based on their pathophysiology.

Methods: Diagnosis was based on the clinical presentation and Whole Exome Sequencing. When needed, the genetic diagnosis was validated with Western Blot or Immunofluorescence. Finally, when a therapeutic target was identified, ad hoc lab studies were carried out to study the response of patient cells to the treatment, ranging from mitochondrial or autophagy measures (ATP production, ROS metabolism, mitochondrial dynamics, network formation, lysosomal biogenesis and cellular localization, etc) to specific metabolic routes evaluation.

Results: To illustrate this approach to the diagnosis and treatment of neuropediatric diseases we present a selection of over 15 patients studied over the last year. All the patients were referred to our service due to a complex neurological presentation -including paediatric parkinsonism and movement disorders, and/or suggestive of neurotransmitter defects. The selection of patients include defects on neurotransmission, mitochondrial and autophagy-related disorders, metabolic defects and transport disorders. Two main scenarios were faced:
a) molecular confirmation of a genetic diagnosis for discordant presentations: These cases conclude with both the confirmation of the patient's diagnosis and description of either a new disease or a new presentation of a known disease.
b) proposal of new therapeutic targets: n-of-1 trials. When an actionable target was identified, we defined a personalized project to test different interventions (either drugs or nutraceuticals) on patient cells, identifying the best option. The lab results were transferred to the clinic, designing a n-of-1clinical trial, altering the natural history of the disease.

Conclusions: Personalized and multidisciplinary study of the disease results in the identification of new therapeutic alternatives for neuropediatric disorders.

Keywords:
n of 1 trials, personalized medicine, treatment, synaptic metabolism

EPNS21-675 Oral or poster
Metabolic Disorders

MAPLE SYRUP URINE DISEASE: INSIGHTS FROM THE ELECTROENCEPHALOGRAPHIC PATTERN

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Objective: To describe EEG patterns in neonates with maple syrup urine disease (MSUD), in particular the frequency, specificity and temporal evolution of the unique Comb-like rhythm. To correlate the occurrence of this rhythm with leucine serum levels. Identification of early EEG patterns could help prompt diagnosis and treatment of patients MSUD, essential to prevent long-term sequelae.

Methods: Retrospective search of the EEG database and the metabolic database from 2002 to 2020 at Great Ormond Street Hospital (UK). All patents with a confirmed diagnosis of MSUD and at least 1 EEG recorded were included and their EEGs analysed. Leucine levels, measured on the same day of the recordings, were correlated to EEG findings.

Results: A total of 24 EEGs were analyzed from a cohort of 15 patients (5 females) aged between 6-83 days of life. EEG background activity was abnormal in all patients, with dysmaturity features. Electrographic seizures of delta frequency were recorded in 2 patients (8 and 15 days of life), involving parasagittal regions, with low seizure burden. Unique Comb-like pattern were found in 11 patients (67% of EEGs). It showed a unique evolution within the first 4 weeks of life: in the first days of life comb-like pattern seemed less marked and confined over the midline; later it increased, became more defined and spread to the central regions bilaterally. During the resolution it exhibited opposite trend tending less to spread and remaining confined over midline. No comb-like pattern were seen after 4 weeks. After its disappearance, transients and later a rhythmic delta-theta activity could be seen in the central regions. The mean leucine levels were higher in presence of Comb-like pattern at the EEG (p=0,01).

Conclusions: Comb-like rhythm has a high prevalence in the EEG of patients with neonatal onset MSUD. It is seen only during neonatal period and have a typical temporal evolution. Findings indicate that EEG is a valuable biomarker for the early diagnosis of MSDU.

Keywords:
MSUD, EEG, Comb-like pattern

EPNS21-717 Oral or poster
Metabolic Disorders

MAPLE SYRUP URINE DISEASE: INSIGHTS FROM THE ELECTROENCEPHALOGRAPHIC PATTERN

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Objective: The aim of this study were to (1) describe EEG patterns in neonates with maple syrup urine disease (MSUD), in particular the frequency, specificity and temporal evolution of the unique Comb-like rhythm and (2) to correlate the occurrence of this rhythm with leucine serum levels.

Methods: Retrospective search of the EEG database and the metabolic database from 2002 to 2020 at Great Ormond Street Hospital (UK). All patents with a confirmed diagnosis of MSUD and at least 1 EEG recorded were included and their EEGs analysed. Leucine levels measured on the same day were correlated with EEG findings.

Results: A total of 24 EEGs were analyzed from a cohort of 15 patients (5 females) aged between 6-83 days of life. The EEG background activity was abnormal in all patients, with excess of slow and dysmaturity. Two infants had seizures (electrographic seizures on 8 and 15 days of lifer respectively) involving parasagittal regions. Comb-like pattern were found in 11 infants (67% of EEGs). It showed a unique evolution within the first 4 weeks of life: in the first days of life comb-like pattern seemed less marked and confined over the midline; later it increased in frequency, became more defined and spread to the central regions bilaterally. Subsequenly an opposite trend was noted with less spread and pattern confined to the midline. No comb-like pattern were seen after 4 weeks. After its disappearance, transients and later a rhythmic delta-theta activity could be seen in the central regions. The presence of Comb-like rhythm were significantly associated with high serological levels of leucine ($p<0.01$).

Conclusions: Comb-like rhythm are a typical EEG pattern in neonates with early onset MSUD. They are only seen during the neonatal period and have a typical temporal evolution. Findings indicate that EEG is a valuable biomarker for the early diagnosis of MSDU.

Keywords:
MSUD, EEG, Comb-like pattern

EPNS21-17 Oral or poster
Cerebrovascular Disorders

An Experience in managing a childhood stroke case according to the new 2017 Stroke guideline: A DGH perspective.

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Objective: Childhood stroke, although rare, occurs and can cause significant long-term morbidity. Compared to adult's stroke, paediatric stroke is a heterogenous entity, both of aetiology and presentation. This makes accurate and timely diagnosis challenging. In 2017, new paediatric stroke guideline, endorsed by RCPCH/Stroke Association, was published to address these challenges.

Methods: We presented 2 similar cases of childhood stroke that happened before and after the publication of the guideline. The second case demonstrated how we adapted current guideline into management of the patient.

Results: Case 1 (2011): 3-year-old girl presented with inability to stand and left hand weakness while playing in the garden. Examination revealed weakness to both arm and leg, with facial droop. No history of trauma. CT head was reported to be normal. She was given aspirin and arranged for transfer to tertiary centre the day after for MR/MRA imaging which confirmed stroke.

Case 2 (2020): 3-year-old girl presented with left sided facial droop, weakness of left side of her body and slurred speech during family visit to the safari park. The new 2017 guideline was used to aid assessment and management. She scored 6 of PedNIHSS and both CT and CTA was normal. Her assessment and imaging was done within thrombolysis window (4.5 hours). She was transferred to tertiary centre afterwards. MRA confirmed right MCA territory acute infarct.

Conclusions: Despite the new stroke guideline, we encountered several challenges in managing the child in the DGH settings. The assessment and imaging were significantly delayed due difficulty in assessing children, unfamiliarity with the new guidelines, difficulty in reporting paediatric neuro-radiology imaging and absence of clear guidance with regards to thrombolysis in children.

As a result, a new regional local guideline is currently under development to create a pathway for assessment centre and decision making for administration of tPA.

Keywords:
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EPNS21-416 Oral or poster
Miscellaneous Topics

Acceptability and tolerability of Greater Occipital Nerve Block in the management of refractory headaches in children and adolescents

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Objective: To study the acceptability and tolerability of Greater Occipital Nerve Block (GONB) in the management of children and adolescents with difficult to treat headaches.

Methods: Children with headaches who failed conventional prophylactic treatments are offered GONB. Verbal explanation and written information about the procedure and possible side effects are given to the patients and their parents, verbal consent obtained. The procedure consists of cleaning the injection area with alcohol wipes, spraying the area with cold (Cryogesic) spray to numb the skin and injecting 1 ml of Depo-Medrone 40mg with Lidocaine 10mg at the occipital groove using a gauge 25 needle. An injection is given on one or both sides. Patients were assessed for effectiveness and side effects in 6 weeks and 3 months. We assessed acceptability and tolerability of the procedure by estimating the number of children who refused the treatment, the reaction at the time of treatment, reported side effects and willingness for a repeat injection if needed.

Results: Fifty-five children were offered GONB and 50 (91%) accepted and received treatment over a 3 year-period; 36 (72%) were female and mean age was 14y (range: 11-17y). Most of the children tolerated the procedure very well. One patient was not able to proceed due to significant anxiety, 2 children found it very painful and 2 patients fainted with full recovery within 30 minutes. Four children had local side effects such as stiff and sore neck, tenderness and infiltration at the site of injection, local hair loss. The majority (31 out of 32) of the children offered to repeat the procedure were happy to receive second injection including 6 patients who did not respond or only partially responded to the first GONB. 7 patients had the procedure repeated 3 times as the effect wears off in a few months time.

Conclusions: GONB is generally an acceptable treatment modality and is well tolerated by most of children and adolescents with refractory headaches.

Keywords:
Headache, children, adolescents, Greater Ocipital Nerve Block

EPNS21-563 Oral or poster
Cerebrovascular Disorders

Radiological Evidence of Neurological Injury Before and After Congenital Cardiac Surgery - A Systematic Review

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Objective: Neurological injury is a common finding following surgery for congenital heart disease (CHD), seen in 36-53% of patients. However, there is little uniformity on presentation of data around the risk of neurological injury following cardiac surgery, with definitions varying between centres. Furthermore, preoperative neurological injury, which may be seen in 26-44% of patients with CHD, is seldom taken into account.

This systematic review aims to compare rates of neurological injury, as determined by MRI changes, in patients with CHD preoperatively to rates postoperatively.

Methods: Papers were included for systematic review if they included congenital cardiac patients undergoing preoperative and postoperative MRI brain scanning, regardless of the aims of the studies. Papers published prior to 2001 were excluded due to advancements in intraoperative and perioperative management. Databases from Medline, Embase, NHS Journals and the Cochrane Library were searched. Eight studies met the inclusion criteria, with two studies being excluded due to age.

Results: For all studies, the rate of new or worsened neurological injury postoperatively was divided by the rate of injury preoperatively to give a risk ratio (RR). None of the RR reached clinical significance for new neurological injury, nor did the overall total (RR 1.08, 95% CI 0.84-1.39). One study looking exclusively at more complex cardiac surgeries showed a statistically significant increase in risk of severe neurological injury (RR 8, 95% CI 2.89-29.52). This meant the combined analysis of all studies also demonstrated an increased risk of severe injury (RR 5.33, 95% CI 1.96-35.67).

Conclusions: The data suggests that cardiac surgery does not, overall, increase risk of radiologically evident neurological injury, but that there is an increased risk of severe neurological injury following more complex congenital cardiac surgery. Further research is required to elicit to true impact on the developing brain of cardiac surgery and CPB.

Keywords:
Stroke, Acquired neurological injury, congenital cardiac disease

EPNS21-689 Poster only
Miscellaneous Topics

Impact and management of drooling in children with neurological disorders: An Italian Delphi consensus

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Objective: The rate of cronich drooling is 0.5% in the pediatric population, rising to 60% in children affected by neurological disorders. Despite the possible deterioration in the quality of life (QoL), the problem of sialorrhea remains neglected. We conducted an Italian study in order to discuss the current diagnostic and therapeutic paradigm of drooling in children with neurological disorders.

Methods: After a review of the literature, the Steering Committee, alongside a Board of 10 Experts, defined the statements to be discussed. The 15 statements covered three topics: clinical manifestations and QoL; quantification of drooling; therapeutic strategies. These were administered between March and April 2021 to a multidisciplinary panel of 55 Italian experts. The consensus considered reached when the sum of the disagreement or agreement was equal to or greater than 66%.

Results: All statements reached a positive consensus. It was agreed that sialorrhea should be assessed in all children with complex needs. More attention should be paid to investigating the presence of posterior hypersalivation. At present, only few scales to assess drooling are available and that limits the possibilities of monitoring the response to treatment. The shared therapeutic paradigm is progressive; treatment should follow a progressive pattern, with conservative approaches preceding pharmacological treatment.

Conclusions: This study demonstrates that a multidisciplinary approach to the management of drooling is of primary importance. At the national level, experts agree that progressive treatment can allow a reduction in the incidence of complications, improve the quality of life of patients and care providers, and save healthcare resources. Finally, this study the treatment strategy should be reconsidered over time according to the progression of symptoms and the specific needs of the patient.

Keywords:
drooling; therapy; neurological disorders; pediatrics; cerebral palsy; Delphi

EPNS21-107
Neuromuscular

Oral or poster

Decreased frequency of respiratory exacerbations in patients with spinal muscular atrophy treated with nusinersen

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Objective: Spinal muscular atrophy is an autosomal recessive inherited disorder characterized by degeneration of alpha motor neurons and resulting muscle wasting. Respiratory impairments are common and represent the major cause of morbidity in SMA patients. New disease-modifying therapies have altered the natural history of this disease and improved motor function and survival, but less is known about the effects on the respiratory system. The aim of this retrospective study was to investigate the effects of nusinersen treatment on respiratory function and frequency of exacerbations in patients with SMA.

Methods: The patients with genetically confirmed SMA, treated in our center, were included. They were studied by the multidisciplinary team and data was collected from the digital records and general pediatricians. The data was statistically analyzed based on the number of patients with all available data. The comparison before and after treatment was analyzed with Chi-square analysis and a p-value of 0.05 was considered statistically significant.

Results: 34 patients (age 10.7 ± 4.9) with SMA were included in the study. They all received nusinersen (10.5 ± 2.5 applications) and were closely monitored by pediatricians. After two years of treatment, they were stable in terms of respiratory support. There were significant differences in hospitalizations due to respiratory exacerbations or respiratory failure in the second year after treatment initiation ($p < 0.001$), although no significant differences were found in home antibiotic use, but there was a trend toward fewer events ($p=0.089$).

Conclusions: The results show a decrease in respiratory exacerbations and interventions after treatment with nusinersen. Improvement in pulmonary function/health is an important aspect of care for these patients and should be further investigated in larger studies that would allow evaluation of other parameters of lung function, such as spirometry and overnight polysomnography.

Keywords:
spinal muscular atrophy, nusinersen, respiratory interventions, treatment effect

EPNS21-138
Neuromuscular

Oral or poster

Design and Rationale of SMART, a Phase IIIb Study Evaluating Intravenous Onasemnogene Abeparvovec in Spinal Muscular Atrophy

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Objective: Onasemnogene abeparvovec (1.1×10^{14} vg/kg) is an approved spinal muscular atrophy (SMA) therapy, with the EU label recommending dosing in patients weighing up to 21 kg. Current clinical trial data include patients weighing ≤8.5 kg. Additional data for patients ≥ 8.5 kg to ≤21 kg are needed to complement emerging real-world use in heavier patients. SMART (NCT04851873) is an ongoing, open-label, single-arm, multicentre study to collect safety/tolerability data for onasemnogene abeparvovec in symptomatic SMA patients weighing ≥8.5 kg to ≤21 kg.

Methods: Approximately 24 participants will be enrolled across three weight groups: ≥8.5-13 kg, >13-17 kg, and >17-21 kg. The primary objective is to assess safety and tolerability over 12 months by evaluating treatment-emergent adverse events (AEs) and serious AEs, important identified and potential risks, and changes from baseline in vital signs, cardiac safety, and clinical laboratory assessments. Safety assessments are intended to characterize the known important identified and potential treatment-associated risks. Efficacy will be measured by motor milestone achievement and change from baseline in Hammersmith Functional Motor Scale-Expanded and Revised Upper Limb Module. Key exploratory endpoints include biomarkers, complement biomarkers, actimetry, humoral immunity, vector shedding, pulmonary and bulbar function, and caregiver burden/experience (ACEND PRO tool). Eligibility will be determined in the screening period. Patients will receive prophylactic prednisolone 24 hours before the infusion and for at least 30 days, followed by tapering. On Day 1, participants will receive a single intravenous administration of onasemnogene abeparvovec followed by in-patient safety monitoring for 48 hours. After study completion, participants will be eligible to enroll in a long-term follow-up study.

Results: Study is ongoing.

Conclusions: SMART will expand clinical trial data to SMA patients that weigh up to 21 kg, in alignment with real-world experience.

Keywords:
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EPNS21-2031 Oral or poster
Neuromuscular

Real-world experience of delivering gene therapy with Onasemnogene Abeparvovec (Zolgensma ®) for children with Spinal Muscular Atrophy (SMA) in the UK

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Objective: To describe the real-world experience of gene therapy delivery with Onasemnogene Abeparvovec (Zolgensma®) to children with SMA in the UK.

Methods: Retrospective review of clinical records of patients who received Zolgensma® therapy. Patients included were eligible for treatment as per the Summary of Product Characteristics. Over 40 Zolgensma® infusions in England (& Wales), 2 in Scotland and 1 in Northern Ireland were delivered by mid-September 2021. Datasets were available for 42 patients.

Results: Age ranged from 2 months to 3-years-10 months, median 8 months; Weight from 4.44kg to 13.5kg, median 7.745kg. 25 patients weighed > 7.5kg.

22/42 patients had received prior treatment with Nusinersen, 1 with Risdiplam. Follow-up of patients varied depending on time since infusion.

Majority of patients developed transient transaminitis post-infusion, typically with mild/moderate ALT/AST elevation. Some had more pronounced/severe transaminitis: ALT>100 IU/L was reported in 11/42 (all >7.5 kg). AST>100 IU/L was reported in 21/42 patients (15 patients >7.5 kg); liver US and coagulation studies were normal. There was good response to increasing steroid dose where indicated (13/42). LFT peaks were generally higher in heavier patients who also, in general, were older patients. No thrombotic-microangiopathy was reported.

Asymptomatic thrombocytopenia occurred in majority early in week 1 and resolved in most by week 2. The lowest count reported was 20x109/L.

Troponin-I data was available for 34 patients. 4 had significant raises >100ng/l, with normal echocardiograms and no clinical manifestation.

CHOP-INTEND scores were available for 22/42 patients. There was improvement noted in all patients except one in whom the assessment was difficult.

Conclusions: This is the second largest cohort data internationally and all patients included in this analysis tolerated the infusion and have recovered well from any transient issues.

No persistent complications from gene therapy or steroid cover were reported.

Keywords:
Gene therapy, Zolgensma, onasemnogene abeparvovec, spinal muscular atrophy, SMA

EPNS21-2038 Oral or poster
Neuromuscular

Nusinersen Effect in Infants in the Presymptomatic Stage of SMA: 4.9-Year Interim of the NURTURE Study [encore]

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Objective: To present interim results from the NURTURE study after a median of 4.9 years of follow up.

Methods: NURTURE is an ongoing study (NCT02386553) of intrathecal nusinersen initiated in infants with 2 or 3 SMN2 copies in the presymptomatic stage of SMA. Enrolled infants were ≤ 6 weeks of age at first dose, clinically presymptomatic, and genetically diagnosed with 5q SMA. The primary endpoint is time to death or respiratory intervention (≥ 6 hours/day continuously for ≥ 7 days or tracheostomy).

Results: NURTURE enrolled 25 infants (2 SMN2 copies, n=15; 3 SMN2 copies, n=10). As of 15 February 2021, the median time on study was 4.9 years (range: 3.9-5.7). All infants were alive and none required permanent ventilation. Four infants (all with 2 SMN2 copies) required respiratory intervention for ≥ 6 hours/day continuously for ≥ 7 days, with all cases initiated during an acute reversible illness. The median time to death or respiratory intervention could not be estimated because of no or too few events, respectively. All 25 infants achieved the WHO motor milestone of sitting without support, 24/25 (96%) were able to walk with assistance, and 23/25 (92%) were walking alone. Most children achieved these motor milestones (21/25 [84%] sitting without support, 15/25 [60%] walking with assistance, and 16/25 [64%] independent walking) within the 99th percentile age window established by the WHO for healthy children. No motor skills gained were lost during the observation period. Nearly all children (22/25 [88%]) reached the maximum score on the CHOP INTEND scale. Mean (SE) change improvement from baseline (first evaluable assessment after Day 700) in HFMSE scores continued to show improvement over time (16.1 [2.4] at month 36; n=11). No new safety concerns were identified.

Conclusions: These data demonstrate the continued long-term safety and benefit of nusinersen in infants who initiated treatment before onset of SMA symptoms, emphasizing the value of newborn screening and early treatment.

Keywords:
spinal muscular atrophy, nusinersen, NURTURE, long-term efficacy

EPNS21-251 Oral or poster
Neuromuscular

Safety, β -Sarcoglycan Expression, and Functional Outcomes From Systemic Gene Transfer of rAAVrh74.MHCK7.hSGCB in LGMD2E/R4

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Objective: Limb-girdle muscular dystrophy type 2E/R4 (LGMD2E/R4) is caused by mutations in the β -sarcoglycan gene (*SGCB*), resulting in loss of SGCB protein and, subsequently, an absence of the dystrophin-associated protein complex (DAPC) at the sarcolemma. LGMD 2E/R4 manifests as progressive hip/shoulder muscle weakness. This first-in-human, phase 1/2 trial (NCT03652259) evaluated SRP-9003, a self-complementary rAAVrh74.MHCK7.hSGCB construct designed to restore SGCB protein production.

Methods: Patients aged 4-15 years with *SGCB* mutation (both alleles) received 1 SRP-9003 IV infusion: Cohort 1 (n=3), 1.85×10^{13} vg/kg; Cohort 2 (n=3), 7.41×10^{13} vg/kg. Endpoints included safety (primary), SGCB protein expression (secondary), and function (North Star Assessment for Limb-girdle Type Muscular Dystrophies [NSAD], time to rise [TTR], 4-stair climb [4-sc], 100-meter timed test [100m], 10-meter timed test [10m]).

Results: Previously reported results: Year 1 (Y1) for Cohort 2 and Year 2 (Y2) for Cohort 1 showed that as of January 2021, SRP-9003 was well tolerated; adverse events occurred early and were manageable. Immunofluorescence showed robust SGCB expression and correct sarcolemmal localization post treatment, leading to DAPC reconstitution, maintained to Y2 (Cohort 1). SRP-9003-treated patients showed functional improvements, maintained at Y2 in Cohort 1 (NSAD, +5.7 points; TTR, -0.6 s; 4-sc, -0.3 s; 100m, -2.8 s; 10m, -0.2 s) and Y1 in Cohort 2 (NSAD, +4 points; TTR, -1.1 s; 4-sc, -0.4 s; 100m, -7.9 s; 10m, -0.6 s). Post hoc analysis showed improved NSAD outcomes versus untreated natural history cohort (9.2-point difference, Y2; 95% CI, 3.2-15.1). An update with 3-year functional data for Cohort 1 and 2-year protein expression and functional data for Cohort 2 will be presented.

Conclusions: These data suggest long-term efficacy of SRP-9003 therapy, supporting advancement of the clinical development program.

Keywords:
AAVrh74 vector; dystrophin-associated protein complex; bsarcoglycan; gene transfer; limb girdle muscular dystrophy; SGCB gene

EPNS21-629 Oral or poster
Neuromuscular

Novel form of congenital myopathy caused by bi-allelic mutations in uncoordinated mutant number-45 myosin chaperone B

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Objective: Congenital myopathies (CM) form a genetically heterogeneous group of disorders, only 60% can be genetically solved.

Methods: We recruited an 11-year old male of consanguineous parents, presenting with proximal weakness, Gower's sign, without cardiomyopathy with a stable disease course. We performed exome sequencing and data analysis was performed with our in-house software Varbank2 according to an autosomal recessive inheritance. We investigated the effect of the missense mutation by complementation assay on the zebrafish steif mutant, an unc-45b loss-of-function model.

Results: We have discovered and published a novel genetically defined form of CM due to a novel homozygous missense mutation in UNC45B (NM_173167.2: c.2261G>A, p.Arg754Gln) also co-segregating in the family with three healthy siblings (Dafsari et al., 2019). In our patient's muscle biopsy, core-like structures were detected mainly in the center of muscle fibers in NADH histochemistry. Electron microscopy showed numerous focal core-like alterations of myofibrillar architecture with Z-bands streaming.

Conclusions: Three isoforms of UNC45B are highly expressed in skeletal muscle, only one also in cardiac muscle. Due to its high evolutionary conservation throughout species, a loss of UNC45 results in different pathological conditions in various species: a knockdown of unc-45 resulted in dilated cardiomyopathy and a reduced muscle contractility in D. melanogaster. Similarly, in unc-45b knockdown zebrafish and also in steif mutants, disrupted myofibrillogenesis associated cardiac dysfunction and paralysis was observed. Injection of mutant unc-45b mRNA did not rescue the steif mutant in contrast to wt mRNA confirming the pathogenicity of the missense mutation.

Keywords:
Novel disease, core myopathy

EPNS21-124 Poster only
Cerebrovascular Disorders

Sinus thrombosis in children and adolescents.

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Objective: The incidence of sinus thrombosis is 0.4 - 0.7 per 100,000 per year. Up to 10% of children have neurological deficits. Aim: to assess the incidence of sinus thrombosis in children and adolescents, their cause, manifest symptoms and frequent localization.

Methods: Methods: clinical, MRI, CT.

Results: Results: in the Primary pediatric stroke center of Morozov City Children Clinical Hospital in 2018-2020, 90 children with sinusthrombosis were treated (newborns were excluded). The average age is 4.2 years (from 2 months to 16 years),53 boys, 37 girls. Manifest neurological symptoms: headache, nausea, vomiting, cranial nerve paresis, impaired consciousness, seizures. Children with sinus thrombosis were diagnosed with: thrombophilia -26, infection (sinusitis, mastoiditis, meningitis) -10 (including COVID 19-two), brain malformations-2, acute leukemia-15, brain tumors-10, autoinflammatory syndrome -4, nonspecific ulcerative colitis -3, Down's syndrome -3, Marchesi's syndrome-1, homocystinuria-8, lupus erythematosus - 4, antiphoslipid syndrome 2, dyslipidemia -2.
The most frequently affected cerebral sinuses: superior sagittal -43, right transverse-35, left transverse 34, inferior sagittal -18, straight 17, right sigmoid 24, left sigmoid -15. 34% of children had lesions of two or more sinuses. Involvement of cortical veins is the most rare -4. Sinus thrombosis was repeated in two children. All patients received anticoagulant therapy.

Conclusions: Sinus thrombosis is a rare cerebrovascular pathology in children. The spectrum of diseases leading to their development is wide. Timely diagnosis is essential to initiate adequate anticoagulant therapy. Prognosis and prevention depends on the main etiological factor.

Keywords:
sinus thrombosis, children

EPNS21-126 Oral or poster
Cerebrovascular Disorders

Arterial ischemic stroke occurring after Pfizer-BioNTech COVID-19 vaccination and reperfusion treatment with mechanical thrombectomy: Case report

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Objective: Timely restoration of cerebral blood flow in stroke with reperfusion therapies is the most effective maneuver for salvage of ischemic brain tissue that is not yet infarcted. Mechanical thrombectomy is more effective than intravenous thrombolysis alone. The effect of COVID-19 vaccines on the risk of stroke is controversial.

Methods: A 16-year-old patient with an arterial ischemic stroke that occurred two days after the first Pfizer-BioNTech COVID-19 vaccination and was treated with mechanical thrombectomy is presented.

Results: A 16-year-old male patient presented with sudden onset left hemiparesis. His muscle strength was 1/5 and 2/5 in his left upper and lower extremities respectively, also with central facial palsy. His NIHSS score was 16. In his medical history, he had open-heart surgery for VSD twice at 2-year-old and had been vaccinated for COVID-19 with Pfizer-BioNTech vaccine two days before admittance. Diffusion MRI was consistent with acute ischemic stroke in the right frontoparietal and lentiform nuclei localization. Cranial CT angiography showed thrombosis in the right MCA M1 branch. He also had a chronic infarct in the cerebellum without any prior neuroimaging. He was performed mechanical thrombectomy in the first six hours. In his thrombosis panel, he had PAI SERPINE 4G/4G homozygous mutation. Echocardiography revealed a patent foramen ovale. Due to hemorrhagic transformation, enoxaparine could start on the 32nd day. His muscle strength in the left extremities was 4-5/5 -with distal muscles weaker- on the 52nd day of the stroke.

Conclusions: We don't know whether there is a relationship between the Pfizer-BioNTech COVID-19 vaccine and the patient's stroke. COVID-19 infection itself has been associated with long-term and high rates of thrombosis. The role of PFO in the etiology of the patient's stroke is also uncertain. The chronic infarct in the cerebellum detected during acute admittance also complicates the management of stroke and patent foramen ovale.

Keywords:
COVID-19, Pfizer-BioNTech, stroke, thrombectomy, thrombosis, vaccine

EPNS21-134 Poster only
Cerebrovascular Disorders

Extensive Posterior Reversible Encephalopathy Syndrome (PRES) following posterior cranial fossa tumour resection

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Objective: We describe a case of posterior reversible encephalopathy syndrome (PRES) following resection of posterior fossa ependymoma with MRI brain series.

Methods: Case report

Results: A 15 year old girl with subacute drowsiness and evolving gait imbalance was diagnosed with a posterior fossa ependymoma. The multicystic, heterogenous tumour originated from the dorsal aspect of the brainstem with poorly defined border, lying within the fourth ventricle, extending across the foramen magnum into the cervical spinal canal, causing obstructive hydrocephalus.

Intraoperatively, she was hypertensive and bradycardic during attempts to excise the tumour over the floor of the 4th ventricle. Hence, a very thin carpet of residual tumour was intentionally left, confirmed by intraoperative MRI.

Post-operatively, she was hypertensive up to 170/110mmHg, with alternating bradycardia and tachycardia, needing intravenous antihypertensives. She was reintubated with profolol and given anticonvulsants for generalised seizures.

On day 3 post-operatively, she developed altered consciousness, left hemiparesis and absent gag reflexes. MRI brain showed bilateral strokes in anterior and posterior circulations but normal MR Venogram and MR Angiogram. Initial repeat MRI showed progression of abnormal signal and restricted diffusion throughout both cerebral hemispheres, posterior fossa, around the residual tumour and the brainstem, suggesting irreversible infarction at these sites. However, serial MRIs showed gradual resolution of previous areas of high T2/FLAIR signal.

Despite the extensive multi-territorial changes, the radiological findings are consistent with PRES. In severe cases it can cause brain ischemia and infarcts.

Conclusions: Although classically affecting the posterior circulation, other vascular territories can be implicated in PRES, further blurring the distinction with reversible cerebral constriction syndrome.

Keywords:
PRES, RCVS, posterior fossa tumour, ependymoma

EPNS21-135 Poster only
Cerebrovascular Disorders

A case of ACTA 2 c.536G>A p.(Arg179His) heterozygous mutation related multi-vessel vasculopathy and muscle weakness.

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Objective: We describe the phenotype and present the imaging of a patient affected by ACTA2 mutation

Methods: Case report

Results: Our patient is a 3.5 year old girl born to non-consanguineous parents with no adverse perinatal events. She presented postnatally with profound lactic acidosis and respiratory failure requiring a prolonged admission. Extensive investigations for neuro-metabolic and mitochondrial disorders were negative.

Ophthalmology examination showed maldevelopment of the iris smooth muscle, with dilated pupils with extended iris processes to lens capsule. Combined with gut malrotation, aneurysmal patent ductus arteriosus, atrial septal defect, slender left pulmonary artery, chronic lung disease, thinning of the corpus callosum , unusual cerebrovasculature and gross motor delay - multisystem smooth muscle disorder was suspected and subsequently, de novo heterozygote ACTA2 mutation confirmed.

A repeat MRI brain at 3 years old to investigate headaches showed ventriculomegaly with dilation of 4th ventricle, and bilateral periventricular T2/ FLAIR hyperintensity within the frontal white matter. The pons was irregular due to compression of the pontine branches of the basilar arteries and there was unusual radial orientation of frontal parasagittal gyri. There was appearance suggestive of a Blakes pouch cyst in the posterior fossa that could contribute to the hydrocephalus. This was felt to be developmental. A ventriculoperitoneal shunt was placed following confirmation of intracranial hypertension.

MR angiogram showed abnormal 'broom like' configuration of bilateral middle cerebral arteries. The arteries around the circle of Willis and the superior cerebellar arteries appeared stretched and there is narrowing of the posterior cerebellar arteries' origin.

Conclusions: MR angiogram should be considered in investigation of leukodystrophies with multisystem smooth muscle involvement as the distinctive broom-like appearance of cerebral arteries is highly suggestive of ACTA2 mutations.

Keywords:
ACTA2; Broom-like; vasculopathy; abnormal iris

EPNS21-144 Oral or poster
Cerebrovascular Disorders

Moyamoya disease: description of 7 cases

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Objective: to analyze the clinical manifestations and effectiveness of surgical treatment of pediatric patients, having moyamoya disease.

Methods: 7 patients with moyamoya disease were analyzed; their average age at the time of analysis was 9.6±5.3 y.o., 4 boys, 3 girls. The diagnosis was confirmed with the help of cerebral angiography in 5 cases and MRI angiography in 2 cases.

Results: According to the data of cerebral angiography/MRI angiography, 4 (57%) patients had a bilateral lesion, 3(43%) patients had unilateral one. According to the angiographic stage: 1 (14%) patient had the second stage on one side, 1(14%) - on two sides, 2(29%) -the third stage on one side, 2(29%) - on two sides, 1(14%) patient had the fourth stage on both sides. The first symptoms appeared at the age of 4.9±2.8 y.o., manifested in the form of headache - 6(86%), convulsions - 1(14%), hyperkinesis - 1(14%), speech disorders- 2(29%), paresis in the extremities - 4(57%), transient ischemic attacks (TIA) - 3(43%). 4 patients (57%) had an ischemic stroke, 1(14%) -a hemorrhagic stroke, 1(14%) hemorrhagic and ischemic stroke, 3(43%) - TIA. 4 patients (57%) had comorbidities: the syndrome of Alagille - 1; fusiform aneurysm of the left PCA - 1; short PQ - 1; medulloblastoma Gr 4, neurofibromatosis type I, a false aneurysm of the left ACA - 1. Surgical treatment (encephaloduroarteriosynangiosis) was performed in 6 cases: bilateral - 1, unilateral - 5, planned - 1. Catamnestic observation ranged from 1 month to 7 years (3.0±2.8). There were no new symptoms. 1 patient died due to medulloblastoma Gr 4.

Conclusions: Surgical treatment is the most effective method for moyamoya disease, that prevents repeated strokes and TIA.

Keywords:
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EPNS21-2032 Poster only
Cerebrovascular Disorders

MECHANICAL THROMBECTOMY FOR ACUTE STROKE IN A TWO-MONTH-OLD PATIENT AND REVIEW OF THE LITERATURE IN INFANCY

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Objective: Mechanical thrombectomy (MT) in pediatric stroke is supported by studies in adults, but there is controversy regarding younger patients. The main growth of intracranial vessels occurs up to two years when there can be more difficulties in MT.

Methods: Description of the MT performed in a two-month-old patient###the youngest infant published to date. We also review the literature on MT for stroke in infants.

Results: A two month old patient presented with an awakening stroke secondary to an occlusion of the M1 segment of the left middle cerebral artery. A successful MT was performed with an aspiration device without clinically significant complications. An etiological study was completed, and neuroimaging showed focal cerebral arteriopathy. The three-month outcome was excellent: the pediatric-modified Rankin score was 0. Including this case, MT for acute stroke has been reported in only 10 infants. MT was successful in 90% mostly using adult conventional stent-retrievers. There were complications only in patients with mechanical circulatory support (MCS) devices, three patients died due to hemorrhagic transformation after MT, and one patient died due to recurrent ischemic stroke.

Conclusions: MT seems effective and safe in infants similarly to other pediatric ages. In children under two years of age, the presence of comorbidities requiring MCS devices is the main factor underlying poor prognosis.

Keywords:
Mechanical thrombectomy. Infants. Acute stroke. Pediatric stroke.

EPNS21-301 Oral or poster
Cerebrovascular Disorders

Central Nervous System Vasculitis in Patients with Primary Immune Deficiency

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Objective: To illustrate the wide etiologic profile and interdisciplinary approach in childhood arterial ischemic stroke (AIS) in a tertiary center.

Methods: We present two cases with immunodeficiency and central nervous system (CNS) vasculitis with AIS.

Results: Case-1
Thirteen-year-old girl being followed-up for common variable immunodeficiency, autoimmune adrenal insufficiency presented with sleepiness and right hemiplegia following abdominal pain, diarrhea, vomiting. Magnetic resonance imaging (MRI) revealed acute ischemia, diffuse saccular and fusiform aneurysms in the left anterior and middle cerebral arteries and branches, and a chronic right caudate infarct. The irregularities and stenosis of major and perforating cerebral arteries suggested vasculitis. The chronic infarct, calcified lesions on ICAs on cranial CT, sulcal and basal ganglia collaterals on MR angiography suggested an acute exacerbation of a slow-progressing, probably non-infectious, vasculitis. Steroid and immunoglobulin were given as acute treatment, cyclophosphamide added afterwards. However she was readmitted 3 weeks later for right hemispheric AIS and subsequent hemorrhage. She developed cytomegalovirus (CMV) pneumonia 2 months after initial admission.
Case-2
This boy was diagnosed with immunodeficiency when six months old and underwent corneal transplantation for CMV retinitis. He received no antiviral treatment. Two years later he was admitted with left hemiplegia and left central facial paralysis. MRI showed acute infarction in both middle cerebral artery territories and bilateral diffuse vascular stenosis at the Willis polygon. Steroid and unfractionated heparin were started; valganciclovir was added for high serum CMV load. Motor weakness improved within two months.

Conclusions: The first patient had vasculitis of autoimmune and the second, viral etiology. A complex course with recurrent AIS, bleeding and infection is conceivable in immunodeficiency/dysregulation.

Keywords:
immunodeficiency, stroke, central nervous system vasculitis

EPNS21-343 Oral or poster
Cerebrovascular Disorders

Could migraine be a symptom of the first atherosclerotic lesions in children?

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Objective: Headaches in children are an important issue due to the prevalence, social consequences and unclear patomechanism. Recent studies performed in adults suggest that idiopathic headaches could be the first sign of atherosclerosis. The aim of the study was to analyse varied factors that could be associated with higher risk of atherosclerosis in children with idiopathic headaches (IH).

Methods: The study population comprised 83 children (52 with IH, 31 controls). The family history, brain-derived neurotrophic factor (BDNF), soluble CD40 ligand (sCD40L), endothelial plasminogen activator inhibitor (PAI I), vascular endothelial growth factor (VEGF), intima media thickness (IMT) measurements were performed. Selected factors were compared with basic laboratory parameters: CRP and lipids concentration.

Results: Children with headaches had more often a positive family history of cardiovascular disease (p=0,049). While no statistically significant differences in biomarkers of vascular changes were observed in the study group as compared to the controls, some trends were noticed. Among children with headaches, boys had a higher BDNF level than girls (p=0,046). Migraine patients with normal weight had significantly lower PAI-I levels than controls (p=0,034). Overall, BDNF showed a negative correlation with sCD40L and VEGF. VEGF showed a positive correlation with sCD40L, PAI-1- with the sCD40L and VEGF. Positive correlation between PAI-1 and the triglycerides (TG) level was observed. IMT did not differ between children with IH and controls, however IMT showed positive correlation with BMI z-score and TG.

Conclusions: No clear clinical signs of atherosclerosis are present in children with IH, however some trends are visible. The headaches are more often related with family history of cardiovascular diseases. IMT is associated with the TG and the BMI z-score value. The measured biomarkers of vascular changes show mutual inter-relations.

Keywords:
headache, atherosclerosis, child

EPNS21-427 Oral or poster
Cerebrovascular Disorders

From the diagnosis of brain arteriovenous malformation to cerebral proliferative angiopathy: a case report

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Objective: In cerebral proliferative angiopathy, there is an increase in cerebral vascularization with abnormal vessels in a healthy brain parenchyma. Because it is rare, it can be confused with arteriovenous malformations (AVMs), although its natural history and pathophysiology are totally different.

Methods: We introduce the case of an 8-year-old child diagnosed with proliferative cerebral angiopathy after having received a diagnosis of AVM for years.

Results: 8-year-old girl who began at 4 with left hemiparesis self-limited episodes lasting 30 minutes. In cranial magnetic resonance imaging (MRI), an extensive right parasagittal vascular malformation is observed, and a diagnosis of focal seizures secondary to this malformation is assumed. They added carbamazepine to her previous treatment. Two years later, she had a focal aware seizure and a focal to bilateral tonic-clonic seizure, for which she was admitted. Cranial MRI showed intracranial hypertension and increased size of AVM. Lumbar puncture showed opening pressure of 48 cm H2O and treatment with acetazolamide was started leading to clinical improvement.

She was referred to our center two years later. The cerebral arteriography was interpreted as cerebral proliferative angiopathy with right hemispheric hypoperfusion. The patient is currently awaiting surgical treatment (encephaloduroarteriosynangiosis) and pharmacological treatment (bevacizumab).

Conclusions: It is important to include cerebral proliferative angiopathy in the differential diagnosis of cerebral vascular malformations. This disease, sometimes mistaken for an AVM, has a different natural history, prognosis, and treatment. Early diagnosis and targeted treatment can improve the quality of life of patients. This case shows us the importance of angiography in the precision diagnosis in cases of cerebral vascular malformations.

Keywords:
cerebral proliferative angiopathy, AVM, epilepsy, angiography, cerebral vascular malformations

EPNS21-471 Poster only
Cerebrovascular Disorders

Vertebrobasilar arterial ischemic stroke due to pathology of the cervical spine on the example of clinical cases.

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Objective: analyze of the features of vertebrobasilar (VB) arterial ischemic stroke by the example of clinical cases.

Methods: 2 patients who underwent treatment for VB arterial ischemic stroke at the Primary Pediatric Stroke Center in Morozov Children Hospital in 2021.
MRI + MRA, CT - AG, X-ray of the cervical spine, cerebral angiography, transcranial Doppler, blood and urine tests.

Results: Patient 1, a boy, 15 y.o., was admitted with complaints of dizziness, unsteadiness of gait, headache. Brain MRI revealed a true restriction of diffusion in DWI and ADC modes in the left cerebellar hemisphere and left cerebellar peduncle. According to the anamnesis, the child is observed for deafness, clinical signs of connective tissue dysplasia. PedNIHSS 7 points. The second stroke was after 2 months: he was admitted due to severe lethargy, drowsiness, dizziness. According to PedNIHSS 13 points. According to MRI true limitation of diffusion in the structure of the bridge on both sides (mainly on the right), as well as in the periventricular parts of the cerebellum on the right, the absence MR signs of blood flow at the level of the basilar artery bifurcation and P1 on both sides. According to cerebral angiography - occlusion of the main artery.
Re-examination revealed the following CT scan of the cervical spine: displacement of the C1 lateral masses relative to the occipital condyles. Blood tests revealed hyperhomocysteinemia.
Patient 2, a boy, 9 years old, after a whiplash injury, severe cerebral symptoms, ataxia were noted, according to PedNIHSS 4 points. According to the MRI of the brain, this is a true limitation of diffusion in the region of the right hemisphere of the cerebellum. A CT scan of the brain revealed Kimmerly's anomaly on the both sides. According to cerebral angiography, stenosis of 95% of the right vertebral artery in the V2-V3 segment.

Conclusions: patients with vertebrobasilar strokes require close follow-up examination in the area of the cervical spine, even in the presence of one of the factors.

Keywords:
stroke, vertebrobasilar stroke, cervical pathology

EPNS21-499 Oral or poster
Cerebrovascular Disorders

Uncommon cause of recurrent Transient ischemic attacks in a child with Noonans Syndrome.

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Objective: We describe a case report of an uncommon but well recognised cause of recurrent transient ischemic attacks in a child with Noonans Syndrome.

Methods: Introduction:
Noonans syndrome is a multiple congenital anomaly syndrome with characteristic facial features, short stature, congenital heart defects and cerebrovascular abnormalities. Disruption of vascular development during the prenatal stage has been proposed as the cause of cerebrovascular disease in Noonan Syndrome. They often present with Transient Ischemic attacks (TIA), headaches or strokes.
Case Report:
A 6 and half year-old girl with Noonan's syndrome presented over a period of 3 months with episodes of being unresponsive. Prior to the episodes, she would feel unwell. The first episode involved drooping of left side of mouth and in the second, her head dropped forward. She also had episodes of being lightheaded with subtle changes in her behaviour and speech, as well as concentration and repetition of words.

Results: EEG showed a persistent slow wave activity in the right posterior parietal occipital region. MRI scan and subsequent angiogram confirmed the presence of neovascularization and features strongly suggestive of moyamoya particularly in the middle and anterior cerebral vessels and significant stenosis of major vessels on angiogram. She underwent bilateral pial synagosis and is on Aspirin and continues to be on regular surveillance.

Conclusions: The association between Noonans syndrome and Moyamoya is uncommon but well established and should be recognised to pursue surgical revascularisation options/pharmacologic treatment options early to prevent catastrophic consequences.

Keywords:
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EPNS21-582 Poster only
Cerebrovascular Disorders

Sickle cell disease, Covid-19, Paediatric Multi-System Inflammatory Syndrome (PIMS-TS) and posterior reversible encephalopathy syndrome (PRES)

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Objective: Acute neurological events e.g. stroke, occur in COVID-19 infection but there are few data in sickle cell anaemia (SCA)

Methods: A 5 year old boy with SCA and autism presented in May 2020 with a 5 day history of fever and multifocal pain.

Results: Haemoglobin was 50 g/L, white cells 33 x 10^9/L and CRP 119mg/L. Pain was attributed to a vaso-occlusive crisis. He was commenced on intravenous antibiotics and received a simple top up red cell transfusion to a haemoglobin of 99g/L and HbS% of 49%. His COVID-19 PCR returned negative but he had positive COVID serology. Blood tests revealed an underlying inflammatory process; CRP 54 mg/L, Ferritin 713 ug/L, lactate dehydrogenase 1225 u/L and D-Dimers 4581 ng/mL. Early cardiac biomarkers were elevated including a troponin of 50 ng/L, creatine kinase of 981 U/L and proBNP of 2476 pg/mL so he was treated for Paediatric Multi-System Inflammatory Syndrome [PIMS-TS] with methyprednisolone [10mg/kg], intravenous immunoglobulin [2g/kg], aspirin and clopidogrel. A transthoracic echo found coronary artery (CA) dilatation with Z-scores of +8.9 and +6.2 for the LCA and RCA respectively.
On day 5 he developed a right focal and generalised tonic clonic seizure lasting 20 minutes; lorazepam led to respiratory arrest requiring ventilation. He had refractory hypertension and EEG consistent with encephalopathy. MRI showed patchy areas of abnormal cortical T2 signal in the occipito-parietal regions, and mild diffusion restriction of the left hippocampus and thalamus consistent with posterior reversible encephalopathy syndrome (PRES).
Seizures were controlled but hypertension proved initially refractory. He recovered well with normalizing inflammatory markers and coronary arteries

Conclusions: PIMS-TS causes symptoms similar to crisis in children with SCA, who are at risk of complications, including hypertension and PRES associated with immunomodulation and fluid therapy. Baseline coronary and inflammatory data are needed in SCA so that PIMS-TS and crisis can be distinguished.

Keywords:
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EPNS21-589 Poster only
Cerebrovascular Disorders

Ischemic stroke due to invasive central nervous system aspergillosis

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Objective: Invasive central nervous system aspergillosis is infrequent. Due to its vascular tropism, invasive aspergillosis may cause vasculopathy in any organ. In central nervous system, it usually affects lenticulostriate or thalamic perforating arteries. We communicate a case of ischemic stroke because of invasive central nervous system aspergillosis.

Methods: 7-year-old patient admitted to hospital with acute lymphoblastic leukemia relapse, who suffers an ischemic stroke secondary to invasive central nervous system aspergillosis.

Results: A 7-year-old child is admitted to hospital suffering a relapse of acute lymphoblastic leukemia, the third one she has. It affects spinal cord and central nervous system. She receives chemotherapy and develops a severe neutropenia. During the hospitalization, she is diagnosed with invasive central nervous system aspergillosis and starts treatment with amphotericin B. Suddenly, she presents an episode of decreased level of consciousness. The brain CT scan shows a subacute ischemic lesion in right basal ganglia, brain angio-CT scan did not demonstrate artery occlusion. Regarding the clinical context and localization of the infarct in lenticulostriate arteries territory, it is considered secondary to intracranial vasculopathy due to invasive central nervous system aspergillosis. She receives voriconazole, showing clinical improvement in the next days.

Conclusions: Although ischemic strokes due to invasive central nervous system aspergillosis are infrequent, it is a potential etiology in immunocompromised patients. Despite its bad prognosis, an early diagnosis and early treatment could suppose an important difference in the clinical response and prevent new cerebrovascular events.

Keywords:
Ischemic stroke. Invasive central nervous system aspergillosis.

EPNS21-600 Oral or poster
Cerebrovascular Disorders

Iron Deficiency Anaemia and Idiopathic Intracranial Hypertension

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Objective: Idiopathic intracranial hypertension (IIH) is a condition which has signs and symptoms consistent with raised intracranial pressure (RICP), including papilloedema but with space-occupying lesions excluded. Venous thrombosis or narrowing or other signs of RICP may be seen on neuroimaging. Many patients experience headaches and visual symptoms, with the risk of visual loss. Current treatments include Acetazolamide, Steroids and Topiramate but underlying triggers may not be managed. The aim of this retrospective service evaluation was to determine the extent to which triggers such as high body mass index (BMI) or iron deficiency/anaemia had been excluded and, if present and treatable, appropriately managed.

Methods: The hospital database was used to obtain anonymised data for paediatric patients with IIH between 01/01/2000 and 31/12/2019 related to lumbar puncture opening pressure, BMI, full blood counts, acetazolamide/steroid/topiramate use, and neuroimaging. Friedman's revised criteria were used in diagnosis and the NICE guidelines were referred to for treatment. Data were analysed using SPSS.

Results: Data were available for 118 patients; after exclusions 59 fulfilled Friedman's criteria (41 females; 69%) of median age 13 years. Median BMI was 25 (range 14.4-53.4). 76% of those for whom BMI was recorded had a z-score for BMI >2 standard deviations above the mean for age. Only 8 had written advice about weight loss. 52 patients had haematological data. In 10/19 (52.4%) patients who had ferritin, values were below normal. 46/59 patients had full blood counts; 22 (45%) had at least one low red cell index count. Of the 22 patients with low indices, 10 were prescribed iron with relief of headache) in 7.

Conclusions: Obesity is common in IIH and may be missed if z-score for BMI is not calculated. Iron deficiency/anaemia should be more thoroughly considered with patients with IIH. Future studies may consider prospective ferritin and prothrombotic sampling and associations with abnormal venous anatomy.

Keywords:
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EPNS21-628 Oral or poster
Cerebrovascular Disorders

Attention difficulties as an outcome of perinatal stroke

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Objective: Behavioural outcomes are not well studied in perinatal stroke; a review carried out in 2013 identified attention and executive functioning outcomes as an area in need of further research.

Methods: To gain an in-depth understanding of attention outcomes in children with a history of perinatal stroke the literature was systematically reviewed from PubMed using the MeSH terms ((Perinat*) OR (Neonat*) OR (Antenat*)) AND (Stroke) AND ((Attention) OR (Conners) OR (Executive))

Results: 116 abstracts were reviewed of which 95 were excluded: 11 reviews, 10 as they did not mention perinatal stroke, and 74 as attention was not an outcome. After full text review, a further 13 were excluded: 1 duplicate, 2 on childhood stroke, 3 not separating childhood and perinatal stroke, 2 focussing on caregivers, and 5 as attention was not an outcome, leaving 8 papers for inclusion in the systematic review.
Three of the 8 studies identified measured sustained attention; all found that sustained attention was significantly impaired in children with perinatal stroke when compared to normative data. Children with neonatal arterial ischaemic stroke or periventricular venous infarction (PVI) appear to have worse attention than those wih presumed perinatal ischaemic stroke. Only 1 study focussed on switching attention finding that children with perinatal stroke had worse attention outcomes than controls. Selective attention was measured in 7/8; all found selective attention was impaired in children with perinatal stroke compared to controls. Only 3 studies measured inattentive behaviours; all found children with perinatal stroke exhibited inattentive behaviour. In 1 study, children with perinatal stroke scored worse on the attention subscale then the hyperactivity scale of the ADHD rating scale.

Conclusions: Perinatal stroke survivors are at significant risk of problems with sustained, switching and selective attention which their families can see as inattentive behaviour. Follow-up to examine management strategies is warranted.

Keywords:
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EPNS21-631 Oral or poster
Cerebrovascular Disorders

Large vessel occlusions are a major prognostic factors in pediatric COVID19 - literature review and single center experience

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Objective: Among the diverse neurological manifestation of CoVID19 in children, the immunomediated are assumed more common than cerebrovascular pathology, and meningitis/encephalitis is very rare. Cerebrovascular diseases affect 2-6% of all CoVID19 patients, large vessel occlusion (LVO) being the most common neuropathology, seen mainly in adults. LVO is a late complication in CoVID19, similar to MIS-C, and is underreported in children. Mortality due to neurological complications is suggested to be several times higher than that of respiratory failure and MIS-C.
Objectives: To reveal the neurological manifestations of CoVID19 in children.

Methods: Retrospective review of all CoVID19 cases, treated in one pediatric department during one year (Sept.1, 2020 - Aug.31, 2021). Cases with uncertain causative relationship with SARS-CoV2 infection were excluded.

Results: From the 58 CoVID19 pediatric cases, treated during the investigated period, only 9 had neurological manifestations: Three cases were diagnosed with LVO, all with thrombophilia. Two were obese and had only lab data of CoVID19, while the third had a previous LVO, and the present LVO developed during CoVID19 clinical presentation. The first and last of these three patients died, as well as another child, that was the third patient's brother and had CoVID19 encephalopathy, fever, penumonia, heart failure and obesity. The other five neuroCoVID19 cases were: one with cerebral sinovenous thrombosis; one with meningitis and MIS-C; two with encephalopathy and MIS-C; one with febrile convulsive status during CoVID19 pneumonia. Facial palsies and Gillain-Barre syndromes with SARS-CoV2 positive PCR were 62 and 2, respectively, but there were no peculiarities in the clinical presentation, neither increase in incidence. No other fatalities occurred in the neurological and non-neurological cases, including 16 MIS-C patients.

Conclusions: LVO is a major cause of death in pediatric CoVID19, and obesity and thrombophilia are major risk factors.

Keywords:
CoVID19, stroke, encephalopathy, Gillain-Barre syndrome

EPNS21-702 Poster only
Cerebrovascular Disorders

Atypical Arteriovenous malformation in baby with sturge weber syndrome

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Objective: Sturge Weber syndrome (SWS) is a neurocutaneous syndrome with capillary malformations of face, eyes and leptomeninges. The two primary diagnostic features of SWS are a facial portwine stain due to cutaneous angioma and leptomeningeal angiomas.
Intracranial vascular abnormalities including leptomeningeal angiomatosis , anomalous cortical venous structures and transmedullary developmental venous anomalies are well recognized.
We describe a rare case of a baby with bilateral facial portwine stain, bilateral leptomenigeal angiomatosis with a rare Arterio-venous malformation
Term baby born by forceps delivery with uneventful antenatal and perinatal period was noted to have bilateral facial portwine stain in the v1-v3 distribution. He was referred to tertiary Neurology centre for assessment. He had focal seizures with onset at 6 months of age. On examination at 5 months of age he has macrocephaly OFC 48.5 cm, blateral portwine stain and normal neurological examination.
MRI brainat 6 months of age showed bilateral cerebral atrophy affecting the right hemisphere more than the left with greater involvement of the parietal, occipital and temporal
lobes. The appearances are in keeping with leptomeningeal angiomatosis. The MRA shows slight asymmetry of major intracranial arteries with an enlarged dominant left posterior communicating artery communicating with a left internal cerebral vein/straight sinus suggesting of arteriovenous malformation. He had further assessment in the neurovascular clinic.

Methods: Case report

Results: As below

Conclusions: Arteriovenous malformation is not commonly described in SWS. We would like to highlight the possibility of occurrence of Arteriovenous malformation as they would need further evaluation as could be high flow vascular malformation with a risk of bleeding. Further progress and beautiful images will be presented in the poster if accepted.

Keywords:
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EPNS21-229 Oral or poster
Epidemiology & Follow-Up

The neurosonography findings in neonates born to mothers with COVID-19 in Crimea.

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Objective: This study presents specific neurosonography features in neonates from mothers with COVID-19 during pregnancy in Crimea. The aim of the study was to evaluate the effect of COVID-19 first trimester of pregnancy that led to neonatal outcomes.

Methods: We retrospectively collected and analyzed data about 30 pregnant wonen tested positive for SARS-CoV-2 in first trimester. 30 infants at 1 month of age had the Head Ultrasound Screening (HUS) for excluded the suggestive of intracranial pathology after COVID-19. The Ventricular Index (VI)(R and L), Anterior Horn Width (AHW)(R and L) and Thalamo-occipital Distance (TOD)(R and L) were measured in 30 infants.

Results: The severity of the SARS-CoV-2 symptoms ranged from mild in 70 % of the patients to moderate in 30% pregnant women. Pregnant women were not vaccinated. 20 neonates were found to be COVID-19 positive, although no indication of vertical transmission of infection was established. Mean gestation age at birth of the study infants was 36±0.8w, with a mean weight of 2479±301. 37% were born at 34w, 33% at 35w and 30% at 37w. 56% were female. Their mean Apgar score on first minute was 7.5 ± 0.9; and at 5 minutes 8.4±0.9. On HUS were detected local hyperechogenicity with mild ventricular dilatation in 10 babies (34%) and diffuse increase in echogenicity of periventricular structures and vascular cysts in 20 infants (66%). Moreover, COVID-19 positive babies demonstrated on HUS: VI in R and L sides was abnormal (VI > 4 mm, above 97th percentile) in 25%, AHW in R and L sides shown values exceeding 6 ± 1.2 mm in 21% and TOD in both sides has abnormal value more 25 mm in 20%.

Conclusions: Possibly COVID-19 first trimester of pregnancy can be a cause of neurosonography changes in neonates and can influence on their neurodevelopment in future. According to these findings, this population requires long term follow-up.

Keywords:
neurodevelopment, COVID-19,pregnancy,intracranial pathology, neonatal neurology

EPNS21-260 Oral or poster
Epidemiology & Follow-Up

The Electroencephalographic findings in neonates born to mothers with COVID-19 in Crimea.

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Objective: This study presents specific EEG- features in neonates from mothers with COVID-19 during pregnancy in Crimea. The aim of the study was to evaluate the effect of COVID-19 first trimester of pregnancy that led to neonatal outcomes.

Methods: We retrospectively collected and analyzed data about 30 pregnancies tested positive for SARS-CoV-2 in first trimester. 30 infants at 1 month of age had the EEG screening for excluded the abnormal bioelectric activity of the brain after COVID-19.

Results: The severity of the SARS-CoV-2 symptoms ranged from mild in 70 % of the patients to moderate in 30% pregnant women. 20 neonates were found to be COVID-19 positive, without clinical symptomes. Mean gestation age at birth of the study infants was 36±0.8w, with a mean weight of 2479±301. 37% were born at 34w, 33% at 35w and 30% at 37w. 56% were female. Their mean Apgar score on first minute was 7.5 ± 0.9; and at 5 minutes 8.4±0.9. The flashes of theta-waves in the occipital regions with an average amplitude of 200± 50 uV, an average frequency of 7± 0.5 Hz, acute transient frontal theta-waves with an average amplitude of 100± 50 uV, an average frequency of 5± 0.5 Hz, light interhemispheric asynchrony were described in 10 babies (34%) and pathological Delta-brushes (spindle-shaped high-amplitude brushes with average values of 250±50 uV , average frequency of 3± 0.5 Hz) localized in parietal regions and acute transient frontal theta-waves with average amplitude values of 150±50 uV, average frequency of 5± 0.5 Hz were presented in 20 infants (66%).

Conclusions: Possibly COVID-19 first trimester of pregnancy can be a cause of EEG changes in neonates and can influence on their neurodevelopment in future. According to these findings, this population requires long-term follow-up and perhaps may benefit from early intervention.

Keywords:
COVID-19 first trimester of pregnancy,EEG changes in neonates

EPNS21-438 Oral or poster
Epidemiology & Follow-Up

Influence of neurological comorbidity on the school performance of paediatric patients suffering from primary headaches

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Objective: To determine the prevalence of primary headaches in a paediatric population and patient's characteristics associated with school performance.

Methods: Cross sectional study of children between 0 to 16 years-old, referred to a department of Paediatric Neurology (population of 32,909) between 01/01/2016 and 31/12/2020 for primary headaches. Two independent reviewers screened medical history for data including age, gender, socioeconomic status, school performance and neurological comorbidity. Crude and stratified data analysis were conducted to study the association between school performance and these variables.

Results: The prevalence of primary headache consultations was 0.98% (324/32909), of which school performance was recorded in a total of 82% (266/324). Of these, 59% were girls (157/266). The mean age was 11.39+/-2.73 years. 45.86% (122/266) had been diagnosed with a neurological comorbidity, while 74.8% (199/266) had good academic achievement. Regarding socioeconomic status 68.4% (182/266) had a medium-high status.
A significant association was found between school performance and age; children with primary headaches 10 years or under had 6 times more chance of having good academic achievement than those above this age (OR=6; CI=2.6-13.8). No statistically significant association was found between school performance and the remaining variables.
With age as the independent variable a statistically significant association was found between school performance and neurological comorbidity in over 10-year-olds (OR=0.44; IC=0.23-0.83); children over the age of 10 without neurological comorbidity had 2.25 times less chance of underachievement than those with comorbidity.

Conclusions: Patients suffering from primary headaches before the age of ten are more likely to have good academic achievement than those over ten.
Over the age of ten, consulting patients for primary headaches who were not diagnosed with neurological comorbidities are more than twice as likely to have good academic results.

Keywords:
Primary Headaches, School Performance, Neuropaediatrics, Neurological Comorbidity

EPNS21-646 Oral or poster
Epidemiology & Follow-Up

Annual income and primary headache referrals in a paediatric population

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Objective: To study the prevalence of primary headache consultations in a paediatric population according to income status in a mediterranean country.

Methods: Cross sectional study of children between 0 to 16 years-old, referred to a department of Paediatric Neurology, (paediatric population of 32,909) between 01/01/2016 and 31/12/2020 for primary headaches. Patients were referred from nine different health centres that are included in the clinical reference area of the hospital where the department is based. The corresponding healthcare population of each one is known. Using figures from the National Statistics Centre, each health centre was divided into two main groups based on postal code; those with an annual income above the national average (25,000 euros) and those below this average.

Results: Of the total 32,909 children residing in the area, 24,935 (75.8%) were assigned to areas with above average income while 7,974 (24.2%) belonged to areas with below average income. A total of 324 patients were referred to the department for primary headaches (0.98%). Of these, 218 were in high-income areas (67.2%) while 106 were in lower income areas (32.7%). A statistically significant association was found between annual income and prevalence of consultations (OR=0.65; CI=0.5-0.8); children from a higher income area had 1.5 times less chance of being referred for primary headaches than those from a lower income area.

Conclusions: The prevalence of consultations in a neuro-paediatric referral unit for primary headaches is significantly higher in patients who belong to a below average income area than in those who do not. These figures are consistent with those of other developed countries. Further studies are needed to investigate other possible factors that could influence this association.

Keywords:
Primary Headaches, Neuropaediatrics, Annual Income

EPNS21-139 Oral or poster
Epilepsy: Diagnosis and Investigations

The yield of video-EEG for surgical and non-surgical patients at a tertiary hospital in the UK

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Objective: Long-term video EEG monitoring (LTVEM) has been proposed to differentiate epileptic from non-epileptic seizures, classify epilepsy syndromes, quantify seizure types and characterize focal seizures during pre-surgical evaluation of patients.
We performed a retrospective audit on LTVEM to determine the yield in recording paroxysmal events of interest or seizures and to assess its impact on diagnosis and management.
Following a thorough literature review, we proposed the following standards: ability to capture events of interest:70% and to provide new diagnostic information:50%.

Methods: Data of 30 inpatients who underwent LTVEM at Royal Manchester Children's Hospital over a six-month period between June 1st and November 30th 2019 were collected using electronic patient records.

Results: Thirty patients were recruited (13 females, 17 males) of which 28/30(93%) were in the epilepsy surgery pathway. 25/30(83%) patients had an abnormal EEG and 18/30(60%) had abnormal MRI findings.
9/30(30%) had no anti-epileptic medication reduced, 15/30(50%) had one drug, 5/30(17%) had two drugs and 1/30(3%) had three drugs reduced. The median stay was 4 days. We recorded events of interest in 28/30(93%) patients;22/30(73%) had epileptic events recorded, 4/30(13%) non-epileptic events, 2/30(7%) of which had mixed events and 2/30(7%) an event was not captured. In 22/30(73%) LTVEM provided new information.
4/30(13%) were approved for resective surgery, 15/30(50%) were not approved (in which group 4/30 were approved for vagus nerve stimulation), whilst 9/30(30%) await outcome. One patient was confirmed to have non-epileptic events and medication was stopped. One patient was found to have Lennox-gastaut syndrome and commenced on Cannabidiol.

Conclusions: In our cohort, video-telemetry recorded events of interest in more than 90% of patients and had a role in changing the diagnosis in at least 2/3. This may be due to careful patient selection for LTVEM and pre-admission review of patients through a multidisciplinary pathway.

Keywords:
Long-term video EEG monitoring, video-telemetry, epilepsy, non-epilepsy, NORCESS.

EPNS21-2056 Oral or poster
Epilepsy: Diagnosis and Investigations

Covid-19 in childhood epilepsy: Clinical presentations and seizure outcome

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Objective: Coronavirus virus 2019 (COVID-19) pandemic impact on children revealed that general symptoms show mild upper respiratory tract involvement and a better prognosis than adults. Although there are many neurological complications including stroke, headache, seizures and encephalopathy, what happens among pediatric neurology patients is still unclear. Our objective was to describe the outcome of the children with epilepsy who experienced Covid-19 infection in our tertiary center.

Methods: Children with diagnosis of epilepsy who were followed up by our outpatient clinic of pediatric neurology were analyzed. We included cases who experienced PCR (+) Covid-19 infection during one year follow-up.

Results: A total of 34 patients (mean age: 8.35±4.94; median:8) were included in the study. Eight of these patients (23.5 %) were being followed by as epileptic encephalopathy including Dravet syndrome. Other groups included idiopathic generalized epilepsy (38.2 %) and focal epilepsy (23.5 %). Five patients (14.7 %) had de novo seizures with the onset of Covid-19. Twenty-five patients (79.4 %) showed mild upper respiratory tract infection symptoms including sore throat, nasal flow, mild fever and headache. Two patients (5.8%) had pneumonia. Two patients (5.8 %) needed to be hospitalized due to neutropenia and encephalitis. All of the epileptic encephalopathy group showed mild symptoms and none of them had increase in seizure frequency and severity.

Conclusions: Our patient population including severe epileptic encephalopathy patients generally showed mild symptoms and signs similar to previously healthy pediatric cases. But an important amount also had de novo seizures with onset of Covid-19 infection. Although pro-inflammatory cytokines affecting glutamate and Gamma-aminobutyric acid (GABA) levels is accused there is much more to investigate in order to define basic patogenesis of Covid-19 related seizures and its effect on epilepsy.

Keywords:
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EPNS21-2071 Poster only
Epilepsy: Diagnosis and Investigations

Two cousins with epilepsy due to PCDH19 mutation

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Objective: PCDH19 epilepsy is a rare genetic epilepsy syndrome. Protocadherin 19 gene is located on chromosome Xq22.1 and is in the top 10 genes cause early-onset epileptic disorders. The symptoms of PCDH19 epilepsy can overlap or look similar to the symptoms in Dravet syndrome.

Methods: Two cousins with the same mutation of PCDH19 are presented.

Results: 1st patient: 3.5 years old girl. Her perinatal history without any pathology. At the age of 5.5 months non-febrile focal seizures started, which evolved to bilateral tonic-clonic seizures and occurred in clusters. EEG: left sided spikes, showing diffuse or bilateral frontal and temporal focal discharges. She was put on valproic acid at first, but her seizures did not stop, so levetiracetam was combined. At the age of 1.5 years status epilepticus developed. Brain MRI at the age of 5.5. months and 3.5 years showed no pathological alterations. Psychomotor development of the girl is delayed, at the age of 3.5 years she uses only 2 words, her receptive language and cognitive development is also severely delayed. She shows the signs of autism spectrum disorder and has obsessive-compulsive symptoms. The Comprehensive Epilepsy Panel Plus confirmed that patient is heterozygous for PCDH19 c.1031C>T, p.(Pro344Leu), which is likely pathogenic.
2nd patient is 5 years old and the first cousin of the first girl (fathers are brothers). Her epilepsy started at the age of 11 months with repeated focal, secondarily generalized seizures and with fever. She had status epilepticus 5 times. She is on valproic acid, levetiracetam and clobasam combination therapy with rare provoked seizures. Her brain MRIs are negative. Her psychomotor development is delayed. Molecular genetic testing confirmed the same PCHT19 gene mutation.

Conclusions: Molecular genetic testing for PCDH19 epilepsy is recommended, especially in girls, with early onset seizure clusters, which resemble for Dravet syndrome or Genetic Epilepsy with Febrile Seizures Plus.

Keywords:
PCDH19 epilepsy, early onset seizure clusters, cousins, autism spectrum disorder

EPNS21-218 Oral or poster
Epilepsy: Diagnosis and Investigations

Double trouble: co-occurence of CACNA1A and NEXMIF variants in epilepsy

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Objective: With the widespread use of next generation sequencing (NGS) for epilepsy and developmental delay, an increasing number of variants are discerned in each patient. We present an illustrative case example of "double trouble", where the interpretation of potentially pathogenic variants was further challenged by variable penetrance and expanding phenotypes in these, and many other, epilepsy genes.

Methods: Analysis of NGS panel data, case-note and literature review

Results: The proband is an 11 year old girl with intellectual disability, ASD and pharmacoresistant epilepsy. Her mother has intellectual disability; and father has intellectual disability, ADHD and seizures. Her seizure onset was at 2y, with absence seizures. She subsequently developed eyelid myoclonia and limb jerks, followed by drops. She is currently on three anti-seizure medications. She has essentially a normal neurological examination.

MRI brain and neurometabolic work-up were normal. EEG was very abnormal with widespread high amplitude spike/polyspike and slow wave discharges over both hemispheres and with a left sided bias. A NGS panel revealed Class 5 pathogenic variants in NEXMIF: c.1882C>T p.(Arg628*) and CACNA1A c.2847_2856del p.(Ala952Serfs*115).

Phenotypic features of the recently described X-linked NEXMIF encephalopathy include developmental delay/intellectual disability, ASD, and epilepsy. Males have more severe developmental impairment, whereas females show wide phenotypic diversity, ranging from completely asymptomatic to severe intellectual disability and pharmacoresistant epilepsy.

CACNA1A channelopathies have been implicated in developmental delay, ASD, epileptic encephalopathy and early onset paroxysmal dystonia, in addition to the typical episodic ataxia.

Conclusions: This case highlights the difficulty of variant interpretation in composite phenotypes in the genomic era. Further phenotyping and testing of the extended family is ongoing and will have implications for disease surveillance and genetic counselling.

Keywords:
Composite phenotypes. Epilepsy. CACNA1A chanelopathies. X-linked NEXMIF encephalopathy.

EPNS21-244 Oral or poster
Epilepsy: Diagnosis and Investigations

The genetic landscape of pediatric epilepsy - experience from a tertiary care epilepsy center

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Objective: Through the following study, we aimed to identify the genetic etiology in pediatric epilepsy patients of the pediatric neurology department of our tertiary center, find the genetic defect, while offering information on management, prognosis and seizure recurrence probability, identifying and describing the clinical phenotype of patients with genetic mutations that explain the clinical picture especially the epilepsy diagnosis. We evaluated the therapeutical and overall management of these patients taking into account their genetic diagnosis and creating a diagnosis and follow-up protocol for patients with genetic epilepsy.

Methods: Between October of 2016 and August of 2020 we conducted a longitudinal retrospective and prospective study within our pediatric neurology department.

Results: We investigated 1693 case of epilepsy in children aged 1 month to 18 years old, and we suspected a genetic etiology in 55% of the cases.In approximately 2% (37 cases) the etiology of the epilepsy was considered to be mixed - both structural and metabolic, the remainder of 43% being epilepsies with other etiologies.Within the genetic epilepsy suspicion group 398 cases (42 %) were idiopathic focal epilepsies,235 cases (25%) were generalized genetic epilepsies and 301 cases (33%) were comprised of other epilepsies with a probable genetic cause.

Conclusions: 14 patients (12%) had a certain diagnosis following the genetic testing results.Within the group where the patients received a certain diagnosis, for 10 of the cases there are currently available treatments,with evidence for precision medicine targeted at the genetic defect and its functional outcomes,thus the diagnosis had a direct influence on their management. We emphasize the importance of variants of uncertain significance(VUS)for diagnosis, especially when positively correlated with the clinical phenotype and family history. Genetic testing should always be corerelated with the patient's phenotype and available treatment options.

Keywords:
epilepsy, genetic, etiology, phenotype, genotype, VUS

EPNS21-258 Oral or poster
Epilepsy: Diagnosis and Investigations

Serum interleukin-6 as a potential biomarker in the course of absence epilepsy

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Objective: To determine serum interleukin-6 (IL-6) concentrations of children with absence epilepsy and the association with antiepileptic drugs, seizure semiology and frequency of seizures by comparing control subjects.

Methods: The study was designed as a prospective case control study. Fifteen children aged between 3-17 years who were followed-up with the diagnosis of absence epilepsy in the pediatric neurology outpatient clinics and 30 healthy subjects as a control group were included. A detailed neurological examination, an electroencephalogram (EEG) record according to 10-20 international system of electrode placement and a brain magnetic resonance imaging (MRI) were performed on all the patients. Serum IL-6 levels of subjects were measured by chemiluminescence method. The data were analyzed using SPSS 21 statistical software.

Results: Serum IL-6 levels in patients with absence epilepsy were significantly lower (2.98±1.02 pg/ml) than in the control group (5.35±0.87 pg/ml) ($p<0.001$). Moreover, the patients receiving valproic acid monotherapy had significantly lower serum IL-6 levels than both the patients receiving other antiepileptic drugs and healthy controls (2.55±0.51 pg/ml, 3.86±1.28 pg/ml respectively; $p=0.04$). We also detected higher serum IL-6 levels in patients with active seizures compared to seizure-free patients (3.52±0.54 pg/ml, 2.72±1.12 pg/ml respectively; $p=0.01$). Abnormal or normal EEG and brain MRI findings did not affect serum IL-6 levels of the patients in our study.

Conclusions: This is the first clinical study investigating role of immune system in absence epilepsy and the possible relations between serum IL-6 levels and the patient characteristics affecting the course of disease. Further clinical studies are needed to prove neuromodulatory role of IL-6 as a potential biomarker in absence epilepsy.

Keywords:
interleukin-6, absence epilepsy, seizure, immune, cytokine.

EPNS21-290 Oral or poster
Epilepsy: Diagnosis and Investigations

Epilepsy features in cerebral palsy patients.

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Objective: Today, the problem of epilepsy, as a frequent comorbid condition in cerebral palsy (CP), is very relevant, and accounts for the big part of symptomatic epilepsies in children with CP.The present study is devoted to learn the features of epilepsy and the seizures treatment in patients with CP.

Methods: This prospective study was carried out with 160 children in the Children's Neurological Hospital in Baku city with a diagnosis of CP.In 78 (68.4%) patients who made up the control group, epilepsy was observed, the remaining 50 (31.3%) patients with cerebral palsy and without epilepsy were included in the control group. Statistical data was carried out using the SPSS 16.0 proqramm. In all tests, the level of statistical significance was taken equal to $p < 0.05$.

Results: Neonatal seizures (OR = 4.4) and maternal infectious diseases during pregnancy (OR = 2.6) were identified as a risk factor for the development of epilepsy in patients with CP($p < 0.05$). The mean age of seizures onset was 16 ± 21.5 months. Among epileptic CP patients, mainly focal 40 (51.3%) and generalized tonic-clonic 22 (28.2%) types of seizures were observed. Seizures occurred significantly more often(55.5%) in children with tetraplegia. Epileptiform activity was recorded in 60 (54.5%) patients, presented mainly with focal epileptiform activity (31.8%). 4 (3.6%) children had normal EEG. Changes during neuroimaging observed in 99 (90%) patients: white matter damage(39.1%), gray matter damage (20.9%) and miscellaneous changes (25,5%). No changes were found in 10% patients. Polytherapy (two AEDs or more) was used in 55 (50%) patients; seizure control was achieved in 13.6% of patients. Our study revealed a history of neonatal seizures (OR = 12.8; $p = 0.02$) and hemiplegic CP (OR = 12.8; $p = 0.014$) as a predictor of polytherapy in patients with CP and epilepsy.

Conclusions: Epilepsy in CP is generally poorly treated and often requires multiple anticonvulsants with a high risk of seizure recurrence after drug withdrawal.

Keywords:
cerebral palsy; epilepsy; EEG; antiepileptic drugs

EPNS21-335 Poster only
Epilepsy: Diagnosis and Investigations

Analysis of lipid levels in Polish children with epilepsy treated in mono- and polytherapy

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Objective: The use of antiepileptic drugs (AEDs) may increase the concentrations of some biochemical parameters like lipids, which were confirmed to be risk factors for cardiovascular diseases, both in adults and in children. The aim of the study was to compare serum lipids concentrations between epileptic children treated with valproic acid (VPA) and children with epilepsy treated with two or more AEDs.

Methods: In the study, 4 children with epilepsy treated with VPA (3 girls and 1 boy) and 21 children with epilepsy treated with two or more AEDs (i.e. LEV, CLB, VPA, LTG, CZP, VGB, TPM, PHB, STP and TPG) for at least 6 months (8 girls and 13 boys) were recruited. Age of the patients ranged from 3 to 18 years old. Serum lipids (i.e. total cholesterol (TC), triglycerides (TG), HDL-cholesterol and LDL-cholesterol) were measured in the blood serum using commercial enzymatic kits. The study was approved by the Ethics Committee. The study was funded within two research projects: 1) Project no. 2020/04/X/NZ5/00159 2) Project no. KNW-1-126/K/6/K.

Results: Children treated with VPA showed higher TC concentrations than children treated in polytherapy (182.55±79.84 mg/dL vs 128.75±26.68 mg/dL, respectively p=0.016). Similarly, mean LDL levels differed between the study groups (157.60±53.31 mg/dL in VPA subgroup vs 102.24±28.20 mg/dL in polytherapy group, p=0.009). Also, HDL levels were higher in VPA subgroup than in children treated in polytherapy (110.57±55.35 mg/dL vs 63.21±15.41 mg/dL, respectively p=0.016). Differences in remained lipid parameters were not significant.

Conclusions: Treatment with AEDs may influence levels of lipid parameters in children with epilepsy depending on number of drugs used. However, further studies are needed to confirm this preliminary findings.

Keywords:
epilepsy, children, therapy, serum lipids

EPNS21-351 Oral or poster
Epilepsy: Diagnosis and Investigations

Intractable epilepsy with Rahman Syndrome

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Objective: Genetic mutations in genes encoding proteins involved in epigenetic machinery have been reported in individuals with epilepsy, intellectual disability, congenital heart disease, and other disorders. Histone Gene Cluster 1 Member E, HIST1H1E, encodes Histone H1.4, is one of a family of epigenetic regulator genes, acts as a linker histone protein, and is responsible for higher order chromatin structure. HIST1H1E syndrome (also known as Rahman syndrome (RS), OMIM #617537) is a recently described intellectual disability (ID) syndrome.

Methods: Here, we report a girl patient with RS.

Results: 14 year old girl was followed up with intractable epilepsy. She also had dysmorphic facial appearance, skeletal anomalies and thoracic deformity. The patient was the sixth child of non-consanguineus healthy parents. She was born at term with a birth weight at 3.3 kg. She walked at 3 years and had a speech delay. She developed psychomotor retardation, intellectual deficiency and behavioral disorders. At the age of 2,5 years, she presented with seizure and developed epilepsy treated with levetiracetam, oxcarbazepine, clobazam. Morphological examination showed had full cheeks, bitemporal narrowing, high hairline, deep set eyes, downslanting palpebral fissures, hyperteloris, dental anomalies and caries, clinodactyly and scoliosis. Brain magnetic resonance imaging (MRI) revealed corpus callosum agenesis and encephalocele. Cardiac examination was normal and she had accessory spleen. To assess the cause of the intellectual deficiency, intractable epilepsy and many dysmorphic findings she had genetic testing. WES (whole exome sequence) revealed heterozygous changes of c.190-191insT in the HIST1H1E (NM_005321.2) gene.

Conclusions: RS is a rare genetic disease. Genetic testing may be necessary in the intractable epilepsy, intellectual disability, and dysmorphic findings. In this case, we tried to describe the clinical findings of this rare disease.

Keywords:
Rahman syndrome, epilepsy, intellectual disability, genetic

EPNS21-370 Oral or poster
Epilepsy: Diagnosis and Investigations

Defined genotypes of early onset epilepsies in Kazakhstan

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Objective:
Infantile and childhood epileptic encephalopathies are group of severe epilepsies that begin within the first year of life and often portend increased morbidity. Medical strategy and tactic for their management depends on genetic cause. There is no possibility for genetic assessment of children in Kazakhstan but we have a collection of data with already defined genes responsible for clinical presentations.

Methods: We analyzed children who had seizures that began in the first 3 years of life. The assumption that epileptic seizures in children are of a genetic nature occurred in the presence of the absence of structural changes on MRI of the brain. Such patients were recommended to undergo genetic testing using epileptic genetic panels in laboratories in other countries, since this type of diagnosis is not available in Kazakhstan

Results: During 2018-2020, we observed 350 infants. Some of them followed our recommendations and provided a genetic analysis privately. In total 12/15 children became eligible for targeted treatment, 3/15 were likely to have non epileptic stereotypies / movements, 2/15 were unlikely to respond to any therapy and all had a high chance of intellectual disability, behavioural and social communication disorders.

Conclusions:
We have demonstrated the potential impact of positive results from gene panel analysis in epileptic encephalopathy in Kazakhstan. Epilepsy gene panel analysis should be available within country and allow clinical-laboratory discussion of variants to confirm genotype/phenotype correlation accurately. More importantly, in country analysis would allow standardization and quality control of both the sequencing and interpretation of variants.

Keywords:
epileptic enchephalopathy, genetic, children

EPNS21-371 Oral or poster
Epilepsy: Diagnosis and Investigations

Etiologies Of Convulsive Status Epilepticus In A Tertiary Healthcare Institution In Children

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Objective: Convulsive status epilepticus (CSE) is one of the neurologic emergencies of childhood with varying degrees of impaired consciousness and motor symptoms.The International League Against Epilepsy catagorized the etiology of status epilepticus in four large groups; acute, remote, progressive and unknown. The aim of this study was to try to define the etiology of patients with CSE.

Methods: Children aged 1 month to 18 years who were diagnosed as having CSE were included in the study. The demographic characteristics of the patients, seizure type, duration of seizure, etiology of seizures, concomitant diseases, epilepsy history, antiepileptic drugs (AEDs) used, brain imaging, EEG reports, length of hospital stay and status were recorded.

Results: One hundred forty-five patients who were diagnosed as having CSE were included in the study, 60.7% of whom were male. According to the etiology of CSE, the most common group was found as unknown (48%) and a history of epilepsy was found in 72.9% in this group. Febrile (17%) and central nervous system infections (8.3%) were found to be the most common in acute etiology, respectively.The seizure type was focal onset in 55.9% of the patients.When the patients were compared according to their seizure type, the frequency of generalized seizures was higher in those who had seizures for acute etiologic reasons, and the frequency of focal seizures was found to be higher in seizures of unknown etiology (p=0.001). Epilepsy history was more common in the remote, unknown and progressive groups (88.9%, 72.9%, and 71.4%, respectively), where as it was found as 26.9% in the acute group Pulmonary complications developed most frequently. The mortality rate was 0.7%.

Conclusions: CSE remains an important neurological emergency in children with a history of epilepsy despite being under treatment.

Keywords:
convulsive status epilepticus; childhood; etiology

EPNS21-405 Oral or poster
Epilepsy: Diagnosis and Investigations

Pontocerebellar atrophy and congenital microcephaly: a novel phenotype related to PPP2R1A

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Objective: Mutations in phosphatases have barely been associated with developmental disorders. Recently, de novo PPP2R1A mutations have been described with a consistent phenotype: severe corpus callosum hypogenesis, epilepsy and severe intellectual disability

Methods: Our patient underwent exhaustive phenotyping and three cranial MRI were evaluated. A trio-based whole-exome sequencing was performed. The effect of the variant was tested at the mRNA level in blood samples. Immunofluorescent labeling of PPP2R1A in the patient's fibroblasts, for locating and quantifying this protein in the patient compared to control was done. The study was performed and quantified with a TCS SP8 spectral confocal laser scanning microscope.

Results: Our patient presented with congenital microcephaly, mild intellectual disability, and mild neuroaxonopathy that remained stable. He presents progressive pontocerebellar atrophy with normal corpus callosum. The WES trio identified a de novo unreported PPP2R1A variant (p.Arg21Cys), considered as deleterious by in silico predictors and located close to the catalytic unit. Confocal microscopy, revealed low cytoplasmic and nucleic PPP2R1A content in the patient's fibroblasts and the presence of aberrant protein aggregates in the cytoplasm, supporting the pathogenicity of the variant.

Conclusions: Pontocerebellar hypoplasia is usually a chronic and usually devastating condition with a heterogeneous molecular basis, where many cases remain unsolved.
PPP2R1A mutations have been associated with a consistent phenotype, most of them clustered close to the regulatory subunit binding region. Our patients' high impact PPP2R1A variant in the N-terminal region, nearer to the catalytic subunit, is out of the described cluster of mutations. Confocal microscopy immunofluorescence supports the pathogenicity of the variant but, still, functional studies are ongoing to support a new phenotype related to PPP2R1A.

Keywords:
protein phosphatase 2A, microcephaly, mild intellectual disability, and mild neuroaxonopathy

EPNS21-418 Poster only
Epilepsy: Diagnosis and Investigations

Epileptic encephalopathy, visual impairment and developmental retardation: CDKL5 deficiency disorder

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Objective: The cyclin dependent kinase like 5 (CDKL5) deficiency is a rare neurologic condition characterized by early onset developmental and epileptic encephalopathy. We aimed to descript of seizure types in patients with CDKL5 deficiency, an assessment of the seizure frequency, cortical visual impairment, and developmental milestones.

Methods: Seven patients with diagnosed with CDKL5 deficiency were compared clinical and EEG findings, seizures' response to treatment and prognosis.

Results: The median age was 17.2±11.3 (11-70) months. Mean age of seizure onset was 2.5±1.6 (1-5) months.Six of the patients were female and one was male. One had focal clonic, three had generalized tonic, two had generalized clonic, and the other two patients had epileptic spasms. All of them had psychomotor retardation. Visual impairment was present in one of patient, and was the first symptom before seizures. EEG of the patient with visual impairment revealed epileptic activities in the posterior regions of both hemispheres. Also one patient had similar epileptic activity at both occipital regions, temporal spikes in one patient, multifocal/generalized epileptic discharges and epileptic encephalopathic findings in the other four patients. Mutational analysis revealed different CDKL5 mutations for each patient. Patients was received multiple antiepileptic, and steroid treatment. Also, two patients received ketogenic diet. Average follow-up time was 17.7±7,5 months.Seizures remained resistant to treatment, and daily continued, but a significant reduction in seizures was observed in two patients with the ketogenic diet.

Conclusions: Early onset epilepsy with severe psychomotor retardation without a known etiology may be caused by a mutation in CDKL5. Visual impairment should be the first sign of CDKL5 deficiency. Clinical severity may be related to the location and type of mutations. The ketogenic diet is also a good alternative for seizure control in this group of epilepsy.

Keywords:
CDKL5 deficiency disorder ,epileptic encephalopathy

EPNS21-420 Oral or poster
Epilepsy: Diagnosis and Investigations

Super-refractory status epilepticus warranting life-saving hemispherotomy in a boy with focal cortical dysplasia and RANBP2 germline variant

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Objective: Focal cortical dysplasia (FCD) represents the most common cause of drug-resistant epilepsy. Somatic and germline variants in mTOR pathway genes are a known cause of FCD type II; genetic causes of FCD type I as well as genetic factors contributing to severe phenotypes of FCDs remain unclear. We present a case report of a patient with an exceptionally rapid development of drug-resistant MRI-negative focal epilepsy after an uncomplicated varicella infection evolving in super-refractory status epilepticus. Given his life-threatening condition, we performed an open brain biopsy that revealed FCD type Ia. Based on this knowledge we proceeded to a life-saving right-sided hemispherotomy. From a clinical perspective, we have never observed in our cohort such a severe phenotype caused by FCD type Ia. Therefore, a genetic contribution seems to be presumable.

Methods: Deep whole-exome sequencing (WES) of dysplastic brain tissue-derived DNA revealed no putative causal somatic variants. WES of blood-derived DNA detected a heterozygous paternally-inherited missense variant in gene RANBP2 - a gene with autosomal dominant inheritance and incomplete penetrance associated with a susceptibility to infection-induced acute necrotizing encephalopathy.

Results: We hypothesize that the missense variant could lead to a decreased function of the protein RANBP2, but not to a complete loss of function. In this line of evidence, the reported patient did not present with necrotizing encephalopathy but the missense variant could potentially have made the patient more susceptible to post-infectious encephalopathy and this susceptibility could have aggravated the symptoms and presentation of the patient's main diagnosis of FCD.

Conclusions: This report demonstrates a uniquely severe clinical course of FCD putatively modified by the RANBP2 variant. In addition, it highlights the significance of neuropathological examination in acute neurological setting that directly influenced our decision-making and treatment plans.

Keywords:
focal cortical dysplasia, epilepsy surgery, refractory status epilepticus, RANBP2, acute infection-induced encephalopathy, hemispherotomy

EPNS21-492 Oral or poster
Epilepsy: Diagnosis and Investigations

Attitude and approach of neonatologist and paediatric neurologist towards neonatal seizures: A multicentre study from the United Arab Emirates

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Objective: Neonatal seizures are difficult to diagnose due to their varied presentation. They can be difficult to diagnose clinically. This study was planned to assess the variation in the approach and management of neonatal seizures by neonatologists and paediatric neurologists in the United Arab Emirates (UAE).

Methods: A survey questionnaire was sent to all the licensed neonatologists and paediatric neurologists in the UAE by email. It contained questions related to overall attitudes and clinical practices.

Results: A total of 30 responses were received. Among them, 24 were neonatologists and 6 were paediatric neurologists working in the different parts of the UAE. Most of them worked in the level 3 Neonatal unit (90%). 19 respondents (63%) usually managed less than one case of neonatal seizures per month. 83% felt that seizures can affect the brain in various ways if untreated. A similar number of clinicians were comfortable in diagnosing clinical seizures based on the video of them. A third of them did not have access to aEEG facility whereas 40% believed that clinical diagnosis is enough and no EEG confirmation is needed. 86% were comfortable treating 'clinical only' seizures, whereas 73% agreed to treat electrographic-only seizures.
Blood glucose was the most common first-line investigation followed by serum electrolytes. MRI brain was preferred in all the neonates with seizures by 40%.
Phenobarbitone remained the first choice of anticonvulsant treatment while Levetiracetam and phenytoin were second and third respectively. 96% of neonatologists would seek a paediatric neurologist's opinion before starting the third line medication. Over half of them would continue antiepileptic treatment for at least 3-6 months. There was no difference between the management of term and preterm infants

Conclusions: In our cohort, we observed variability in the approach in the management of neonatal seizures by neonatologists and paediatric neurologists from the UAE.

Keywords:
neonatal seizures, attitude, EEG

EPNS21-527 Oral or poster
Epilepsy: Diagnosis and Investigations

Focality in Typical Absance Epilepsy in Childhood

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Objective: Childhood absence epilepsy (CAE) is one of the most frequently seen epileptic syndromes during childhood period and it is one most seen prototypes of generalized epilepsies. Although the typical electroencephalography (EEG) pattern is generalized 3Hz spike and wave discharges (SWD), focal inter-ictal discharges had also been documented in case reports and in a small number of documents. The aim of the the study was to investigate the amplitudes of inter-ictal 3Hz SWD within the 1st second in drug naive Typical Absence Epilepsy (TAE) patients in order to address areas with maximal electronegativity at the initiation of generalized discharges.

Methods: EEG records of children with TAE prior to the drug treatment had been evaluated retrospectively by 2 child neurologist first than by artificial intelligence for the amplitudes of 1st second of 3Hz SWD. Maximum electronegativity areas had been documented and classified as focal, bilateral and generalized accordingly.

Results: Eleven patients in which 6 (54,5%) of them were girls enrolled to the study. One hundred and twelve 3Hz SWD had been evaluated from 11 patients. Among those discharges within the 1st second; maximum electronegativity areas were documented as focal for 44 (39,2%), bilateral for 8 (7,1%) and generalized for 60 (53,5%). Among focal electronegativity areas mostly right central, left occipital and midline parietal areas were documented with the rates of 12 (27,3), 7 (15,9%) and 6 (13,6%) respectively. Eight (7,1%) of maximum electronegativity areas detected bilaterally in which 7 (87,5%) of them were originated from fronto-polar areas.

Conclusions: Focal maximal electronegativity areas within the 1st second of 3Hz SWD were frequently observed in drug naive TAE patients. Focal areas within the brain may be responsible and contribute to absence seizures that appear bilaterally symmetric and generalized clinically.

Keywords:
childhood absence, typical absence epilepsy, focal epilepsy

EPNS21-536 Oral or poster
Epilepsy: Diagnosis and Investigations

Epilepsy and its imitators in children referred to a first seizure clinic of a tertiary hospital

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Objective: To describe the distribution of diagnoses in children referred to a tertiary hospital's first seizure clinic.

Methods: We retrospectively reviewed medical records of children referred to the first seizure clinic of a tertiary hospital between 2008 and 2018 after experiencing one or more seizure-like events. This outpatient clinic combines consultation with routine EEG recording. The initial diagnosis, made at first consultation, is compared to the definitive diagnosis after follow-up and additional examinations. Data collection for our study is ongoing (currently ±50% of total data).

Results: We included 489 children (56% boys) with a mean age at first consultation of 6.8 years (range 0.2-17.4). Epilepsy was eventually diagnosed in 168 children (34%), and in 115 (69%) already at first consultation. We saw epileptiform abnormalities on routine EEG recordings in 107 (63%) children with epilepsy, and 84 (50%) children with epilepsy were eventually diagnosed with an epilepsy syndrome. Epilepsy etiologies were, among others, presumed and established genetic in 37% and 17%, respectively, followed by structural in 20%. We rejected the epilepsy diagnosis in 297 children (61%) and in 201 (68%) directly at first consultation. Of the children without epilepsy, 23 (8%) showed epileptiform EEG abnormalities. The most common diagnosed epilepsy imitators were staring spells (29.8%), provoked (mainly febrile) seizures (10.6%), and vasovagal syncope and reflex anoxic seizures (9.4%). The final diagnosis remained unclear in 24 children (5%). The mean time to the definitive diagnosis was 2.9 months (median 0, range 0-113). We correctly diagnosed more than 85% of all children within six months, and more than 90% within 12 months.

Conclusions: Our first seizure clinic population is heterogeneous, and the diagnostic value of routine EEG recording is moderate. Our outpatient clinic, however, proves itself efficient in promptly and accurately diagnosing epilepsy.

Keywords:
childhood epilepsy; first seizure; first seizure clinic; epilepsy imitators; diagnostic accuracy

EPNS21-538 Oral or poster
Epilepsy: Diagnosis and Investigations

GABRA5 gene mutation: An emerging cause of genetic epilepsy in infants and review of the literature

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Objective: There may be neurometabolic, infective, intracranial and genetic causes of epilepsy. Here, we present a case that has a de novo mutation in the GABRA5 gene. Seizures started from the postnatal 40th day. p.Val294Phe mutation was detected in the c.880G>T in the GABRA5 gene. This pathogenic change has been reported four times before in the literature.

Methods: A 10-month-old boy was evaluated in our clinic with tonic-clonic seizures starting at 40 days after birth. There was no family history of epilepsy. He presented with axial hypotonia. His maximal motor capacity was to sit with support. There was no spasticity. He could recognize his mother but did not have other social interactions or babbling. His seizures were generalized lasting 5 to 6 seconds in attacks occurring several times daily. EEG initially showed voltage suppression but repeat recordings had active epileptic focus in the centro-temporo-occipital regions, more on the left, spike and wave discharges in the anterior temporal region more on the right. His cranial CT and MRI showed benign subarachnoidal enlargement (extraventricular hydrocephalus).

Results: He was treated with phenobarbital, vigabatrin, and levetiracetam with partial response. The whole-exome sequence sequencing analysis was requested. A p.Val294Phe variation in the GABRA5 gene c.880G> T nucleotide was detected at chromosome location 15q12. This was later confirmed by Sanger sequencing. This dominant mutation had appeared de novo in 4 patients reported so far. After genetic tests, previous medications but phenobarbital were stopped and he was initiated with topiramate and clobazam. The response has been obtained with 90% reduction in seizure frequency.

Conclusions: In addition to well-known cases of genetic epileptic encephalopathy, there are newly emerging developmental and epileptic encephalopathy cases, mainly in children. Some of these are the faults of receptors related to electrophysiological inhibition such as has happened with our case.

Keywords:
genetic, resistant, epilepsy, GABA,

EPNS21-549 Poster only
Epilepsy: Diagnosis and Investigations

Periventricular nodular heterotopia, causes of epilepsy pharmacoresistant.

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Objective: To describe the characteristics of epilepsy in patients with nodular periventricular heterotopias (PVNH) (single and multiple), delineate the landscape of genetic abnormalities, and assess the cognitive and neurodevelopment outcomes.

Methods: Observational and retrospective study. We reviewed medical records of 17 patients with NPVH. We collected clinical data (age, sex, family history, perinatal events, age at seizure onset, seizure types, neurological exam, previous and current treatment and response, neurodevelopment, and cognitive impairment), complementary tests performed and results (genetic studies, intercritical video-EEG, and description of brain MRI PVNH (unilateral, bilateral, focal or diffuse, and other associated structural abnormalities).

Results: 60% were females, 30% had prenatal complications, 30% had a family history of epilepsy and PVH. Neonatal onset symptoms (hypotonia) in 30%. Seizures onset was < 5 years, and in 30% of early onset started prior to the age of 12 months, with intercritical anomalies in vEEG, the seizures could be either focal or generalized, and refractory in 14 patients. High genetic variability. 50% presented drop attacks. Pharmaco-sensitive at valproic acid and clobazam. Ten patients had precipitants (physical stress, emotions, fever, sleep deprivation) and aura (distorted vision and objects appear smaller). 50% presented post ictal confusion and headache. Multiple heterotopia were associated to epilepsy severity. 10% improved with stimulation of the vagal nerve. 40% presented neurodevelopmental delay (30% autism spectrum disorder).

Conclusions: We present a series of 17 pediatric patients with epilepsy and PVNH characterized by an early onset of epilepsy, refractory generalized seizures, impairment in neurodevelopmental and intellectual disabilities.

Keywords:
Heterotopia,epilepsy,pharmacoresistant,seizures.

EPNS21-572 Oral or poster
Epilepsy: Diagnosis and Investigations

Therapeutic drug monitoring of Fenfluramine and its metabolite norfenfluramine: pharmacokinetic variability and the impact of age and concomitant antiseizure medications

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Objective: Determine the plasma concentration and pharmacokinetic variability of fenfluramine (FFA) and its main active metabolite norfenfluramine (norFFA) in relation to the prevalence of adverse effects. Explore the impact of age and concomitant medications including stiripentol (STP).

Methods: Patients receiving stable FFA treatment for refractory epilepsy could be included. Plasma concentration of (nor)FFA was determined by liquid chromatography tandem spectrometric analysis in samples collected between June 2015 and December 2020. Demographic and clinical variables were collected retrospectively. Data was analysed with a linear mixed model. Intrapatient coefficient of variation and interpatient variability was calculated.

Results: We collected 321 samples from 61 patients (33 males, 28 females), 49 with Dravet syndrome, 7 with Lennox-Gastaut syndrome and 5 with a Developmental and Epileptic Encephalopathy. Mean (± SD) age was 14.8±9.1years. Average treatment duration was 5.1±7.4y at 0.33 ± 0.16 mg/kg/day. The median FFA plasma concentration was 41.4 µg/L (range 5.1 - 712.5), median norFFA concentration 28.1 µg/L (range 2.6 - 149.6). Interpatient variability was higher than intrapatient variability (114% vs 36%). FFA concentration was linearly related to the daily dose ($p<0.001$). FFA C/D increased with age ($p< 0.001$), with a 179% increase in the median FFA C/D in patients aged >=18 years compared to those <18y (STP excluded). Median FFA C/D was 428% higher ($p<0.001$), norFFA C/D 83% lower ($p<0.001$) and norFFA/FFA 23% lower ($p<0.001$) in samples from subjects treated with STP.
Higher C/D FFA ratio was associated with fatigue ($p=0.017$) and somnolence ($p<0.001$), but not anorexia ($p=0.245$). Gender and other ASMs were not associated with significant variations in (nor)FFA C/D.

Conclusions: An extensive inter- and intrapatient variability is seen in (nor)FFA plasma concentrations. Reduced weight-normalized doses are required with aging and STP use since higher FFA C/D are associated with fatigue and somnolence.

Keywords:
Fenfluramine, therapeutic drug monitoring, plasma concentration, pharmacokinetics, antiseizure medication

EPNS21-588 Poster only
Epilepsy: Diagnosis and Investigations

Combined oxidative phosphorylation deficiency 24 - novel biallelic variants in NARS2 gene

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Objective: Combined oxidative phosphorylation deficiency 24 (COXPD24) is an autosomal recessive mitochondrial disorder with large phenotypic variability. Symptoms most often appear in the first months of life and include mainly epileptic seizures, global developmental delay, hypotonia and hearing impairment. COXPD24 arises as a result of biallelic mutations in asparaginyl-tRNA synthetase 2 gene (NARS2) located on chromosome 11q14. The gene encodes the enzyme, asparaginyl-tRNA synthetase, crucial for mitochondrial aminoacylation, which is required to initiate mitochondrial protein synthesis.
Here we present a patient with early-onset severe epilepsy leading to several super-refractory status epilepticus, diagnosed with novel variants in NARS2 gene associated with his clinical presentation.

Methods: Within diagnostic investigation repeated MRI scans and video-EEG monitoring were realized. Blood samples of the patient and his parents were sent, among other things, to genetic laboratory in Munich where the whole exome sequencing (WES) was completed. Exonic DNA fragments were enriched using the SureSefect Human All Exon Kit (Agilent, 60Mb V6).

Results: Our patient with repetitive super-refractory status epilepticus with focal finding of continuous epileptiform activity on video-EEG monitoring and enlarged subarachnoid space with progression in one month on MRI scans was genetically tested using WES method. An autosomal-recessive filter identified two rare compound-heterozygous variants in NARS2 (NM:_024678.6): [c.749G>A; p.(Arg250Gln] + c.418C>T; p.(Arg140*)] classified as likely pathogenic in the ClinVar database. Each of the healthy parents was a carrier for one of the identified variants.

Conclusions: Patients with unidentified epileptic encephalopathy with recurrent super-refractory status epilepticus are suitable candidates for whole exome sequencing. By obtaining the genetic results we were able to avoid further repeated diagnostic procedures. This only highlighted the importance of genetic testing.

Keywords:
combined oxidative phosphorylation deficiency 24, super-refractory status epilepticus, whole exome sequencing, NARS2 gene

EPNS21-60 Oral or poster
Epilepsy: Diagnosis and Investigations

Epileptic seizures and Electroencephalogram characteristics in children with Neurofibromatosis type 1, a five years experience of a tertiary center

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Objective: Neurofibromatosis type 1 (NF-1) is the most common neurocutaneous phakomatosis in children. Epilepsy is a rare comorbidity. Underlying pathophysiological pathways of NF-1 epileptogenesis are not well understood. Reports of seizure characteristics and Electroencephalogram (EEG) findings are sparse. We aim to study children with both NF-1 and epilepsy in our center for characterization of clinical and neuro-diagnostic evaluations.

Methods: We have reviewed all patients' children who were seen in our institution as new or follow-up patients with NF-1 for 5 years (2016-2020). Retrospective chart review was carried out. Patients with epilepsy diagnosis based on the International League Against Epilepsy revised definition of 2017 were identified. Demographic, clinical, neuro-radiological and neurophysiological data were reviewed and analyzed.

Results: 118 pediatric NF-1 patients were identified. Out of them, 16 patients (13%) were diagnosed with epilepsy. 10 patients were female and 6 were males. Average age of epilepsy diagnosis was 8 years old. 11 patients (69%0) had focal seizure semiology, whereas 5 patients (31%) had generalized seizures. 75% of patients were well controlled on no or a single seizure medication. Independent or multifocal Focal epileptiform discharges were the most prevalent EEG signature in 81% of patients, although 1 patient (6%) had normal interictal EEG. No significant correlation between patterns of epileptiform discharges and presence or distribution of intracranial tumors.

Conclusions: Epilepsy is a relatively rare NF-1 comorbidity, although it is probably underdiagnosed given the higher prevalence in our study. Seizures are often of focal semiology and likely to be easily controlled. Focal and multifocal spike epileptiform discharges are the typical interictal EEG findings. Correlation of clinical and EEG findings with intracranial lesions is poor.

Keywords:
Neurofibromatosis, epilepsy, EEG

EPNS21-603 Oral or poster
Epilepsy: Diagnosis and Investigations

Refractory epilepsy associated with lobar hemimegalencephaly

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Objective: Malformations of cortical development are a common cause of refractory epilepsy. PTEN mutations have a wide spectrum of clinical phenotypes referred to as PTEN hamartoma tumor syndrome and the association with megalencephaly has been described.

Methods: Case report.

Results: Eight months-old female, only daughter of non-consanguineous parents, unremarkable perinatal period. Somatometric parameters adequate for age except head circumference in 97th percentile. No dysmorphisms. Since the third day of life, she presented with frequent short lasting, focal seizures characterized by upper eyelid myoclonia, conjugated eye deviation and followed by clonic movements of the left hemibody. She was started on phenobarbital and levetiracetam, with poor response. EEG showed signs of severe right hemispheric dysfunction, with frequent temporo-occipital epileptic discharges. Cranial MRI revealed an extensive cortical development malformation of the right temporal and occipital lobes, suggesting lobar hemimegalencephaly. Therapeutic strategy was optimized with vigabatrin in association with phenobarbital, and then phenytoin, with scarce response. She started ketogenic diet (KD) at 6 weeks of age with complete seizure control. Extensive diagnostic workup for metabolic and genetic causes was made. NGS panel for cortical anomalies and neuronal migration defects revealed a PTEN (NM_0003114.6): c.389G>T p. (Arg130Leu) variant, classified as pathogenic. Parent testing is ongoing. Currently, the infant has a moderate developmental delay and is seizure free, under KD, vigabatrin and phenytoin.

Conclusions: Despite the patient's young age, KD was a safe and successful option, allowing epilepsy control until the possibility of surgery treatment. We highlight KD should be considered early during the course of epilepsy, even in this age group. Further studies of KD in neonates and infants with cortical malformations would be useful.

Keywords:
epilepsy, megalencephaly, ketogenic diet, PTEN

EPNS21-605 Oral or poster
Epilepsy: Diagnosis and Investigations

Epilepsy and BRAF Mutations: Phenotypes, Natural History and Genotype-Phenotype Correlations

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Objective: Cardiofaciocutaneous syndrome (CFCS) is a rare developmental disorder caused by upregulated signaling through the RAS-mitogen-activated protein kinase (MAPK) pathway, mostly resulting from de novo activating BRAF mutations. The aim of our study was to define the natural history of epilepsy in this syndrome and exploring genotype-phenotype correlations

Methods: We performed an observational study, including 34 patients with molecularly confirmed diagnosis (11 males, mean age: 15.8 years). The mean follow-up period was 9.2 years. We performed neurological examination, cognitive assessment when possible, neuroimaging, electrophysiological assessment and systematic assessment of epilepsy features. Correlation analyses were performed, taking into account epilepsy features and genotype.

Results: All subjects presented developmental delay. Cognitive impairment was profound in eight subjects, severe in twelve, moderate in seven and mild in five individuals. Seven patients showed autistic traits.
Epilepsy was documented in 64% of cases, a higher prevalence compared to previous reports. Patients were classified into three groups based on their electroclinical features, long-term outcome and response to therapy: group 1 with severe epileptic phenotype, group 2 with mild epileptic phenotype, group 3 epilepsy-free.

Conclusions: Our data indicate that epilepsy occurs in CFCS more commonly than previously reported, and that patients can be classified into different groups based on their electroclinical features, long-term outcome and response to therapy. The neurocognitive impairment and regression occurring in patients with severe epilepsy. A genotype-phenotype correlation linking the presence/severity of epilepsy to the nature of the structural/functional consequences of mutations was observed, providing a stratification based on genotype to improve clinical management of these patients

Keywords:
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EPNS21-657 Oral or poster
Epilepsy: Diagnosis and Investigations

Rethinking FIRES - are we missing the source of the flames?

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Objective: Febrile infection-related epilepsy syndrome (FIRES) is a severe epileptic encephalopathy which affects well children and is thought to be immune-mediated. We present a case of a child whose clinical course was consistent with FIRES, with a finding that questions long-held etiological paradigms.

Methods: An 8y old girl with mild learning difficulties was admitted to the Pediatric Intensive Care Unit with 2 consecutive prolonged, refractory status epilepticus (SE) episodes lasting 4 and 6 weeks respectively following a febrile illness. No infectious, metabolic, toxic or structural explanation was identified and she was treated empirically with a diagnosis of FIRES with anti-seizure medications (ASMs), IVIG, plasmapheresis, steroids, ketogenic diet (KD) and electro-convulsive therapy. After the 2nd episode of SE, her functional status significantly deteriorated and she is non-ambulant, with limited verbal communication. She continues to have short seizures, despite multiple ASMs, vagal nerve stimulation and the KD. A Next Generation Sequencing epilepsy panel was performed 8 years after seizure onset.

Results: The panel demonstrated a pathogenic variant on the DNM1L gene. This mutation has been reported in a neonate with a lethal encephalopathy, a child with global developmental delay and refractory epilepsy and 4 children with previously near-normal development until onset of refractory epilepsy during childhood. We did not identify this variant in other patients diagnosed with FIRES in our hospital.

Conclusions: While FIRES and its umbrella diagnosis NORSE have been attributed to a fulminant inflammatory response in the CNS, our finding highlights the role that a genetic etiology may have in a subset of patients, and the imperative to perform genetic testing on all children presenting with FIRES. Further understanding of genetic causes of childhood onset refractory epileptic encephalopathies will guide management of this complex population.

Keywords:
FIRES; genetics; status epilepticus

EPNS21-710 Oral or poster
Epilepsy: Diagnosis and Investigations

Neural correlates of working memory function in children with focal lesional epilepsy

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Objective:
Epilepsy is one of the most common brain disorders. In addition to seizures, children with epilepsy face a high risk of cognitive impairments, including deficits in executive functions (EF) such as working memory (WM). Bilaterally represented EF like WM are likely to rely on interhemispheric white matter tracts like the Corpus Callosum (CC), but the link between CC integrity and EF in children with epilepsy is not yet known.

Methods: Using Diffusion Tensor MRI, we assessed the link between CC microstructure and EF in focal lesional epilepsy. CC integrity was quantified by Fractional Anisotropy (FA) in the CC genu, body, and splenium in 17 children with lesional epilepsy and 24 controls. WM was assessed from the digit span subtest of the WISC.

Results: In a Univariate ANOVA controlling for age, FA was lower in patients in the CC body and genu but not the splenium. Patients had lower digit span, and group*FA interactions on WM were evident in the CC body, such that the digit span correlated positively with CC body FA in patients but not in controls.

Conclusions: EF deficits in children with focal lesional epilepsy are linked to lower microstructural integrity of the body of the CC.

Keywords:
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EPNS21-80 Poster only
Epilepsy: Diagnosis and Investigations

Neonatal Seizures - Don't Forget the Alkaline Phosphatase

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Objective: Pyridoxine dependent epilepsy (PDE) is a rare cause of neonatal seizures. We present an exceedingly rare case of congenital hypophosphatasia presenting with pyridoxine responsive seizures.

Methods: A healthy term male infant was admitted at six days of age with refractory multifocal clonic seizures associated with cyanosis. These were refractory to phenobarbitone, phenytoin and levetiracetam. He was commenced on pyridoxine and intubated and transferred to paediatric intensive care. Brain MR, EEG and metabolic investigations including CSF studies were normal. He had no further seizures and was extubated after 48 hours and was discharged after nine days, having remained seizure free. He represented on Day 22 of life with significant apnoeas requiring intensive care. No seizures were noted and a repeat EEG was unremarkable. At this stage, it was noted that his alkaline phosphatase (ALP) was undetectable on all prior blood results, with normal corrected calcium and phosphate. Subtle rib thinning was noted on his chest X-ray. Urine and CSF phosphoethanolamine were elevated. A clinical diagnosis of hypophosphatasia was made. Asfotase alfa was commenced urgently within a few hours of the diagnosis. Targeted gene testing confirmed a heterozygous mutation in the ALPL gene consistent with hypophosphatasia. Following discharge, he has had no further seizures on pyridoxine and is showing good developmental progress at 6 months.

Results: PDE is commonly seen secondary to defective alpha-aminoadipic semialdehyde (AASA) metabolism. In severe forms of hypophosphatasia, tissue-nonspecific ALP is unable to hydrolyse pyridoxal-5-phosphate (phosphorylated pyridoxine), leading to pyridoxine deficiency and reduced inhibitory GABA transmission, triggering seizures.

Conclusions: Recognition of low ALP in a neonate with seizures is crucial as detection of congenital hypophosphatasia is associated with improved outcomes with early treatment initiation.

Keywords:
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EPNS21-97 Oral or poster
Epilepsy: Diagnosis and Investigations

PHENOTYIPING AND DIAGNOSTIC TIMING IN NGS-DIAGNOSED GENETIC DEVELOPMENTAL ENCEPHALOPATHIES WITH EPILEPSY AND MOVEMENT DISORDERS

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Objective: To characterize the relevance of phenotyping and diagnostic timing to achieve a molecular-genetic diagnosis in developmental encephalopathies with epilepsy and movement disorders (DEEMD).

Methods: A retrospective analysis of patients (period 2010-2020) with genetically confirmed DEEMD was realized. According to their movement disorders phenotype, patients were divided in Group A (hyperkinetic movement disorders) and Group B (hypokinetic movement disorders).
Clinical info, compatibility with published phenotypes, timing for the etiological diagnosis and the temporal distribution of the diagnostic delay were collected.
Statistical analysis (SPSS26.0) included: descriptive parameters, Chi2-test, ANOVA and Bonferrori correction for groups comparisons (p= 0.05).

Results: 61 patients (32 females and 29 males), with a mean age of 15,77±9.31 years and 37 different genetic diseases, were recruited.
The mean age at the molecular genetics diagnosis was 8.69±8.83 years with a mean diagnostic delay of 6.29±8.12years. The diagnostic yield of molecular genetic investigations was higher in the period 2015-2020.
Group A included 47 patients (27 females and 20 males) and Group B had 14 patients (5 females and 9 males). The mean diagnostic delay was longer in Group B (13,47±13,60 versus 4,15 ±3,38 years).
In Group A an earlier onset of seizures was observed (2,77±3,29 versus 4,05±3,9 years) while the onset of movement disorders was noticed earlier in Group B (2,5±3,59 versus 3,21±3,61 years).
The initial epileptic manifestations mainly included generalized motor onset seizures (Group A) and focal seizures with impaired awareness and motor onset (Group B). The compatibility with published phenotypes was higher in Group A

Conclusions: The reported cohort analysis suggested a) variable combinations of epilepsy and movement disorders phenotypes in genetically determined DEEMD b) a higher diagnostic difficulty in patients with hypokinetic movement disorders.

Keywords:
epilepsy, movement disorders, developmental encephalopathy, genetics

EPNS21-141 Oral or poster
Epilepsy: Medical & Surgical Treatment

The efficacy of vagus nerve stimulation in epilepsy with polymicrogyria

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Objective: To evaluate the efficacy of vagus nerve stimulation (VNS) as an alternative treatment for drug-resistant epilepsy with polymicrogyria (PMG).

Methods: We analyzed the efficacy of VNS in 5 patients with PMG, the mean age was 17.4±3.92 years old, 4 females and 1 male. The follow-up period after VNS implantation was 3±1.6 years. According to MRI, 2 patients had unilateral frontoparietal PMG, 1-unilateral frontoparietal and perisylvian PMG, 1-unilateral parasagittal parieto-occipital PMG, 1-bilateral frontoparietal and parasagittal parieto-occipital PMG. 3 patients had periventricular heterotopia: 2-unilateral, 1-bilateral. 3 patients had concomitant brain abnormalities: hemiatrophy(1), white matter abnormality(2), Dandy-Walker anomaly and hypoginesia of the corpus callosum(1). The average age of epilepsy onset was 3.3±1.8 years old. All patients had drug-resistant epilepsy with focal seizures, 2-with bilateral tonic-clonic. The maximum frequency of seizures was daily, the maximum remission period was from 0 to 24 months (8.5±7.8). All patients had cognitive impairment: mild(2), moderate(2), severe (1). 2 patients had hemiparesis, 2-coordination disturbance. According to EEG data, all patients had focal and bilaterally synchronous epileptiform activity. Current settings of VNS were: output current 1.75-2.25mA, signal frequency 30Hz, pulse width 500sec, signal on time 30sec, signal off time 1.8-5min.

Results: VNS efficacy was as follows: 2 patients showed a significant improvement (the reduction of seizures by 75-100%), 3-a slight improvement (0-25%). The best efficacy was achieved in the patients with unilateral frontoparietal PMG, without heterotopia. Both patients had hemiparesis, mild/moderate cognitive impairment.

Conclusions: VNS therapy had an excellent result in 2(40%) patients with PMG. Both patients were similar in clinical presentation. This theme requires further research because few studies about treating epilepsy related to PMG with VNS are available.

Keywords:
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EPNS21-145 Oral or poster
Epilepsy: Medical & Surgical Treatment

Approach to EEG surveillance and preventive epilepsy treatment in tuberous sclerosis complex - results of international survey.

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Objective: Tuberous sclerosis complex (TSC) is characterized by high risk of early-onset epilepsy and developmental delay. Recently, EEG monitoring in infants with TSC and preventive antiepileptogenic treatment have been proposed to improve epilepsy and neurodevelopmental outcome.
To explore how recent studies and recommendations regarding EEG monitoring and preventive epilepsy treatment have influenced the clinical practice of epilepsy management among children with TSC.

Methods: A survey on the epilepsy management approach in infants with TSC was sent by e-mail to 165 clinicians who actively participated in TSC international research conferences in years 2016 - 2019. Additionally, the e-mail addresses of TSC referral centers were collected from national TSC organizations. The survey was also distributed by the newsletter of the American Epilepsy Society. Only responses from centers taking neurological care of children with TSC were included in the study.

Results: Sixty-one responses from 23 countries were analyzed.
Sixty respondents answered questions concerning infants, and 95% of them (57/60) perform at least one EEG study before epilepsy onset and 70.0% (42/60) conduct regular EEG monitoring. Most of the clinicians perform video EEG (42/61, 68.8%). 51.7% of respondents, mostly from Europe, Australia, and South America, declared preventive antiepileptic treatment in infants with TSC. Vigabatrin is a preferred drug in patients younger than 2 years both in focal (61.7%) and generalized (56.7%) seizures.

Conclusions: The concepts of pre-seizure EEG monitoring and epilepsy prevention is already implemented in the number of TSC centers.

Keywords:
tuberous sclerosis complex epilepsy prevention EEG surveillance

EPNS21-150 Oral or poster
Epilepsy: Medical & Surgical Treatment

Electroclinical Features and Seizure Outcome of Patients with Hemimegalencephaly: A Single Center Experience

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Objective: Hemimegalencephaly is a rare and severe congenital brain malformation usually resulting in severe epilepsy and cognitive impairment. We aim to review the clinical, electrographic characteristics and treatment outcome of patients with hemimegalencephaly.

Methods: Patients who were admitted to video-EEG monitoring unit between 2007-2021 were included. Clinical, radiological features, EEG data and treatment outcome were reviewed.

Results: Ten patients (M/F: 5/5) were evaluated. Age at seizure onset was median two days (0-120 days). Age at video-EEG monitoring was median 9 months (21 days-4 years). Hemimegalencephaly was left-sided in eight patients and right-sided in two. Nine patients had isolated, and one patient had a syndromic form of hemimegalencephaly. All patients had a history of status epilepticus, and numerous daily seizures. The patients were on 2-6 (median 4) antiseizure medications at the time of admission. One patient had focal non-motor, five patients had focal motor seizures, four patients presented with multiple seizure types. Interictal EEGs revealed unilateral discharges convergent with neuroimaging findings, in all but one patient. Ictal EEGs showed onset over the affected hemisphere in seven patients, generalized onset in one patient and both generalized and unilateral onset in one patient. One patient had independent ictal onset from both hemispheres. In addition to polytherapy, two patients received ketogenic diet, one patient received sirolimus, and two patients received both. Four patients underwent hemispheric surgery, one died perioperatively. One patient had Engel class 1 seizure outcome and two had Engel class 3 outcome at final follow-up visit. The remaining six patients continued to suffer from daily seizures at final follow-up.

Conclusions: Hemimegalencephaly constitutes a unique etiology which should be managed in specialized pediatric epilepsy centers. The results of the current study highlight the potential challenges of treatment in patients with hemimegalencephaly.

Keywords:
Hemimegalencephaly, video-EEG monitoring , epilepsy, children

EPNS21-171 Oral or poster
Epilepsy: Medical & Surgical Treatment

Long term use of the ketogenic diet in difficult to treat epilepsy: An evaluation of outcomes and adverse effects

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Objective: The ketogenic diet (KD) is known to be an effective treatment for difficult to treat epilepsy and GLUT-1 deficiency. Important side effects include dyslipidaemia and renal stones. Patients are usually treated for 2-3 years, although some remain on KD for considerably longer. This study aimed to evaluate the KD's efficacy, as well as the factors associated with long-term adverse effects.

Methods: 49 children who had been on KD for at least 12 months between January 2015 and February 2019 were included in this study. Treatment efficacy and side effects were recorded via standardised proformas. Patients with renal stones were compared to those without, focusing on clinical characteristics including; syndromic diagnosis, mobility levels, use of carbonic anhydrase inhibitors, as well as laboratory values including urine calcium-creatinine ratio and serum lipids.

Results: 91.7% of patients' parents/carers reported at least 50% reduction in seizures with the KD. Six patients (12.2%) developed renal stones or nephrocalcinosis independent of clinical characteristics. Rates of high urine calcium-creatinine ratios were not significantly different between groups (renal stones 50% vs no renal stones 39.29%, p=ns). Equally, rates of high triglycerides did not differ between groups (50% vs 48.65%, p=ns). Hypercholesterolaemia was more frequently seen in those with renal stones (50% vs 11.9%, p=0.05) and patients who were treated for longer than 5 years displayed a significantly higher rate of hypercholesterolaemia (44.44% vs 10.26%, p=0.031).

Conclusions: Although treatment efficacy of the KD is encouraging, we encountered significant adverse effects including the formation of renal stones and hypercholesterolaemia. Longer-term patients may be at risk of hypercholesterolaemia and should be monitored for associated complications. Future work should seek to validate these findings and look for other potential associations that this study was unable to comment on.

Keywords:
Epilepsy, ketogenic diet, renal stones, seizure, drug-resistant, GLUT-1

EPNS21-2015 Oral or poster
Epilepsy: Medical & Surgical Treatment

Comparison of cognitive and behavioural outcomes and quality of life of Low Glycemic Index Therapy and Modified Atkins Diet among children and adolescents with Drug Resistant Epilepsy: An open label randomized trial

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Objective: Ketogenic diet has been the mainstay of treatment of drug-resistant epilepsy(DRE). No large comparative trials have been conducted to assess the cognitive and behavioural outcomes of less restrictive diets like Modified Atkin's Diet(MAD) and Low-Glycemic-Index-Therapy(LGIT). This study compares the cognitive and behavioural outcomes as well as the quality of life of children and caretakers with DRE on MAD and LGIT.

Methods: The study was an open label randomized trial(NCT03764956). Children with DRE were randomized to receive either MAD or LGIT as an add-on to the ongoing anti-epileptics. Cognition and behavior of the subjects were assessed by VSMS and CBCL scales. The quality of life of subjects and caretakers were assessed using PedQL(< 5 years), QOLCE-55(>5 years) and WHOQOL BREF scales respectively.

Results: 113 children(92 boys) with mean age of 6.2 years(1.2-15 years) received MAD(n=56) or LGIT(n=57). 94 children completed 24 weeks of therapy and one child in the LGIT group expired due to reasons unrelated to therapy. Paired t test revealed significant decrease in CBCL score(-1.075+0.99, p=0.033) in MAD arm after 24 weeks therapy which correlated with better behavioural profile. In both arms WHOQOL BREF scores increased significantly which indicated better quality of life of caretakers after 24 weeks(MAD: 2.46+1.24, p=0.0002; LGIT: 2.35+1.27, p=0.0006). No statistically significant differences were detected in CBCL in LGIT arm or VSMS, PedQL and QOLCE-55 in either arm. Mean(+SD) percentage seizure reduction of 58.4%(69.1-47.6) in the MAD sub-group and 59.2%(68.9-49.6) in the LGIT sub-group was noted and the difference was statistically not significant. Adverse effects occurred in 30.9% subjects in the MAD group and 21.8% in the LGIT group.

Conclusions: MAD therapy can lead to better behavioral outcome independent of seizure reduction. Both MAD and LGIT therapy can lead to better quality of life in the caretakers. Both LGIT and MAD are efficacious in seizure reduction after 24 weeks of therapy.

Keywords:
Drug refractory Epilepsy, Modified Atkins Diet, Low Glycemic Index Therapy

EPNS21-2047 Oral or poster
Epilepsy: Medical & Surgical Treatment

Neuro-technology: A systematic review on medical devices utilized for epilepsy prediction and management

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Objective: The aim of this systematic review was to elucidate the latest advancements of medical devices for the management and prediction of epileptic seizures.

Methods: This systematic literature review was guided by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). Databases such as PubMed, Scopus, and Embase were used for the literature search. The search strategy included terms for prediction, management and treatment devices for epilepsy.

Results: A final total of 27 articles were selected and systematically studied and included in this review. The 27 articles included 18 clinicals studies, 4 preclinical animal studies, 4 algorithm-based research, and 1 survey. Based on the search, very few papers investigated the use of artificial intelligence or deep learning to aid in the prediction and management of epilepsy The available strategies to approach epilepsy patients were studied and constructive suggestions were included.

Conclusions: Overall, accessible interventions still require further studies and improvement in order to provide a better healthcare for epilepsy patients. The use of medical devices for epilepsy could improve patient's independence and quality of life.

Keywords:
electroencephalography, medical technology, seizure prediction, wearable device, extracerebral signals, SUDEP

EPNS21-205 Poster only
Epilepsy: Medical & Surgical Treatment

Long-term effectiveness of add-on stiripentol: an observational study in Dravet syndrome and non-Dravet developmental and epileptic encephalopathies.

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Objective: To assess long-term effectiveness and tolerability of stiripentol as adjunctive treatment in Dravet syndrome and non-Dravet refractory developmental and epileptic encephalopathies (RDEEs).

Methods: Retrospective observational study of all children and adults with RDEE and prescribed adjunctive stiripentol at Hospital Ruber Internacional (Madrid) from January 2000 to June 2020. Outcomes were retention rate; responder rate (proportion of patients with greater or equal to 50% reduction in total seizure frequency relative to baseline); seizure freedom rate; responder rate for status epilepticus; rate of adverse events (AEs) and individual AEs. Outcomes are reported overall, and for Dravet and non-Dravet subgroups.

Results: Of 55 patients, 33 had Dravet syndrome and 22 had non-Dravet RDEE. Median age was 68 months years (interquartile range [IQR] 40.5-162 months), and mean age of epilepsy onset was younger in the Dravet group (5.0 months) than non-Dravet (12.5 months). Median duration of treatment with stiripentol was 28.0 months (IQR 5.5-62.0 months), was longer in the Dravet group (44.0 months) than non-Dravet (10.5 months). At 12 months, the responder rate was 48.9% overall (23/47), 50.0% in the Dravet group (14/28) and 47.4% in non-Dravet (9/19), and no patients were seizure-free for 12 months. There were no statistically significant differences between groups on these seizure outcomes. Freedom from status epilepticus was achieved in 60.0% (18/30) at final visit, and this was significantly higher in the Dravet group (20/21, 95.2%) than non-Dravet (3/9, 33.3%). Adverse events were reported in 83.3% of patients (30/36), most commonly somnolence, anorexia, and irritability.

Conclusions: In this population of patients with epileptic and developmental encephalopathies, outcomes with adjunctive stiripentol were similar in patients with non-Dravet RDEE to patients with Dravet syndrome.

Keywords:
stiripentol, Dravet syndrome, non-Dravet refractory epileptic encephalopathies, ASM, seizure, epilepsy, Doose syndrome, status epilepticus.

EPNS21-221 Poster only
Epilepsy: Medical & Surgical Treatment

The efficacy of vagus nerve stimulation in genetic epilepsy

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Objective: To evaluate the efficacy of vagus nerve stimulation (VNS) as an alternative treatment for drug-resistant genetic epilepsy.

Methods: We analyzed the efficacy of VNS in 8 patients with genetic epilepsy (4 male/4 female): 6 patients had monogenic mutations (in TUSC3, CHD2, ACTB, PCDH19, 2 patients (not relatives) in KCNT1 genes) and 2 patients with chromosomal rearrangements (heterozygous deletion of chromosome 15q26.1 and duplication of chromosome 3p25.3). The mean age of patients was 11.75± 4.3 years old. The mean age of epilepsy duration was 9.25 ± 4.17 years. One patient (ACTB) had platybasia, craniostenosis and hippocampal malrotation; one (heterozygous deletion of chromosome 15q26.1) had microcephaly and six patients had normal MRI brain. One patient had only focal seizures (12.5%), seven patient had both focal and generalized seizures (87.5%). Current settings of VNS were: output current 1.25-2.25mA, signal frequency 30Hz, signal on time 30sec, signal off time 3-5min. The follow-up period after VNS implantation was 2 years±1.1 years. VNS efficacy was evaluated based on seizure reduction and general well-being. Anticonvulsant therapy did not change during VNS therapy.

Results: Seven patients had positive effect at 12 months after the VNS-implantation: seizure reduction was from 20 to 95% (CHD2 - 94%, TUSC3 - 80%, PCDH19 - 45%, ACTB and 2 patients with KCNT1 - 20%, a heterozygous deletion of chromosome 15q26.1 - 35%), 2 patients (TUSC3, KCNT1) had improve general mental condition and seizures became less intense. Patient with a duplication of chromosome 3p25.3 had non-lasting effect for 4 month with consequent aggravation.

Conclusions: In our study, patients with genetic epilepsy due to mutations in genes CHD2 and TUSC3 had the best effect from VNS therapy.

Keywords:
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EPNS21-242 Oral or poster
Epilepsy: Medical & Surgical Treatment

Hand Postures and Localization in Patients at Video EEG Monitorization

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Objective: One third of pediatric patients with epilepsy are resistant. Epilepsy surgery can be applied to appropriate patients when antiepileptic therapy is insufficient in resistant epilepsy. Long-term video EEG monitoring is performed to evaluate suitability for epilepsy surgery. Movement artifacts during the seizure and the rapid spread of discharges to both hemispheres may cause the epileptogenic zone to not be fully determined. The hand postures of patients with generalized or focal epilepsy who underwent video EEG monitoring in Gazi University Department of Pediatric Neurology during ictal activity and the relationship of these postures with the epileptogenic zone were evaluated.

Methods: The ictal activities of patients hospitalized in the video EEG monitoring unit between 2013-2021 were examined. Hand postures of patients during ictal activity were classified into six subgroups. These hand postures are defined as fist, politician fist, cup, pincer, extended hand and pointing. Epileptogenic foci of the patients were classified as generalized and focal.

Results: Five hundred and twenty-three patients who were monitored in the VEM unit were screened, and fifty-five patients were evaluated. Hand postures were evaluated by three different researchers at different times and independently of each other. The most common epileptic hand postures were "fist" and "politician fist". The epileptogenic zone of 18 patients out of 55 could not be differentiated and was found to be generalized. It was observed that 14 patients originated from the temporal, 9 patients from the frontocentral, 8 patients from the frontotemporal, 3 patients from the temporoparietal, 2 patients from the frontocentrotemporal and 1 patient from the central region.

Conclusions: Fist, politician's fist and extended hand posture were evaluated as contralateral lateralized sign, and pincer, pointing hand and cup postures were evaluated as ipsilateral lateralized signs.

Keywords:
epilepsy, epilepsy surgery, video EEG monitoring, hand posture

EPNS21-313 Poster only
Epilepsy: Medical & Surgical Treatment

Source localization of ictal epileptic activity based on high-density 256-channel EEG: a prospective study in children with lesional refractory epilepsy.

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Objective: Electrical source imaging (ESI) is a well-established non-invasive approach to localise the epileptogenic zone in patients undergoing evaluation for epilepsy surgery, especially when based on high-density scalp EEG (HD-EEG) and based on the patient's own MRI. ESI has, so far, primarily been used on interictal epileptiform discharges (IEDs). Here, focusing on using an affordable protocol in clinical practice, we investigate the added value of ESI derived from ictal discharges to estimate the epileptogenic zone in lesional paediatric cases.

Methods: We prospectively analysed 3 children admitted for presurgical evaluation. Patients were known to have a lesion on the MRI. 256-channel scalp EEG recordings were analysed. Artifact-free EEG epochs at ictal onset and IEDs clusters were visually selected and classified for further analyses. ESI derived from HD-EEG was computed on ictal events (iESI) and on each averaged IEDs focus (iiESI). For iESI, wMEM method was used considering the frequency band calculated from the strongest power change captured around seizure onset. Individual head models were used. Anatomic concordance of iESI and iiESI was compared to the epileptogenic lesion.

Results: Median age at inclusion was 8 years (range from 5,5 to 9). Eight ictal recordings and 7 interictal clusters from 3 patients were analysed. One patient had frontal lobe epilepsy and 2 had posterior cortex epilepsy. MRI revealed a focal cortical dysplasia in all cases, including a case of Tuberous Sclerosis Complex. Using wMEM, iESI and the epileptogenic lesion were fully or partly concordant in all cases.

Conclusions: iESI based on HD-EEG is feasible in children and brings complementary information to iiESI in focal lesional-related epilepsy. Future research is needed to determine the place of iESI in the presurgical evaluation of focal epilepsy.

Keywords:
epilepsy surgery, presurgical assessment, ictal discharges, high-density EEG, Electrical Source Imaging, ictal discharges, paediatric.

EPNS21-320 Poster only
Epilepsy: Medical & Surgical Treatment

A case of non ketotic hyperglycinaemia treated with ketamine.

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Objective: We describe a six year old boy with a diagnosis of non ketotic hyperglycinaemia (NKH).

Methods: NKH is an inborn error of metabolism, defined by deficient activity of the glycine cleavage enzyme system. This enzyme complex consists of four protein subunits: the P-protein; the H-protein; the T-protein; and the L-protein. This defect results in an accumulation of glycine in the body's tissues and fluids, specifically in the brain. Glycine is a major inhibitory neurotransmitter, but also has modulating effects at one of the glutamate receptors, the N-methyl-D-aspartate (NMDA) receptor. NKH, in it's classical form, normally presents in the neonatal period, with encephalopathy, seizures, respiratory failure, coma, and often death.

Results: This child experienced neonatal onset encephalopathy, requiring intensive care, and was subsequently diagnosed with NKH. Despite early treatment with benzoate and dextromethorphan, he experienced an ongoing significant seizure burden that highly impacted on quality of life for him and his family. Over a number of years, he was treated with anti-epileptic medications, all to little avail. We finally were able to treat with ketamine, a non-competitive NMDA receptor antagonist, which he was able to tolerate extremely well. Seizure frequency very quickly improved, and this benefit continued as we gradually titrated the dose upwards. This has produced an almost total resolution of seizures, with a subsequent improvement in quality of life.

Conclusions: We present his clinical findings, along with imaging and EEGs, both before and after commencement of ketamine, and long term outcomes; and we suggest that ketamine be considered more readily for NKH.

Keywords:
non ketotic hyperglycinaemia; ketamine

EPNS21-347 Oral or poster
Epilepsy: Medical & Surgical Treatment

Risk of seizure recurrence and long-term outcomes after withdrawal of antiepileptic drugs in seizure-free children

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Objective: The aim of our study was to determine predictors of seizure recurrence and long-term seizure outcomes in seizure-free children after withdrawal of antiepileptic drug (AED).

Methods: This analysis was a single-center and retrospective cohort study in a tertiary university hospital. Seizure-free children with epilepsy who decided to discontinue AED treatment and were followed up for at least 18 months after drug withdrawal were retrospectively evaluated for seizure recurrence. The time to a seizure recurrence and the predictive role of baseline clinical-demographic variables including gender, age at first seizure, number of seizure episodes before starting AED and while taking AED, seizure semiology, etiology of epilepsy, presence of mental retardation, family history of epilepsy and febrile seizure, parental consanguinity, history of status epilepticus and febrile seizure, seizure-free period before AED withdrawal, AED tapering time, result of brain magnetic resonance, electroencephalograms before and after AED withdrawal, and number of AEDs administered for seizure control were analyzed.

Results: The children with epilepsy (n = 269) had been followed for a median of 46 months (range 18-126 months) after AED withdrawal and 90 (33.5%) of them relapsed. The etiology of epilepsy, EEG findings after drug withdrawal, the number of seizure episodes while taking AEDs, and the presence of mental retardation were determined as the clinical features associated with the risk of recurrence in statistical analysis. The median time to seizure recurrence from the withdrawal of AED was 8 months (range:7 days-117 months; IQR:2-25). Pharmacological control of seizures with monotherapy was restored in 93.3% of the patients who relapsed.

Conclusions: The structural etiology of epilepsy, abnormal EEG findings after drug withdrawal, increased number of seizure episodes while taking AED, and accompanying mental retardation appear to be relevant predictors of seizure recurrence.

Keywords:
Epilepsy, Withdrawal, Antiepileptic drug, Relapse, Risk factors

EPNS21-357 Oral or poster
Epilepsy: Medical & Surgical Treatment

Does the Phenobarbital Interfere With pyridoxal-5-phosphate in Cerebrospinal Fluid in neonates?: A Single-Center Cohort Study

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Objective: Pyridoxal-5-phosphate (PLP) is the active form of pyridoxine. In the brain, it maintains its functional integrity by acting as a cofactor for multiple enzymatic reactions. PNPO deficiency is a primary defect of PLP biosynthesis characterized by neonatal epileptic encephalopathy and low levels of PLP in CSF. However, some antiepileptic drugs can also decrease PLP in body fluids. Our aim is to investigate if phenobarbital (PB), the treatment of choice in neonatal seizures, is associated with decreased levels of PLP in CSF in neonates.

Methods: Retrospective and observational study. We included 21 neonates with neonatal idiopathic seizures in whom levels of CSF PLP were analyzed. Neonates with pyridoxine-dependent epilepsy; PNPO deficiency; prematurity; sepsis; inborn errors of metabolism; hypoxic-ischemic encephalopathy or cases that received pyridoxine before the lumbar puncture (LP) were excluded. The patients were divided in two groups: with and without PB treatment at the time of PLP analysis in CSF. Mann-Whitney U test was used to compare means of PLP levels of the two groups, and the Spearman rank correlation test was used to measure the degree of association between the levels of CSF PLP and the PB serum level and the doses of bolus of PB.

Results: Fourteen patients were treated with PB before the LP and 7 had the PLP analysis prior PB treatment. Concentrations of PLP in newborns with PB, in monotherapy or polytherapy, were under the reference grade and lower than in newborns without PB ($p=0.039$ and $p=0.022$, respectively). There was no correlation between neonatal CSF PLP levels and serum levels or cumulative bolus doses of PB. There was not statistical difference between the levels of neurotransmitters between the groups.

Conclusions: The use of PB was associated with a decrease in the CSF PLP in neonates. These results should be considered for the use of PB in neonates because it could negatively influence adequate brain development by decreasing the CSF PLP.

Keywords:
Neonate, phenobarbital, pyridoxine, pyridoxal-5-phosphate (PLP), B6

EPNS21-384 Oral or poster
Epilepsy: Medical & Surgical Treatment

Clinicians' Perspectives about the Long-Term Effects of Fenfluramine on Individuals with Dravet Syndrome: A Qualitative Analysis

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Objective: Clinical trial data indicate that fenfluramine (FFA) provides meaningful reductions in seizure frequency and improvements in executive functions for individuals with Dravet syndrome (DS). This study sought to assess how FFA treatment affects quality of life (QOL) of individuals with DS and their families from the clinician's perspective.

Methods: Study participants were European clinicians who treated patients with DS who had participated in an EU FFA Early Access Program. They participated in 1-on-1 semi-structured interviews; responses were summarized and descriptive analyses were performed. Interviews with European caregivers of children with DS will begin Fall, 2021.

Results: Ten clinicians (9 epileptologists/1 neurologist; M22.2 years in practice, SD 7.8; 60% male; M49.2 years of age, SD 7.6) reported both seizure-related (ie, reductions in seizure activity and triggers and post-ictal recovery times, and improved post-seizure function) and non-seizure-related benefits (ie, cognition, alertness, behavior, problem-solving, motor function, speech, education, mood, sleep) with FFA treatment. Clinicians also noted that caregivers had better mood and more time for things they enjoyed, felt less overwhelmed, had better sleep quality, and less personal and family stress. 100% of clinicians said they would "very likely" recommend FFA to patients with DS.

Conclusions: Real world experience with FFA treatment is associated with meaningful improvements in many QOL domains for individuals with DS and their families. Clinicians provided specific examples of the benefits of FFA for their patients and their families and are very likely to recommend FFA to patients with DS.

Funding: Zogenix, #ZXIIS2020-007

Keywords:
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EPNS21-445 Oral or poster
Epilepsy: Medical & Surgical Treatment

Antiepileptic drug regime concordance in teenagers with epilepsies: a clinical audit update

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Objective: To measure the concordance of teenagers with epilepsies with their antiepileptic drug (AED) regimes.

Methods: Each patient attending the teenage epilepsy clinic, completed a standard questionnaire, if they had not already completed it. Simple descriptive statistics were used. This was a registered clinical audit (21-102C).

Results: 43 patients aged 13-18 years (median 16) were included, 17/43 (63%) with generalised and 24/43 (56%) focal epilepsies. 30/43 (70%) were taking one and 13/43 (30%) two AEDs.
During the previous month, 23/43 (53%) reported no missed doses: concordance score (CS) 6/6; 17/43 (40%) 1-5/60: CS 5/6; and 3/43 (7%) 6-10/60 missed doses: CS 4/6.

Among the 23 reporting the best CS 6/6:

13/23 (57%) were taking one and 10/23 (43%) two AEDs; 16/23 (70%) had an AED dose between 25-74% of top of target dose range for the first AED and 5/23 (22%) had AED dose more than 75% of top of target dose (this was 4/10 (40%) and 2/10 (20%) for the second AED);

17/23 (77%) had >90% reduction of their seizures, 4/23 (17%) had 50-90% reduction; and 1/23 (4%) had more than twice as many seizures.

Among the 3 reporting a poor CS 4/6:

all were on one AED, 2/3 had an AED dose between 25-74% of top of target dose range, and 1/3 had an AED dose more than 75% of top of target dose;

none had a seizure reduction >90%, 2/3 had a seizure reduction between 50-90%, and 1/3 (33%) had less than 50% reduction in seizures.

Conclusions: Among our patients, most reported good concordance with AED treatment. Best concordance was associated with good seizure control whereas none of the patients with the worst concordance had a >90% seizure reduction. More data will be collected to confirm these preliminary findings, validate the CS method, and explore potential aids.

Keywords:
compliance, adherence, adolescents, children, young people

EPNS21-447 Oral or poster
Epilepsy: Medical & Surgical Treatment

Ketogenic diet treatment in a child with infantile spasms due to SPATA5. Personalized treatment?

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Objective: Describe the effect of ketogenic diet (KD) in a patient with refractory infantile spasms (IS), intellectual disability, microcephaly and hearing loss due to homozygous SPATA5 mutations. Review the pathophysiology mechanisms of SPATA5 deficiency and mechanisms of action of KD.

Methods: Case report description and literature revision of SPATA5 deficiency.

Results: A 5-year-old male affected by development delay, congenital deafness, microcephaly and autistic features. Onset of IS at 28 months with clusters of epileptic spams and preserved background activity despite fractionated interictal epileptiform abnormalities during sleep on Video-EEG. On physical exam: HC -3.76SD, facial minor dysmorphias, nystagmus, lack visual attention, axial hypotonia and autistic features. Complementary tests including brain MRI, metabolic screening (B,U,CSF), and genetics (15q11q13 metilation test, aCGH, clinical exome) were normal. IS were treated with single and combination of different AED (VPA, VGB, IM-ACTH, ESM, CLB) without response. Six months after seizure onset, KD was initiated (Ratio 4:1) becoming seizure free one month later and so far with KD monotherapy. WES-Trio detected a homozygosis pathogenic variant in SPATA5 c.251G>A, p.Arg84Gln. SPATA5 encodes a spermatogenesis-associated factor 5, with predominant mitochondrial location. Functional studies on rat cortical neurons demonstrated the important role of SPATA5 in mitochondrial dynamics and axonal growth. The deficit in energy production alters the electrical neuronal balance, leading to seizures

Conclusions: SPATA5 deficiency mimic a primary mitochondrial disorder, probably related to SPATA5 role in mitochondrial dynamics. KD is a metabolism based treatment used in specific epileptic syndromes as mitochondrial epilepsies. We hypothesize that KD function as modulator of mitochondrial dynamics could explain the seizure control in our patient. Precision metabolic treatments as KD could be a future option for epilepsy in SPATA5 deficiency.

Keywords:
infantile spasms, ketogenic diet, mitochondrial dynamics, SPATA5

EPNS21-459 Poster only
Epilepsy: Medical & Surgical Treatment

Possible autoimmune epilepsy responsive to immunotherapy. The importance of immunotherapy in infantile epilepsy.

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Objective: Autoimmune epilepsy is a growing aetiology among children, but continues to be a diagnostic and therapeutic challenge. We present a case of infantile seronegative possible autoimmune epilepsy responsive to immunotherapy (IT).

Methods: Clinical history, physical exam, complementary tests and follow-up of the patient were reviewed.

Results: A 12 years old healthy patient presented with up to 20 daily episodes of focal aware seizures with disconnection from his surroundings and out-of-body experiences (derealization) and aphasia, sometimes preceded by epigastric aura and autonomic symptoms, and followed by clonic movements of the right arm and eventually secondarily generalized seizures. Postictal symptoms included altered short-term memory and nomination. Physical exam was always normal between episodes. A 24 hour video electroencephalogram showed 6 registered seizures of left temporoparietal origin with slow basal activity. A cranial magnetic resonance imaging (MRI) showed a left insular and hippocampal hiperintensity in Fluid Attenuated Inversion Recovery sequences. Neuronal Surface Antibodies (NSAbs) were negative. Valproic acid and lacosamide were started with no seizure control. The patient had a Response to Immunotherapy in Epilepsy (RITE) score of 7, so IT was started with intravenous corticosteroids and immunoglobulins (Igs), replacing corticosteroids eventually with azathioprine and maintaining monthly Igs, achieving seizure control. However the patient eventually developed mild cognitive deficits and atrophy of the implicated areas on MRI.

Conclusions: It is important to be familiarized with the possibility of an autoimmune epilepsy in children as they may have an atypical presentation and NSAbs are not always found. Because of this, diagnosis may be a challenge, so scores like the RITE score or diagnostic algorithms based on serological status and response to IT may be helpful in making the decision to start a trial with IT early in order to prevent important sequelae.

Keywords:
Autoimmune Seronegative Epilepsy Immunotherapy Responsive

EPNS21-473 Poster only
Epilepsy: Medical & Surgical Treatment

Epilepsy surgery in toddlers after stroke.

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Objective: Analysis of the effectiveness of epilepsy surgery (functional hemispherotomy) in epilepsy in children after a stroke on the example of clinical cases.

Methods: 3 patients treated for stroke and epilepsy at the Primary Pediatric Stroke Center in Morozov Children Hospital in 2021. Brain MRI, cerebral angiography, EEG

Results: 3 patients under the age of 2 years. 1 - rupture of the M1 aneurysm of the MCA at the age of 6 months, during endovascular surgery - cerebral vasospasm with the development of arterial stroke in the MCA basin. 2 - hemorrhagic disease at the age of 2 months with compression and cystic-gliosis transformation of the hemisphere. 3 - AVM rupture in the M1 segment MCA at the age of 6 months with the formation of cystic-gliosis transformation. All patients had a vascular accident in the left MCA basin with the outcome in right-sided hemiparesis and developmental delay. All patients had early seizures with subsequent transition to structural epilepsy. Kinematics of seizures - asymmetric tonic spasms.
After the onset of spasms, all patients developed epileptic encephalopathy. One patient was not pharmacoresistant, but taking into account the lack of effect on VPA therapy, the extent of the lesion and the high likelihood of pharmacoresistance, an early intervention was decided. Two others had a history of prescribing more than 3 drugs with no effect on seizures, progressive epileptic encephalopathy. All patients had an outcome according to Engel 1A, no epileptic encephalopathy, restoration of lost skills. At present, follow-up observation and rehabilitation are ongoing.

Conclusions: Patients with extensive stroke, the formation of hemiparesis with a short duration of epilepsy, at an early age have a good prognosis after epilepsy surgery to stop epileptic encephalopathy, which means a good prognosis for neuropsychic development.

Keywords:
epilepsy, epilepsy surgery, stroke, children, structural epilepsy, infantile spasms, epileptic encephalopathy

EPNS21-530 Oral or poster
Epilepsy: Medical & Surgical Treatment

Hemispherotomy is the most efficient surgical procedure for drug-resistant hemispheric epilepsy in children

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Objective: The aim of our study is to present the first series of children with drug-resistant hemispheric epilepsy treated with hemispherotomy in Bulgaria. We reviewed the indications and results from this aggressive neurosurgical operation.

Methods: Our retrospectively analyzed cohort includes eight consecutive children operated on during 10-year period (2011-2020). We have used lateral (peri-insular) technique in 7 children, and vertical (parasagittal) technique in one child.

Results: The most frequent hemispheric lesion in our series was a large porencephalic cyst associated with gliosis due to hypoxic-ischemic injury (4 children). The other hemispheric pathologies were Sturge-Weber syndrome (2 children), Rasmussen encephalitis (1 child) and hemimegalencephaly (1 child). Complete seizure control was achieved in all 8 children. Anti-seizure medication was stopped in 4 children. There was no worsening of the preoperative neurological deficit. The only complication in a child with Sturge-Weber syndrome was a postoperative communicating hydrocephalus after peri-insular hemispherotomy, and was successfully treated with lumbo-peritoneal anastomosis.

Conclusions: Hemispherotomies are the most successful operations for drug-resistant hemispheric epilepsies in children. Nowadays, after 15 years of experience, the epilepsy surgery in Bulgaria includes the whole spectrum of surgical interventions - from minimally invasive procedures such as vagus nerve stimulation to the most complex and extensive surgeries such as hemispherotomy.

Keywords:
epilepsy, children, drug-resistant, hemispherotomy, surgery

EPNS21-570 Poster only
Epilepsy: Medical & Surgical Treatment

The ketogenic diet for the treatment of KCNB1 encephalopathy

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Objective: Little has been known about effective targeted treatments for KCNB1 encephalopathy. Here we assessed the efficacy of ketogenic diet (KD) in patients with de novo heterozygous missense variants in KCNB1 gene.

Methods: Clinical and EEG data were obtained for two patients with KCNB1 related encephalopathy. Epilepsy gene panel was performed. Both children started a classic KD with a ratio 3:1 followed the non-fasting inpatient protocol. The KD efficacy was examined at 1, 3 and 6 months after initiation.

Results: Our first patient is a 4-year-old girl with early onset global developmental delay with predominant language difficulties, hypotonia, ataxia and behavioral impairment. Since the age of 30 months she developed myoclonic-atonic seizures more than hundred a day. The child was constantly irritated, did not respond to any commands, and had sleep disturbance. Long-term video-EEG revealed slow background and diffuse slow spike and slow wave activity. Epilepsy gene panel testing identified the pathogenic KCNB1 variant - c.629C>T, p.(Thr210Met).
The second patient is a 4-year-old boy with severe developmental delay, language disorder, sleep problems, hypotonia and focal seizures started at the age of 20 months. EEG before KD showed CSWS evaluated as ESES. Genetic testing detected a VUS, c.1130C>T (p.Thr377Ile) in the KCNB1 gene. This variant was absent in parents.
In both cases seizures were refractory to multiple AEDs (VPA, ZCD, CLZ, LTG, ATZ, ESX-1st patient; VPA,TPM,LEV-2nd patient) and treatment with KD was initiated. Favorable responses were seen to KD with significant (>90%) reduction in frequency of seizures and the number of IEDs and improvement of communication, mood and sleep.
Both patients are currently following the KD.

Conclusions: Two patients with KCNB1 missense variants presenting with developmental and epileptic encephalopathy were responders to the KD exhibited a decrease in seizure frequency and beneficial effects on behavior and sleep.

Keywords:
Ketogenic diet, KCNB1 encephalopathy, Epilepsy

EPNS21-581 Poster only
Epilepsy: Medical & Surgical Treatment

Treatment of FIRES (febrile infection-related epilepsy syndrome) with anakinra - a case report

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Objective: FIRES is a rare epilepsy syndrome characterized by a febrile infection 2 weeks to 24 hours prior to the onset of refractory status epilepticus (RSE). The prognosis can be devastating, with poor cognitive outcomes and refractory epilepsy or even death. Therefore, new therapeutic approaches are needed. Based on assumed hypothesis of an immune-mediated patomechanism, there is an increasing evidence supporting the use of anakinra, a recombinant interleukin-1 antagonist.

Methods: We report a previously healthy 10-year old girl presented with focal motor epileptic seizures after non-specific febrile infection. The seizures progressed into super-RSE.
While establishing a diagnosis we used diagnostic work up - electroencephalogram (EEG), MRI, cerebrospinal fluid (CSF) analysis, extensive infectious, metabolic and autoimmune investigations.

Results: Her daily EEG monitoring confirmed delta slowing and migrating seizures arising from bilateral hemispheres. The CSF analysis showed slightly elevated polymorhopnuclear leukocytes, other extensive infectious, metabolic and autoimmune causes were negative. Brain MRI revealed T2/FLAIR hypersignal changes in both temporal regions. Despite numerous antiseizure medications, continuous midazolam, corticosteroides and immunoglobulin, she continued in super-RSE. For this reason on day 8 we added high doses of anakinra three times per day in total dosage 17 mg/kg/day (600 mg/day) and continuous infusion of thiopental, which led to burst suppression pattern on EEG (day 16). We started to slowly wean anakinra after one month by reducing the dose by 100 mg/day with further reduction every 2 months. She was able to successfully wean off anakinra after 11 months. At follow up, she had only 6 seizures in one year.

Conclusions: The purpose of this case study is to report a significant response of early treatment with high doses of anakinra, which should be considered in treatment of FIRES.

Keywords:
FIRES, anakinra, EEG

EPNS21-637 Oral or poster
Epilepsy: Medical & Surgical Treatment

Effectiveness and Tolerability of Treatment with Lacosamide in Children: A Systematic Review

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Objective: lacosamide which has low drug interaction; is suitable for monotherapy and polytherapy in children. The present study is a systematic review, conducted by searching the databases between 2011-2019 were reviewed.

Methods: This study is conducted by searching the databases of Elsevier, PubMed, Springer, and Wiley and with the keywords of status epilepticus, children, lacosamide, seizures, efficacy, and tolerability; these words were often used separately and in some cases as a combination of two words. Inclusion criteria were full-text articles in the field of effectiveness and tolerability of treatment with lacosamide in patients, articles published after 2011, and articles published in English and exclusion criteria were articles without full-text, articles published before 2011, and review articles.

Results: A total of 949 epileptic children between the ages of less than 1 year and 18 years were studied in these 17 articles. In 357 children (37.62%) side effects were observed following the consumption of this drug. Most of these complications were minor . The greatest effect of this drug in controlling and reducing status epilepticus was related to a study by Ngampoopun et al.; during this study, a 100% reduction was observed in seizures, within 24 hours . The lowest efficacy of this drug was observed in a study conducted by Heyman et al., which reported a 35% reduction in seizures . The effectiveness of this drug as monotherapy was between 8.2% (in focal and generalized seizures) to 100% (in acute seizures) and as polytherapy was between 40% (in patients with partial epilepsy) to 90% (in patients with Lennox-Gastaut syndrome).

Conclusions: Although during this systematic review it was shown that the consumption of lacosamide in children with epilepsy decreases seizure frequency and improves the process of control and treatment of this disease, major studies are required, in order to assess the effectiveness, tolerability, and safety of this medication for children.

Keywords:
Lacosamide, Children, Efficacy, and Tolerability

EPNS21-641 Poster only
Epilepsy: Medical & Surgical Treatment

Treatment with Ketogenic Diet for Severe Epilepsy - Experiences from Uppsala university Children's hospital, Sweden

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Objective: The purpose was to report experiences from the ketogenic diet team and study the treatment effect for various diagnoses.

Methods: The Department of Pediatric Neurology at Uppsala University hospital offers several treatment modalities for severe epilepsy including anti-epileptic drugs (AED), epileptic surgery, treatment with vagal nerve stimulation and deep brain stimulation. In order to expand the treatment options, ketogenic diet was introduced 2018. In this study we included children treated with ketogenic diet 2018-21 who suffered from severe epilepsy. Several of the children also had other neurological diseases and/or intellectual disabilities. The children received oral or enteral feeding, or a combination. In specific situations parenteral nutrition was needed and performed. Treatment modalities included classic, modified and MCT based ketogenic diet.

Results: Twenty-five patients were treated with ketogenic diet, 16 boys and 9 girls, aged between 3 months and 15 years. Ten terminated the treatment, 5 due to lack of compliance and 5 due to treatment failure. Four children became seizure free and 3 of them was able to end their AED treatment. Seizure reduction greater than 50% were achieved in 10 of the patients and 5 children had less than 50% reduction. Only 6 children had no treatment effect. We could not discover any correlations between diagnosis and treatment results. Some parents also reported increased alertness in their children as a possible effect of the ketogenic diet.

Conclusions: Ketogenic diet can be an effective treatment option for children with various forms of severe epilepsies. Individualized treatment and teamwork are important factors to obtain compliance and thus seizure reduction. Results from a larger cohort of patients are needed to obtain a clearer picture of treatment effects for different diagnoses.

Keywords:
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EPNS21-643 Poster only
Epilepsy: Medical & Surgical Treatment

EFFECTIVENESS OF KETOGENIC DIET IN THE TREATMENT OF ABSENCE EPILEPSY

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Objective: Ketogenic diet (KD) mimics hunger and is one of the first methods tried in the treatment of epilepsy in history. Studies have reported that KD treatment is beneficial in drug-resistant symptomatic epilepsies. However, the results of idiopathic generalized epilepsy have not been specifically reported. Absence epilepsy is a common form of childhood idiopathic generalized epilepsy. Retrospective studies have shown that KD can also be effective in typical absence epilepsy. In our study; we have aimed to investigate the efficacy of KD on epilepsy treatment and the effect of gender on the response to treatment in the genetic absence epilepsy rat model (GAERS).

Methods: 24 GAERS on the 30th postnatal day were randomly divided into two groups as 6 males and 6 females in each group, and KD was initiated in the experimental group. The control group have had continued to be fed with standard diet (SD). Stereotaxic surgeries of GAERSs were performed at 1 month and 3 weeks of age. Weekly blood glucose and ketone levels were measured from the week of stereotaxic surgery, and weekly weight was monitored. After waiting for a one-week recovery period after surgery, EEG records were taken once a week for 2 weeks for the SD group, once a week for 3 weeks for the group with KD. The total spike wave discharge (SWD) time, number and average SWD time that occurred when there was normal rhythmic activity in the EEG were compared between the two groups.

Results: KD shortened the Mean DDD duration ($p < 0.05$) but had no effect on total DDD duration and number ($p > 0.05$). Gender did not affect the KD response in absence epilepsy. KD led to ketonemia, a decrease in venous blood glucose and a decrease in weight gain.

Conclusions: Our study is an original study investigating the efficacy of KD on absence epilepsy on 30-day-old rats, considering the gender factor too. The results of our study constitute a step to understand the effectiveness of KD in the treatment of absence epilepsy.

Keywords:
Epilepsy, absence seizure, EEG, spike wave discharge, ketogenic diet

EPNS21-654 Oral or poster
Epilepsy: Medical & Surgical Treatment

The Adverse effects of Cenobamate, a new FDA approved medication for epilepsy: a systematic review

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Objective: Cenobamate is a new carbamate derivative drug approved in the United States in 2019 for the treatment of adults with focal seizures.The mechanism of action of cenobamate is thought to be to reduce repetitive neural firing by rapidly and slowly inactivating sodium channels and has been proposed to additionally enhancing the inhibitory effects of the GABAergic system.

Methods: We investigate studies to answer our main concern. This study was performed in databases such as PubMed, ProQuest, ScienceDirect and Scopus from beginning to January 23, 2021, for related published articles. The following MeSH keywords (in the title/abstract) were used: "Cenobamate" AND "Epilepsy" OR "Seizure" AND "Side effects" OR "Adverse effects".

Results: Common side effects following taking cenobamate, like other antiepileptic drugs, were neurological symptoms (drowsiness, dizziness, fatigue, diplopia, etc.), which usually increase with increasing doses. However, most of them were mild to moderate. Severe side effects ranged from 4 to 21% depending on the prescribed dose.The findings of the present study showed that cenobamate in many cases had more side effects than routine drugs. In this regard, in studies of Krauss et al., It was stated that the side effects of cenobamate were main reason for stopping drug in more than 12% of study population (in the treatment and placebo groups). Also, in another study at a dose of 300 mg per day, there were no significant side effects that led to discontinuation of drug. Only one case of drug rash with eosinophilia and one case of drug allergy occurred at 500 mg .
In Chong's study, the reasons for discontinuation of cenobamate included discontinuation by patient (18.8%), side effects (9.4%), other cases (8.7%), and lack of follow-up (7%) .
According to Krauss et al.,

Conclusions: Cenobamate as adjunctive therapy in patients with seizures leads to more side effects compared with placebo and decreased frequency of seizures.

Keywords:
cenobamate, epilepsy, seizure, adverse effects

EPNS21-85 Oral or poster
Epilepsy: Medical & Surgical Treatment

Effectiveness of treatment with Brivaracetam in children with epilepsy: Asystematic review

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Objective: Brivaracetam is one of the newest drugs used in the treatment of epilepsy, which with very few drug interactions, is a suitable option in the treatment of patients in whom previous AEDs have not been effective.

Methods: The present study is a review study that was conducted by searching the databases of Elsevier, PubMed, Springer, and Wiley, and with the keywords of Refractory Epilepsy, children, Brivaracetam, Seizures, and Efficacy. Inclusion criteria were full-text articles in the field of the efficacy of Brivaracetam in children with epilepsy and articles published in English, and exclusion criteria were articles without full-text and review studies.

Results: A total of 286 epileptic children aged 1 month to 20 years were studied in 8 studies and the findings showed that the use of BRV was associated with improved physical condition and reduced seizures in these children , The major side effects of this medication included nausea, drowsiness, dizziness, psycho-behavioral disorders, irritability, decreased or increased appetite, exacerbation of seizures. The highest rate of response(>50% reduction in seizure frequency) to BRV was observed in studies by McGuire et al and Visa-Reñé et al. with 65% and 63.63%, respectively. On the other hand, the lowest response rate to this drug was seen in the study by Liu et al.; In this study, only 21% of children with epilepsy responded to treatment with BRV medication. In these 8 studies, the maximum follow-up period was 1 year and the minimum was 3 months. In addition to BRV, all children studied in these 8 studies used 1-3 concomitant antiepileptic drugs (AEDs).

Conclusions: Although it was shown that the use of BRV in children with epilepsy reduces seizures and improves the control and treatment of the disease, due to very limited and mostly retrospective studies (7 of 8 studies) in this regard , it is necessary to do conduct further studies on the effectiveness, tolerability, safety, and appropriate doses of this drug in children.

Keywords:
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EPNS21-98 Oral or poster
Epilepsy: Medical & Surgical Treatment

ADMIRAL: A UK Open-Label Phase 1/2a Study to Investigate the Safety and Pharmacokinetics (PK) of Multiple Ascending Doses (MAD) of Antisense Oligonucleotide (ASO) STK-001 in Children and Adolescents with Dravet Syndrome (DS)

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Objective: DS is a severe and progressive genetic epilepsy that typically begins in the first year of life; characterized by frequent and refractory seizures. Non-seizure comorbidities include intellectual disability, ataxia, and a high risk for sudden unexpected death. Approximately 85% of cases are caused by heterozygous loss of function mutations in the *SCN1A* gene which encodes the voltage-gated sodium channel type-1 α ($Na_V1.1$) protein. STK-001 is an ASO treatment designed to upregulate and restore physiological $Na_V1.1$ by leveraging the non-mutant (wild-type) *SCN1A* gene copy, thereby reducing seizure frequency (SF) and non-seizure comorbidities.

Methods: ADMIRAL is a multi-center study of patients aged 2-18y with DS [disease onset <12 months of age; recurrent seizures (focal motor, hemiconvulsive, or generalized tonic-clonic)] and genetically confirmed *SCN1A* variant. ADMIRAL primarily aims to assess safety, tolerability, and PK of intrathecally (IT) administered STK-001 in MAD (up to 70 mg). Each dose cohort includes at least two patients aged 13-18y and two aged 2-12y. Secondary objectives are percentage change from baseline in convulsive SF, overall clinical status, and quality of life. A 28-day baseline period occurs prior to dosing to evaluate SF. On Day 1, patients undergo CSF collection followed by IT STK-001 administration; this is repeated on Days 57 and 85 with a 6-month follow-up. AEs are monitored continuously, and plasma is collected for PK at multiple times. Outcomes may provide evidence of clinical effect.

Results: Demographics and preliminary results will be reported.

Conclusions: STK-001 has the potential to be the first-in-class, disease-modifying therapy to address the genetic cause of DS by upregulating Nav1.1 proteins and to potentially reduce SF and non-seizure comorbidities. Together with the ongoing phase 1/2a MONARCH study in the U.S., ADMIRAL data may inform future clinical trials of STK-001.

Keywords:
mRNA, splicing, United Kingdom

EPNS21-109 Oral or poster
Epilepsy: Miscellaneous

A clinical and metabolomic fingerprint of potential dysbiosis in epilepsy

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Objective: Patients with neurodevelopmental disorders, including epilepsy, may show abnormal intestinal functioning, ranging from mild bloating to severe constipation. Our study aimed to identify a clinical and metabolomic fingerprint of gut dysbiosis in patients with epilepsy.

Methods: We recruited patients with epilepsy of broad aetiologies and age-matched, neurotypical controls. Gastrointestinal (GI) function was assessed using the Bristol Stool Test (BST) chart and the validated Rome IV Diagnostic Questionnaire. Untargeted metabolomic analysis was performed on urine samples.

Results: 148 non-related individuals (mean age, 9.4±3.9 years) were enrolled. The epilepsy group included 84 patients with a mean age of 9.3±4.5 years. Thirty patients showed Isolated Epilepsy (IE), while 54 had Epilepsy plus neuropsychiatric comorbidities (Epi+). BST scores were significantly abnormal in epilepsy patients as compared to controls (p=.0026). Comparison of BST scores between patients with or without GI symptoms showed a value of p=.0001. Metabolomic analysis of urine samples revealed specific metabolic profiles associated with the epilepsy subtype and involving specific pathways including those of ABC transporters, and metabolism of aminoacids, butanoate, vitamin B6, and lysine.

Conclusions: This study supports the implementation of a clinical and metabolomic fingerprint of gut dysbiosis in patients with epilepsy, and eventually provides a basis for the optimization of patients' treatment.

Keywords:
Bristol Stool Test; Epilepsy; Metabolomics; Microbiota-gut-brain axis; Neuropsychiatric disorders.

EPNS21-112 Poster only
Epilepsy: Miscellaneous

Gait abnormalities in Dravet syndrome might partially be explained by muscle weakness

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Objective: Walking problems, e.g. crouch gait, progressively occur in Dravet syndrome (DS). Muscle weakness is hypothesized as a contributing impairment. Our objective is to determine the feasibility and validity of strength measurements and outline strength problems in the framework of gait analysis.

Methods: Hand grip strength (HGS), handheld dynamometry (HHD) and functional tests (underarm throwing, standing long jump, sit-to-stand, stair climbing) were performed in 46 persons (5.2-24.8 years) with DS following an instrumented 3D gait analysis. Strength measurements were compared to age-related reference values. Partial correlations, controlling for height and weight, were calculated to determine concurrent validity of functional and analytical strength measurements as well as to relate strength to an index of overall gait pathology (gait profile score, GPS) and deviations in sagittal (GPS_sag), coronal (GPS_cor) and transverse plane (GPS_trans).

Results: Twenty-seven subjects (59%) were not able to complete the assessment due to cognitive, behavioural and motor difficulties. The remaining 19 subjects (41%) scored generally below the 5th percentile of norm values. HGS correlated to HHD of elbow flexors (r=0.71) and knee extensors (r=0.65). Underarm throwing and sit-to-stand correlated to HHD of elbow flexors (r=0.65; r=0.73) and extensors (r=0.64; r=0.61). HHD of hip flexors was negatively correlated to GPS (r=-0.61) and GPS_trans (r=-0.72).

Conclusions: HHD seemed most valid to detect isolated muscle strength. Validity of the functional tests was limited, as motor proficiency, balance and coordination may interfere. On a group level, strength indeed seems reduced in DS. The negative correlation between hip flexor strength and gait pathology confirms the presence of gait abnormalities that might be explained by reduced muscle strength. However, we cannot confirm that crouch directly results from muscle weakness since no correlations are observed in the sagittal plane.

Keywords:
Dravet syndrome, gait, muscle strength, feasilibity, validity

EPNS21-116 Poster only
Epilepsy: Miscellaneous

Developmental and epileptic encephalopathy 35 and 37: Similarities an Differences

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Objective: ITPA related epileptic encephalopathy (epileptic encephalopathy, early infantile/DEE-35) is a rare inborn error of metabolism. FRRS1L related encephalopathy is a rare cause of epileptic encephalopathy (DEE-37). Only a few cases have been reported thus far, Hypotonia and seizures tend to be drug refractory. Here we present two patients admitted to our clinic with severe hypotonia and drug resistant seizures.

Methods: Molecular genetic study (NGS) demonstrated homozygous mutation in ITPA and FRRS1L gene.

Results: Both patients got drug resistant seizures and severe hypotonia. A 10-month-old girl from consanguineous parents presented with global developmental delay and refractory generalized seizures. Microcephaly, poor visual fixation, and intermittent dystonic posturing were observed on clinical examination. MRI brain (figure) revealed delayed myelination and restricted diffusion involving optic radiations, cerebral peduncles, red nuclei, globus pallidi, and corticospinal tract. EEG showed background slowing and multifocal epileptiform discharges and NGS resulted homozygous ITPA mutation. A 18-months-old boy from consanguineous parents presented with history of hypotonia, delayed speech, 'abnormal movements' from 12 months of age. Electroencephalogram (EEG) monitoring demonstrated the 'abnormal movements' to be atypical absence seizures and EEG showed continuous spikes-and-waves during slow sleep (CSWS) pattern and NGS resulted homozygous FRRS1L mutation. There was no abnormalities on brain MRI.

Conclusions: Drug resistan epilepsy, infatile seizures, and global developmental delay are common features of developmental and epileptic encephalopathies. Both conditions are extremely rare but also suspected in this clinical findings.

Keywords:
ITPA, FRRS1L

EPNS21-2077 Poster only
Epilepsy: Miscellaneous

COVID-19 Related Seizures in Pediatric Patients: Single Center Experience

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Objective: To investigate the proportion, characteristics, risk factors and prognosis of children presenting with seizures in acute COVID-19 infection period.

Methods: We conducted a systematic retrospective study to identify all children presenting to the emergency departments of a tertiary academic medical center between February 1, 2021 and February 15, 2022, with PCR-based SARS-CoV-2 infection. Clinical and demographic data were extracted and reviewed from electronic medical records.

Results: Nine patients presented with seizures. Their ages ranged between 12 months to 17 years, and 5 were male. Four patients had febrile seizures and only one of this patients presented with a simple febrile seizure. Five had a previous history of neurological disorders. Two presented with status epilepticus and responded to anti-seizure medication infusions. One of these patients had been died from pneumonia.

Conclusions: Pediatric patients with a diagnosis of COVID-19 have a high risk of presenting with complicated seizures, both in patients with pre-existing neurological conditions and in patients at the age of febrile seizures.

Keywords:
COVID-19, seizure, pediatric

EPNS21-2081 Oral or poster
Epilepsy: Miscellaneous

West Syndrome: evolution and prognosis - A case series review

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Objective: West syndrome is an epileptic disorder characterized by a triad of infantile spasms, hypsarrhythmia, and delayed psychomotor development. The long-term prognosis is thought to be related to the etiological cause but a lot of factors contribute to the evolution. The aim of this study was to evaluate the evolution and prognosis of a case series of children diagnosed with West Syndrome and identify modulating factors.

Methods: Retrospective observational study with revision of the clinical process of children diagnosed with West Syndrome between January 2001 and December 2020.

Results: 28 children diagnosed with West Syndrome were included. The mean follow-up time was 5 years and 4 months. The mean age of symptoms onset was 7 months. 1 death was reported. An etiology was identified in 64% of patients (genetic, structural or infectious). In 89% of patients Vigabatrin was used as initial therapy and in 74% corticotherapy was associated (45% corticotherapy, 35% corticotherapy and ACTH). 62% of patients had persistent epileptic seizures throughout the follow-up. 77% of patients evolved with motor development delay and 88% with cognitive development delay. There was an association ($p<0.05$) between the persistence of the hypsarrhythmia pattern in the EEG after the initial therapy and the persistence of epileptic seizures and motor and cognitive development delay throughout the follow-up. The presence of epileptic seizures prior to the onset of symptoms also showed association ($p<0.05$) with progression to other types of epilepsy in the future.

Conclusions: In our study the main factors influencing the prognosis of West Syndrome patients were the presence of previous epileptic seizures and the persistence of the hypsarrhythmia pattern in the EEG after initial therapy. Considering that patients since 2001 with different therapeutic approaches were included, the results reinforce the guidelines where the steroids are used earlier in the treatment.

Keywords:
West Syndrome, Epilepsy prognosis, Neurodevelopmental outcome

EPNS21-217 Poster only
Epilepsy: Miscellaneous

Seizure-Related Outcomes With Real-World Use of Cannabidiol (CBD) in Lennox-Gastaut Syndrome and Dravet Syndrome: BECOME, A Caregiver Survey

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Objective: We developed a cross-sectional caregiver survey, BECOME (global outcomes survey assessing changes in **BE**havior, **CO**gnition, and **M**ore with **E**pidiolex®), to characterise/quantify real-world seizure and non-seizure outcomes in patients with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS). This first abstract describes seizure-related outcomes.

Methods: US-based caregivers (N=498) of people with LGS (80%) or DS (20%) treated with plant-derived highly purified CBD (Epidiolex®, 100 mg/mL oral solution) for ≥3 months compared the past month to the period prior to CBD initiation. The survey included multiple choice and rank order questions using symmetrical 3-, 5- and 7-point Likert scales (from worsening to improvement). Continuous variables were summarised as means, medians and ranges, and categorical variables as frequency distributions and percentages. CBD-associated adverse events can include transaminase elevations, somnolence, decreased appetite, diarrhoea, pyrexia, vomiting, fatigue, rash, sleep disorders and infections, but they were not assessed in this survey.

Results: A notable proportion of respondents reported improvements in seizure frequency (84%), seizure severity (68%) and seizure free days per week (67%). A substantial proportion of caregivers reported improvements in convulsive seizures (72%), drop seizures (71%), non-convulsive/non-drop seizures (68%) and night-time seizures (62%). 6-22% of respondents reported worsening in ≥1 seizure outcome. Many respondents reported decreased number of emergency room visits (54%), hospitalisations (53%), seizure-related injuries (48%), and reductions in rescue medication use (57%). Seizure freedom (for at least the last month) was reported in 16% of patients.

Conclusions: Nearly all caregivers (93%) planned to continue CBD treatment, primarily because of reduced seizure burden but also because of improvements in non-seizure related outcomes, such as emotional function, alertness, cognition and communication.

Keywords:
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EPNS21-220 Poster only
Epilepsy: Miscellaneous

Non-Seizure Related Outcomes With Real-World Use of Cannabidiol (CBD) in Lennox-Gastaut Syndrome and Dravet Syndrome: BECOME, A Caregiver Survey

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Objective: We developed a cross-sectional caregiver survey, BECOME (global outcomes survey assessing changes in **BE**havior, **CO**gnition, and **M**ore with **E**pidiolex®), to characterise/quantify real-world seizure and non-seizure outcomes in patients with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS). This second abstract describes non-seizure behavioural and cognitive outcomes.

Methods: US-based caregivers (N=498) of people with LGS (80%) or DS (20%) treated with plant-derived highly purified CBD (Epidiolex®, 100 mg/mL oral solution) for ≥3 months compared the past month to the period prior to CBD initiation. The survey included multiple choice and rank order questions using symmetrical 3-, 5-, and 7-point Likert scales (from worsening to improvement). Continuous variables were summarised as means, medians, and ranges, and categorical variables as frequency distributions and percentages. CBD-associated adverse events can include transaminase elevations, somnolence, decreased appetite, diarrhoea, pyrexia, vomiting, fatigue, rash, sleep disorders, and infections, but they were not assessed in this survey.

Results: A notable proportion of respondents reported improvements in ≥1 question for all domains: emotional functioning (82%), cognition and executive function (81%), language and communication in non verbal (79%) and verbal patients (74%), activities of daily living (51%), sleep (51%), and physical functioning (46%). 6-26% of respondents reported worsening in ≥1 question of each domain. Most frequently reported improvements included: alertness (71% of respondents), learning new things (71%), being aware (70%), ability to engage with others (68%), paying attention (66%), happiness (66%), smiling (63%), saying sentences and phrases (58% and 60%), and calmness (56%).

Conclusions: Nearly all caregivers (93%) planned to continue CBD treatment, primarily because of reduced seizure burden but also because of improvements in non-seizure related outcomes.

Keywords:
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EPNS21-222 Oral or poster
Epilepsy: Miscellaneous

Non-Seizure-Related Benefits of Cannabidiol (CBD) Among Individuals With Dravet or Lennox-Gastaut Syndromes: A Qualitative Study

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Objective: This qualitative study aimed to increase understanding of the impact of CBD on non-seizure-related outcomes (e.g., behaviour, cognition, mood, and health-related quality of life [HRQoL]) among individuals with Dravet syndrome (DS) or Lennox Gastaut syndrome (LGS) and their caregivers.

Methods: Caregivers (N=21) were recruited of individuals with DS (n=14) or LGS (n=7) in the UK, US, and Germany who have been treated with plant-derived highly purified CBD medicine (Epidyolex®, 100 mg/mL oral solution) for ≥6 months. Participants were sent a background questionnaire. Interviews were conducted via telephone and explored the symptoms and impacts of DS and LGS, and non-seizure-related effects of CBD. Data were analysed using thematic analysis.

Results: Current symptoms included frequent seizures, cognitive impairment, communication, mobility and behavioural difficulties, sleep disruption, and reduced appetite. All individuals required 24-hour supervision, and the majority (n=19) needed assistance with self-care. Caregivers reported that children's symptoms impacted their overall HRQoL.
Most caregivers (n=19) reported beneficial HRQoL impacts of CBD, with improvements in awareness, mood, language, social skills, mobility, behaviour, appetite, school participation and information retention. Seizure frequency/severity reduction was also reported (n=16), resulting in caregivers having greater confidence to go out and socialise and having more time for themselves. A few caregivers (n=4) reported no effects, or only short-term beneficial effects. Some caregivers (n=10) reported adverse events of CBD, including loose stools, diarrhoea, somnolence, worsening behavioural difficulties, reduced appetite, and burning sensation in throat.

Conclusions: In addition to reduced seizure frequency, CBD may have a range of non-seizure-related beneficial effects, which warrant further investigation. Quantitative studies with larger sample sizes are required.

Keywords:
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EPNS21-345 Poster only
Epilepsy: Miscellaneous

PCDH19 mutation and epilepsy, case of family history

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Objective: Epilepsy and Mental Retardation Limited to Females (EFMR) is an infantile onset disorder characterized by clusters of seizures. EFMR is due to mutations in the X-chromosome gene PCDH19

Methods: In our hospital we have a family where mother and daughter suffer from epilepsy

Results: 22 years old lady had had seizures since 18 months old: all of them were a focal, often repeated throughout the day (clusters) with increasing temperature, clusters frequency was different, seizures could only be stopped in the hospital (using benzodiazepines). Last seizures were at 14th years old. She finished school, bud have a slight cognitive and communicative deviations. She has taken LTG and LEV. At the age of 20 years old lady had a normal pregnant, delivery by cesarean section. Her daughter has a muscle dystonia, delay of physical development and clusters seizures with fever since 10 months old.
At first, we conducted a genetic test for daughter - she has a pathogenic variant of two genes: PCDH19 - Deletion (exon 6) - is associated with X- linked early infantile epileptic encephalopathy in females and PIGN - is associated with autosomal recessive multiple congenital anomalies - hypotonia-seizures syndrome.
Then we did a genetic test for mother: she has a pathogenic variant of PCDH19.

Conclusions: After genetic tests we stop a maternal antiepileptic therapy: she has no seizures for eight years and we know that with PCDH19 mutation seizures were stopped after puberty (Kolc K. et al. Molecular Psychiatry 2019; 24:241-251).
Also, we held a conversation about high risk of having subsequent children with genetic problems.
Daughter has taken a LEV. If she has clusters of seizures we can use a benzodiazepines or steroids in hospital as urgent therapy (Higurashi N. et al. Seizure 2015; 27:1-5)

Keywords:
PCDH19 mutation, epilepsy

EPNS21-362 Oral or poster
Epilepsy: Miscellaneous

Inflammatory markers in epilepsy

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Objective: Recent studies revealed that inflammation could contribute to pathogenesis of epilepsy. Changes of inflammatory regulation can lead to neuronal degeneration and could induce seizures, especially in intractable epilepsies. There is limited number of studies assessing the correlation of different inflammatory markers with repetition rate of seizures in children with different type of epilepsies. Our objective is to observe the correlation between inflammatory cytokines (INF-μ, Chemokines (CCL2, CCL3, CCL4), Eotaxin (CCL11), Prostaglandin-PGE2) and repetition rate of seizures in clinical setting.

Methods: Study included 56 patients of both gender, aging 4-16 y. They were divided into three groups: Group 1 - non epileptic controls; Group 2A - patients with controlled seizures, Group 2B- patients with intractable epilepsies. All children underwent neurological examination as well as EEG. Diagnosis of epilepsy was done upon ILAE classification of the epilepsies (2017). Cytokines were assessed by Enzyme Linked Immunosorbent Assay (ELISA) method.

Results: Assessment demonstrated lower mean levels of cytokines in control group compared with study groups ($p<0.05$). PGE2 and CCL11 were significantly increased in Group 2B compared with Group 2A ($p<0.05$). The increase range for CCL11 was within 1000-2000pg/ml and was strongly correlated with repetition rate of seizures (R2-0.78), especially for patients with epileptic encephalopathies (West and Dravet syndromes) where high rate of seizure recurrence was observed. The correlation between CCL11 levels, age and gender was not revealed (R2-0.35).

Conclusions: Significant correlation between cytokine expression and frequency of seizures may be related with resistancy to antiepileptic drugs (AEDs). Further confirmation of our data will significantly support step towards understanding the mechanism of drug resistancy and could draw out possible future strategies of using targeted anti inflammatory drugs as add-on therapy of AEDs in epilepsies.

Keywords:
inflammation, cytokines, epilepsy, epileptogenesis.

EPNS21-365 Oral or poster
Epilepsy: Miscellaneous

Language problems in Myoclonic-Atonic Epilepsy

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Objective: Myoclonic-Atonic Epilepsy (MAE) or Doose syndrome is an early-onset epileptic syndrome characterized by a variety of generalized seizures and typical EEG features. Cognitive and epilepsy outcome may range from relatively favorable outcome to (Developmental) Epileptic Encephalopathy((D)EE). The objective was to study cognitive abilities, particularly language.

Methods: We retrospectively reviewed files of 30 children with MAE, who received epilepsy treatment at our tertiary epilepsy center and support at school. Wechsler Scales IQ testing was classified in five groups: I:FS-IQ< 60 (or not testable);II:60-69;III:70 -79; IV:80-89; V:FS-IQ> 90(or reported normal). Developmental Course was scored based on clinical data, 0=normal; 1=EE (cognitive or behavioral deterioration regardless of actual IQ); 2=DEE (cognitive disorders without deterioration).
Language Problems were classified as 0:none; 1:Qscores<79 on Language Testing (Schlichtingtest, WPPSI-III General Language Composite, Peabody Receptive Vocabulary Test) or reported speech/language problems. Rates of children in IQ groups and Developmental Course were contrasted to Language Problems (chi-square).

Results: Mean onset age of epilepsy was 2.9 years (SD=1.3), present age 7.5 (2.6), range 3-14 years;19 boys. Treatment consisted of various (combinations of) ASM, 5 used ketogenic diet, 2 Vagal Nerve Stimulation. 16 children were classified as EE,9 as DEE, only 5 had normal course. Wechsler Scales IQ testing (n =23) showed in 70%, IQ<90, mean VIQ =77.8 (10.9), PIQ=82.1 (14.6). Language Problems were present in 20 children (66.7%), in all IQ-groups (p=0.39) and more likely (p=0.05)in children with EE or DEE (75%,78%) than in favorable course (20%).

Conclusions: In our tertiary epilepsy patients, language problems were frequent, they are seen in all IQ groups and are associated with encephalopathy. Clinicians should be aware of the elevated rates of language and neurodevelopmental problems in MAE and refer to language and neuropsychological evaluation.

Keywords:
Myoclonic-Atonic Epilepsy, Doose syndrome, Developmental Epileptic Encephalopathy, language evaluation, neuropsychological evaluation, epilepsy

EPNS21-368 Oral or poster
Epilepsy: Miscellaneous

Survey of use of CBMPs in the East of England

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Objective: In June 2018, Cannabis based medicinal products (CBMPs) were licensed for use in the UK but restricted for use in Dravet syndrome (DS), Lennox-Gastaut's syndrome (LGS) and recently, Tuberous Sclerosis, in children. The British Paediatric Neurology Association (BPNA) was tasked to develop clinical guidance for clinicians prescribing CBMPs for children, including blood monitoring. We carried out a regional survey in the East of England to assess the practice and identify variance.

Methods: Retrospective data collected using the electronic hospital system on all children on CMBPs, from a database maintained centrally at tertiary epilepsy hospital. Local hospitals were contacted for missing information.

Results: 28 children were started on CBMPs between 2018 - 2021; 19 males, 8 females. 29% of children had a diagnosis of Dravet syndrome (DS), 64% Lennox Gastaut's syndrome (LGS) and 7% had a diagnosis of probable LGS - which was made following robust discussion at a national meeting of epilepsy experts. In line with the recommendation from NICE (National Institute of Clinical Excellence),UK, 94% were on Clobazam before starting CBMP's - the remaining were on another benzodiazepine or had side effects. More than half of the children were on more than 3 AEDs before starting CBMPs. Pre-treatment bloods were done in all patients before starting CBMPs but only 86% had bloods regularly after starting on CBMPs. Altered LFTs was the commonest side effect followed by loss of appetite and weakness(25%). 7 children had delays in repeat prescriptions including issues with timely re-prescription, pharmacy supplies and home delivery. All children had named doctors but only 92% had a named nurse whom parents could contact for emergencies.

Conclusions: Key recommendations included improving recording of blood tests whilst on CBMPs, need for establishment of a standard regional pathway to minimize delays and ensuring the key professionals to be contacted are recorded in the medical records of each child on CBMPs.

Keywords:
CBMPs, Dravet syndrome, Lennox Gastaut's syndrome, AEDs (anti epileptic drugs)

EPNS21-37 Poster only
Epilepsy: Miscellaneous

Evaluation of ECG findings in patients with Dravet syndrome

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Objective: Dravet syndrome (DS) is an epileptic encephalopathy related mainly to mutations in the SCN1A gene. The disease is associated with a defect in neuronal sodium channels.DS patients have a high risk of sudden unexpected death in epilepsy (SUDEP). In this study, we evaluated the electrical and autonomic cardiac functions of patients with DS.

Methods: We assessed ventricular repolarization and heart rate variability (HRV) on standard electrocardiography (ECG) and on 24-h ECG Holter monitoring, respectively, in 19 patients affected by DS (11 ± 4 years, 11 female). The QT and PR interval was measured on standard 12-lead ECG, and the corrected QT interval (QTc) was calculated according to the Bazzett formula. Mean, min and max heart rates recorded.

Results: Mean heart rate was 87 bpm ± 14 and QT interval was 410 ms ± 15. There was a significant difference between the maximum heart rates of the patients (p:0.06). This indicates that heart rate variability may be affected in patients with dravet syndrome.

Conclusions: In conclusion, DS patients may have an imbalance of cardiac autonomic function toward a relative predominance of adrenergic tone. HRV analysis can be helpful in predicting the risk of sudden death in patients with DS.

Keywords:
dravet syndrome, heart rate variability, electrocardiogram

EPNS21-404 Oral or poster
Epilepsy: Miscellaneous

EARLY CHILDHOOD EPILEPTIC ENCEPHALOPATHY (DEE42): THE MOST UNKNOWN PHENOTYPE ASSOCIATED WITH CACNA1A

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Objective: Recently pathogenic variants of CACNA1A were identified in patients with developmental and epileptic encephalopathy (DEE42), a very severe phenotype. We review the clinical characteristics of the patients reported in the literature presenting with epilepsy caused by CACNA1A variants and the underlying molecular and functional mechanisms.

Methods: Our systematic review includes patients published from 11/1996 to 11/2021, with DEE or a defined epileptic childhood syndrome at presentation. Data is categorized according to the ILAE recommendations. By using the cryo-electron microscopy structure of the rabbit CaV1.1 complex and several voltage-gated Na+ channels, the localizations of CACNA1A mutations can be predicted. Structural and functional data about variants are reviewed. Clinical description of two new patients and a new variant are included.

Results: 90 subjects meet the inclusion criteria, most of them show seizures before two years of age, and present with EOEE. Most patients present generalized onset seizures and concomitant different types of seizures. Therapeutic approaches are very varied. Cerebellar atrophy is the most common finding on MRI, even though it may be not present during the first months of life. More than forty different missense variants are linked to DEE42, many of them already related to other classical CACNA1A phenotypes, and some variants are overrepresented (V1393M, A713T, R1349Q, E101Q). Most patients presented de novo mutations. Among the pathogenic variants with known effect on channel activity there is a predominance of gain-of-function, but the consequence on gating is unknown for the majority of variants.

Conclusions: This is the first systematic review of DEE42 and childhood epilepsy caused by CACNA1A genetic variants. We provide information to understand the underlying functional mechanisms and to increase awareness of this rare condition and its emergent epileptic phenotype. Together they can help in the election and development of personalized therapies.

Keywords:
CACNA1A; DEE42; Early-onset epileptic encephalopathy

EPNS21-413 Oral or poster
Epilepsy: Miscellaneous

How do we feel in our roles as ESN's?

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Objective: Introduction
As epilepsy nurses we provide education for schools, support the family with seizures and emergency medications. We educate parents on safety, SUDEP, effects and administration of medications.
We present a survey of ten paediatric epilepsy nurse specialists from around London with the aim to explore
1. How confident they feel
2. How supported they feel
3. What resources they currently use

Methods: Method
Survey was designed within our service and sent to thirty Epilepsy nurses from within the North Thames Paediatric Epilepsy Network. We asked the nurses to answer each question on a scale of one to ten of how confident they felt in each area, one being lowest and ten being highest. All confidentiality and safety measures were taken.

Results: Results
55% rated themselves 8-10 answering parent's questions on underlying causes and prognosis. 45% said 5-7.
55% rated themselves 8-10 in confidence discussing medicines and their side effects. 45% rating themselves 5-7.
100% rated themselves 8-10 in confidence answering questions from schools on a child's emergency care plan, and providing education on this.
89% rated themselves 8-10 in confidence answering questions and educating families in a child's emergency care plan. 11% said 5-7.
55% rated themselves 8-10 in confidence discussing SUDEP with families and schools. 45% said 5-7.
Resources used to gain information, supporting families and training within roles included- British paediatric neurology association's paediatric epilepsy training (PET) courses and webinars, Charities such as SUDEP action, NICE guidelines, medicines for children, peer support, royal college of nursing, network groups, meetings and journals.

Conclusions: Conclusion
The survey highlights the current resources epilepsy nurses are using to tackle the challenges of their vital roles in supporting families with epilepsy. There is a need of one platform of resources for epilepsy nurses on the above.

Keywords:
Paediatric Epilepsy Nurse Specialists

EPNS21-446 Oral or poster
Epilepsy: Miscellaneous

Lighting the FIRE(S): Clinical profile and treatment response in Febrile infection related Refractory Epilepsy Syndrome

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Objective: Febrile infection related Refractory Epilepsy Syndrome(FIRES) is a devastating epileptic encephalopathy in school-age children defined by acute onset recurrent seizures or refractory status epilepticus preceded by mild febrile illness without evidence of infectious cause. Etiopathogenesis is still yet to be elucidated. Overall prognosis is poor with significant morbidity and mortality. This study describes a retrospective cohort of the same.

Methods: Case records of subjects fulfilling diagnostic criteria of FIRES, presenting to a tertiary care teaching center in north India, from 2014 to 2020, were retrospectively reviewed. In the current study, clinical features, response to therapy and outcome of the cases have been described.

Results: Twenty cases[median age:6 years; range:1-13 years; Males:12(60%)] presented during the study period. All of them presented with fever, altered sensorium and seizures(generalised tonic-clonic in 65%), while a quarter of them(25%) were in shock at the time of presentation. Neuroimaging showed basal ganglia involvement(5,25%) and diffuse cerebral edema(2,10%), while cerebrospinal fluid examination was non-contributory. Raised intracranial pressure(ICP) was seen in 10(50%) and 18(90%) required mechanical ventilation and 2 or more anti- seizure medications to achieve seizure control. 8 of them(40%) died, while the remaining 12 were discharged. The mean duration of hospital stay for those who were discharged was 1.7+1.1 months. 9 of the 12 discharged(75%) developed neurodevelopmental sequelae and epilepsy. Raised ICP at presentation(8/8 vs 2/12, p=0.0004) and need for midazolam infusion in refractory status epilepticus(5/8 vs 1/12, p=0.01) differed significantly between those who died and survived respectively.

Conclusions: FIRES is associated with poor outcome in terms of morbidity and mortality. Certain characteristics like raised ICP and need for midazolam infusion in refractory status epilepticus may be associated with mortality.

Keywords:
FIRES, febrile illness, refractory status epilepticus

EPNS21-470 Poster only
Epilepsy: Miscellaneous

Electroclinical features, therapeutic options and long term prognosis in patients with "Sunflower syndrome"

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Objective: Sunflower syndrome (SFS) is a rare childhood-onset generalized epilepsy characterized by photosensitivity, heliotropism, and drug-resistant stereotyped seizures possibly self-induced by hand-waving maneuvers. Data on the long-term prognosis are scantly and evidence over best treatment strategies is lacking.

Methods: We retrospectively describe the electroclinical features, and therapeutic response in a group of 21 patients with SFS, without intellectual disability.

Results: 16 patients were female (67%), with a median age at onset of 7 years. In all patients, ictal episodes began with sun-staring, and hand-waving in front of the sunlight, accompanied by brief typical absence seizures. 17 patients (81%) showed interictal EEG abnormalities, mainly characterized by spike and polyspike-and-wave discharges. Ictal epileptiform activity occurred approximately less than one second after the start of handwaving. At the last follow-up (median length 8.2 years), 12 patients (57%) were drug-resistant. Nine of them (75%) achieved seizure control with the use of tainted lenses, either alone or compared with anti-seizure medications (ASM). Disappearance of seizures was associated with EEG improvement/normalization when tinted glasses were used during EEG recordings.

Conclusions: While the clinical and EEG characteristics of SFS are well defined, the best therapeutic approaches are still under debate. Our data confirms a high rate of drug-resistance and frequent need of polytherapy. Of note, in drug-resistant patients, lenses (but not ASM) were able to suppress PPR in our patients. Although additional data are needed, lenses seem to have a powerful potential role for the management of SFS.

Keywords:
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EPNS21-514 Poster only
Epilepsy: Miscellaneous

Epilepsy with frontal absences in the child: prognosis, evolution and pharmacological response

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Objective: Absence seizures with secondary bilateral synchrony may be a manifestation of frontal seizures and although they are little studied, they seem to present greater refractoriness to treatment and behavioural and learning problems in these children. This is why we decided to analyze the clinical evolution and pharmacological response of epilepsy with frontal absence in a tertiary hospital.

Methods: Retrospective study of cases of patients with epilepsy with typical absences in children under 14 years of age in a tertiary hospital during the last 5 years. Epidemiological variables, frontal focality in the electroencephalogram, neuroimaging tests, psychomotor and behavioural development, treatment and pharmacological response were the variables analyzed.

Results: Seventy-six patients (mean±3.05 SD 8.2 years; 41 females/35 males) with typical absence seizures were included: In 10/76 cases (13.1%) the focality preceded in succession the critical 3 Hertz spike and wave discharges. There was no higher number of associated seizures in this group. A higher need for bitherapy was found in the group of patients with epilepsy with frontal absence with statistically significant association (60 % versus 16.7 %). In the electroencephalogram, intercritical paroxysms were recorded in 55/76 patients (72.3%, 35 located in the frontal lobe and 20 in another location) with no relation to the pharmacological response, although there was statistical significance when relating frontal intercritical paroxysms to a behavioural alteration prior to the onset of seizures. We did not observe any behavioural differences or differences in remission between the two groups after starting pharmacological treatment.

Conclusions: The debut and clinical presentation of epilepsy with frontal absence with secondary bilateral synchrony was similar to childhood absence epilepsy. Their management required further pharmacological escalation but the prognosis was similar.

Keywords:
Epilepsy, frontal absence, eeg, frontal epilepsy

EPNS21-638 Oral or poster
Epilepsy: Miscellaneous

Siblings with Refractory Epilepsy with Homozygous Mutation in EMC1 and Use of Ketogenic Diet Therapy

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Objective: The EMC1 gene is a transmembrane protein that facilitates phospholipid transfer from the endoplasmic reticulum to the mitochondria. EMC1 mutation has been reported in a small number of patients presenting with symptoms such as growth retardation, epilepsy, and vision loss.
In this article, the cases of two siblings with a homozygous EMC1 variant are presented. One of them seizures brought under control through the use of ketogenic diet therapy (KDT)and it has not been reported before.

Methods: Case 1:
A six-year-old male with G2P2A0K0 who was delivered via C/S at term. The patient, who was purple at birth, and had respiratory distress. The parents have a 1st degree consanguineous marriage. In physical examination, no DTR's could be taken, and the patient could not sit without support or walk. He had been using levetiracetam, clobazam, and topiramate for myoclonic seizures. EEG revealed that the spike and multi-spike slow wave activity was sometimes generalized. Bilateral small amplitude p100 potentials were obtained on visual evoked potential test (VEP). Cerebellar atrophy and unmyelinated parenchymal areas in both cerebral hemispheres detected on brain MRI. KDT was started at a ratio of 2:1. He was followed without seizures for the last 1 year, he used KD for a total of three years.

Results: Case 2:
A two-year-old girl was born electively with C/S at 39 GW and had no history of asphyxia. In the physical examination, there was no eye tracking, sitting, or walking. When the seizures continued despite levetiracetam, valproate was added due to the jerking nature of the patient's seizures. EEG showed cerebral dysmaturity and epileptic activity in the frontocentral regions. Moderate cerebellar atrophy was demonstrated on the brain MRI. The same homozygous EMC1 mutation as her brother was detected in WES examination.

Conclusions: In conclusion, we though that detailed genetic analysis of patients with resistant epilepsy of unknown cause may shed light on individual treatments.

Keywords:
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EPNS21-670 Poster only
Epilepsy: Miscellaneous

Epidemiology of Frontal Absence Epilepsy with secondary bilateral synchrony in the child

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Objective: Absence seizures with secondary bilateral synchrony may be a manifestation of frontal seizures, clinically indistinguishable, although with a different prognosis and control. That is why we decided to describe the childhood epidemiology of Frontal Absence Epilepsy in the health area of a tertiary hospital.

Methods: A retrospective study of cases with typical absence epilepsy in children under 14 years of age in the area of a tertiary hospital during the last 5 years. The following variables were analyzed: sex, age, number and duration of seizures, associated seizures, cranial magnetic resonance imaging, frontal focus in the electroencephalogram with and without relation to the onset of generalized discharge.

Results: A total of 81 patients (mean: 8.3 years±3.05 SD; 44 females/37 males) with typical absence seizures were included: In 80% it was the only seizure type (66/81). In 70/81 simple; 55/81 some electroencephalogram focus and in 35/81 the focus was frontal. In 10/81 cases (12.5%) the focus preceded in succession the critical 3 Hertz spike and wave discharges. There were no significant differences in age, seizure duration or the presence of other seizure types. Morphology was similar to absence epilepsy but the number of seizures per day was significantly lower. Cranial MRI was normal in all cases. The remaining corresponded to 47/81 childhood absence epilepsy, 19/81 juvenile absence epilepsy, 4/81 absence epilepsy with myoclonus-palpebral (Jeavons Syndrome) and 1/81 epilepsy with myoclonic-absence.

Conclusions: Frontal absence epilepsy accounts for a significant percentage (12.5%) of absence epilepsy with an incidence of about 1/4,500 newborns per year, with seizures of identical morphology, age and duration, although less frequent.

Keywords:
Frontal Absence Epilepsy; Absence Epilepsy; Epidemiology

EPNS21-693 Poster only
Epilepsy: Miscellaneous

Epidemiology of Frontal Absence Epilepsy with secondary bilateral synchrony in the child

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Objective: Absence seizures with secondary bilateral synchrony may be a manifestation of frontal seizures, clinically indistinguishable, although with a different prognosis and control. That is why we decided to describe the childhood epidemiology of Frontal Absence Epilepsy in the health area of a tertiary hospital

Methods: A retrospective study of cases with typical absence epilepsy in children under 14 years of age in the area of a tertiary hospital during the last 5 years. The following variables were analyzed: sex, age, number and duration of seizures, associated seizures, cranial magnetic resonance imaging, frontal focus in the electroencephalogram with and without relation to the onset of generalized discharge.

Results: A total of 81 patients (mean: 8.3 years±3.05 SD; 44 females/37 males) with typical absence seizures were included: In 80% it was the only seizure type (66/81). In 70/81 simple; 55/81 some EEG focus and in 35/81 the focus was frontal. In 10/81 cases (12.5%) the focus preceded in succession the critical 3 Hertz spike and wave discharges. There were no significant differences in age, seizure duration or the presence of other seizure types. Morphology was similar to absence epilepsy but the number of seizures per day was significantly lower. Cranial MRI was normal in all cases. The remaining corresponded to 47/81 childhood absence epilepsy, 19/81 juvenile absence epilepsy, 4/81 absence epilepsy with myoclonus-palpebral (Jeavons) and 1/81 epilepsy with myoclonic-absence.

Conclusions: Frontal absence epilepsy accounts for a significant percentage (12.5%) of absence epilepsy with an incidence of about 1/4,500 newborns per year, with seizures of identical morphology, age and duration, although less frequent.

Keywords:
frontal absences, frontal epilepsia,

EPNS21-90 Oral or poster
Epilepsy: Miscellaneous

The Role of Epileptic Seizures in the Caregiver and Family Burden of Tuberous Sclerosis Complex (TSC)

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Objective: TSC is a rare and variable genetic condition characterised by benign tumours in multiple organs; epilepsy and neuropsychiatric disorders are among its most prevalent manifestations. The study objective was to examine the impact of seizure frequency on the caregiver and family burden of TSC.

Methods: A rapid literature review on the caregiver and family burden of TSC, and the impact of seizures on caregiver burden and health-related quality of life informed the development of a prospective caregiver survey. The online survey included bespoke de novo measures, PedsQL^{TM} Family Impact Module, and Hospital Anxiety and Depression Scale (HADS). Primary caregivers of symptomatic patients with TSC were recruited via a United Kingdom (UK)-based TSC patient association. Close-ended responses were analysed using descriptive and inferential statistics. Open-text responses were analysed using qualitative content analysis.

Results: Fifty-nine primary caregivers fully completed the survey. Most were female (95%) and parents (90%) of the patients with TSC. A mean of 2.3 (standard deviation [SD] 1.6) household members were reported to be involved in care activities. Primary caregivers and all household members combined spent a mean (SD) total of 104.3 (51.7) and 128.4 (67.7) hours on care in the previous week, of which 7.4 (16.2) and 11.2 (28.3) hours were spent on care while the patient was having/recovering from seizure(s). Open-text responses highlighted the continuous nature of their care and the need to be available at all times due to the unpredictability of seizures. Primary caregivers scored [mean (SD)] 43.3 (19.1) on the PedsQL^{TM} Family Impact total score, indicating worse parent/family functioning compared with a community sample of parents, 11.2 (4.8) on HADS Anxiety, and 7.9 (4.4) on HADS Depression, indicating higher anxiety and depression than UK population norms.

Conclusions: The study findings highlight the role of epileptic seizures in the considerable caregiver and family burden of TSC.

Keywords:
TSC; carer; caregiver; burden

EPNS21-94 Oral or poster
Epilepsy: Miscellaneous

Epilepsy phenotype and management in patients with EAST syndrome

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Objective: To present epilepsy phenotype and management in two siblings diagnosed with EAST syndrome and to review literature for other effective antiepileptic medications.

Methods: Retrospective review of epilepsy phenotype and antiepileptic therapy for two siblings diagnosed with EAST syndrome and review of other reported effective antiepileptic therapy.

Results: Four-month-old boy presented with staring episodes and recurrent generalised tonic clonic seizures. First EEG 6 weeks following the first presentation was normal. Keppra was commenced and dose was increased in view of increasing GTC seizures at 1 year of age with no improvement. He had normal development at 1 year with normal EEG and MRI. 82 EIE gene panel and metabolic screen were negative. He continued to have intractable seizures, so levetiracetam was weaned and he was commenced on valproate and clobazam with reasonable seizure control. He started to have ataxia with hearing problems at age of 3.5 years. His sister was born when he was 4 years old and she started to have similar seizures pattern from age of four months so she was commenced on sodium valproate and clobazam with reasonable response. 78 EIE panel was sent for her, and this came positive for KCNJ10 gene mutation for EAST syndrome. Her brother was immediately assessed for possible tubulopathy and was found to have mild hypokalaemia and hypomagnesemia and was started on replacement and he was found to have KCNJ10 mutation on specific testing. Their epilepsy is well managed on valproate and lamotrigine.

Conclusions: Children with EAST syndrome usually have generalised afebrile seizures as the first presentation at around 3 to 4 months of age. Different antiepileptic medications as sodium valproate, lamotrigine, topiramate and carbamazepine have shown to be effective in seizure control from a cohort of patients in different reports.

Keywords:
EAST, SeSAME, epilepsy, ataxia,sensorineural hearing loss, deafness, tubulopathy

EPNS21-2023 Oral or poster
Fetal and Neonatal Neurology

Is Prenatal Diagnosis of CASK-Related MICPCH Feasible?

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Objective: Pathogenic variants in the CASK-gene are associated with microcephaly with pontine and cerebellar hypoplasia (MICPCH, OMIM #300749). There are no studies on the fetal presentation. Following the recent diagnosis of a CASK-gene deletion, in a fetus with a small trans-cerebellar diameter (TCD), and deceleration of head circumference (HC) growth rate at the end of pregnancy in two additional patients with CASK variants we contemplated that MICPCH could sometimes already manifest during pregnancy.

Methods: This is an international multicenter retrospective study. We contacted a CASK parents' social media group and world known experts in MICPCH, and asked them to supply clinical information, and prenatal and postnatal ultrasound, and MRI scans. Percentiles and standard deviations were calculated according to age by nomograms.

Results: The study consisted of 47 patients, 42 females and 5 males. Information regarding prenatal head circumference (HC) was available in 17/47 patients; 59% had a fetal HC<-2SD, range -2.02 to -4.1 SD. Progressive prenatal deceleration of HC growth rate was observed in 76%. HC at birth measurements were available in 40/47 patients, 48% had a HC<-2SD, range -3.3 to -2.02 SD. A total of 6/15 fetuses had a TCD Z-score <-2, range -2 to -5.88.

Conclusions: CASK-gene related disorders can be suspected prenatally, in fetuses that present with a progressive deceleration of HC growth rate, a HC under -2SD and/or a small TCD. Closer monitoring with consecutive measurements of fetal growth is especially important when measurements are within the low range of the norm. Amniocentesis for genetic studies is advised in the presence of a progressive deceleration of HC growth rates and a small TCD.

Keywords:
CASK; Microcephaly; Pontocerebellar hypoplasia; Trans-cerebellar diameter; Head circumference; Fetus; Prenatal Diagnosis

EPNS21-523 Poster only
Fetal and Neonatal Neurology

Comparison of the prenatal imaging findings to the pathology findings in fetuses with brain malformations

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Objective: In the fetal neurology clinic (FNC), experts from different fields are cooperating in order to diagnose brain anomalies and assess neuro-developmental outcome of the unborn fetus. Advances in the field of pre-natal imaging (US and MRI) and genetic testing have facilitated the ability to identify brain anomalies that might cause severe outcomes. In Israel, if the risk for such outcomes exceeds 30%, termination of pregnancy (TOP) is permitted. Few studies compared the pre-natal imaging studies to the fetal pathology findings. In most cases the CNS anomalies were discovered in early stages of pregnancy.

Methods: Retrospective cohort in which pathology reports were compared to imaging studies in all fetuses screened in our FNC and underwent TOP due to brain anomaly between 2009-2019. The rate of agreement (macroscopic and microscopic) was rated on a scale.

Results: We identified 113 cases of TOP due to brain malformations. All consultations were given from the 2nd trimester onward and most in the 3rd trimester. We found full agreement in 73% of cases. in 6.5% the findings were similar but the pathology added more information; in 17% findings in imaging were not seen in the macroscopic examination but were confirmed by the microscopic examination in half of these cases; complete disagreemnt was seen only 3.5% but the TOP was still justified. In 12% the new information from the microscopic examination changed the final diagnosis.

Conclusions: To our knowledge this the largest study comparing pre-natal brain imaging findings to the pathology findings in fetuses that were screened late in pregnancy. We found good correlation between the imaging and the pathology findings, similar to previous studies. Even in cases of disagreement, the TOP was justified. The microscopic examination added valuable information that enabled us to give more accurate consultation to the couples. Albeit the good correlation seen in our study we conclude that the post-mortem pathology examination is of paramount importance.

Keywords:
Fetal Neurology, Brain anomalies, Pre-natal screening

EPNS21-632 Oral or poster
Fetal and Neonatal Neurology

Novel bi-allelic variants in KIF21A cause a novel phenotype of fetal akinesia with neurodevelopmental defects

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Objective: Fetal akinesia (FA) is a complex disease entity, sharing arthrogryposis as a common feature.

Methods: Using whole-exome-sequencing we identified 8 mutations that are loss of function mutations predicted to cause premature stop codon or essential splice site mutations that would lead to aberrant KIF21A isoforms.

Results: We report 5 unrelated individuals with bi-allelic variants in the kinesin family member 21A gene (KIF21A), a member of the kinesin-4 family that is functional in axon growth and guidance by transporting cargo anterograde to the synapses. We showed that the affected individuals with those variants had severe phenotypes with neurodevelopmental disorder, structural brain abnormalities, arthrogryposis of multiple joints, muscular hypotonia, and hypokinesia. Furthermore, all these phenotypes strongly correlate with the recently published porcine phenotype that also has bi-allelic truncating variants, with a few of patients showing features of a neuropathy.

Conclusions: In contrast with our findings, previous reports have indicated that the known phenotypic effect of KIF21A caused by the heterozygous variants that lead to missense mutations or deletions and are significantly clustered in the motor domain or coiled-coil region of KIF21A, which in turn causes an isolated ophthalmologic phenotype with congenital fibrosis of the extraocular muscles type 1 (CFEOM1). Conclusively, we describe a novel disease in the FA spectrum with a primary neurogenic defect due to bi-allelic variants in the KIF21A.

Keywords:
fetal akinesia, axonal transport

EPNS21-125
Genetics

Oral or poster

Identification of a candidate gene for complex hereditary spastic paraplegia not previously associated with a human disease phenotype: Synergin, Gamma (*SYNRG*)

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Objective: The hereditary spastic paraplegias (HSP) are characterized by progressive spasticity due to corticospinal tract dysfunction. Complex forms of HSP also show other central and peripheral nervous system symptoms. Variants in the Synergin, Gamma (*SYNRG*) gene have not yet been identified with any phenotype in the literature. This gene encodes a protein that has the ability to act to bind the adaptor protein 1 (AP-1) complex to other proteins. Herein, we report a homozygous variant in the *SYNRG* gene of 2 siblings with complicated HSP phenotype.

Methods: Whole-exome sequencing was performed with the Sofia IDT xGen Exome Research Panel v2 and Illumina Novaseq platform. The detected variant was confirmed by Sanger Sequencing with ABI 3130xl.

Results: Patient 1; A 17-year-old male presented with tremor in his hands and not being able to walk. He had dysarthria, spasticity with lower predominance, cerebellar signs. His parents noticed that his gait was abnormal at 3-year-old and, he had progressive neurological deterioration afterward. His parents were first-degree cousins and, he had four other siblings. Cranial MRI revealed enlarged lateral ventricles with wavy posterior contours and cerebellar atrophy. **Patient 2**; 5 8/12 years old male, sibling of patient 1, also admitted with the complaint of unsteady gait since the last year. He had a spastic diplegic gait. Cranial MRI revealed very mild posterior periventricular white matter hyperintensity on T2 weighted images. Genetic analysis identified a homozygous p.Leu1202Pro variant in the *SYNRG* gene in patients 1 and 2. The variant was heterozygous in his parents and a healthy sibling, and not detected in the other two healthy siblings.

Conclusions: The AP complex family has five members: AP-1, AP-2, AP-3, AP-4, and AP-5. We know that pathogenic/likely pathogenic variants in AP-4 and AP-5 coats are responsible for many HSP phenotypes. We believe homozygous variants in the *SYNRG* gene which interacts with AP-1 are responsible from a complex HSP phenotype.

Keywords:
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EPNS21-137 Poster only
Genetics

A case report of a 3-year-old girl with refractory partial epilepsy and a homozygous mutation in the CNTNAP gene

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Objective: Homozygous and compound heterozygous mutations in the CNTNAP2 gene can lead to loss of normal protein function, which found to be related to Cortical dysplasia - focal epilepsy syndrome (CDFES) and Pitt-Hopkins 1 syndrome (PTHSL1).

Methods: A 2 ½-year- old girl with free family and perinatal history, was admitted to our department because of recurrent episodes of focal seizures with left eyelid myoclonias and body stiffness. Aggressive behavior, self-injuries and speech delay were also present. Initial EEG, blood tests, metabolic screening (blood, urine and CSF) and brain MRI scan didn't reveal any pathological signs. She was commenced on anticonvulsant treatment with Carbamazepine, with good response for a short period of time. Phenobarbital, Lacosamide and Vitamin B6 were also added to her treatment plan with partial control of seizures. Anticonvulsant therapy was modified to Oxcarbazepine (40mg/kg/d) and Topiramate (6mg/kg/d). For 18 months she is free of seizures. Repeat EEG revealed slow wave activity at the left temporal lobe. A brain MRI scan (3T) didn't reveal cortical dysplasia.

Results: Due to the disruptive behavior and the refractory epilepsy, a Next Generation Sequence (NGS) (focused on Epilepsy panel) was carried out and the nucleotide change c.1361_1362del, p.(Asp454Argfs*24) was detected in CNTNAP gene in homozygous state. As far as we know, parents haven't attended any genetic counselling yet.

Conclusions: According to the international medical literature, children who carry the same variant (homozygous state), but in the CNTNAP2 gene, have shown cortical dysplasia - focal epilepsy, mild motor retardation, refractory epilepsy and regression in speech, learning abilities and social behaviors. Therefore, this specific nucleotide change, in our case could be characterized as possible benign and correlated with our patient's clinical picture.

Keywords:
epilepsy, CNTNAP2 gene, psychomotor delay

EPNS21-157 Poster only
Genetics

From epilepsy to an insulinoma, how genetics can be confusing

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Objective: Mendeliome analysis often reveals multiple variants in one patient. With this case report, I want to emphasize the importance of detailed clinical phenotyping in order to make correct genetic correlations.

Methods: An 11 year old boy presented with multiple episodes of sudden loss of tone, vomiting and wide pupils, followed by loss of consciousness and generalised tonic clonic convulsions. Genetic testing revealed a paternal inherited heterozygote variant (p.Arg387His) in CACNA1A and a de novo variant in MEN1. He was diagnosed with epilepsy. The patient was treated with Tegretol when he presented for a second opinion in our clinic. An EEG showed frequent runs of high voltage delta waves over the bilateral occipital regions. He had another episode in the hospital, with low blood glucose (38 mg/dL) and high insuline and C-peptide. On MRI an insulinoma of 2 cm diameter was found in the pancreas.

Results: The paternally inherited CACNA1A variant in this patient has not been described in the literature, is known in 1 patient in GnomAd and according to VarSome he is probably pathogenic.
CACNA1A has been linked to multiple phenotypes, such as developmental and epileptic encephalopathy, episodic ataxia type 2 (clinical variability within families), spinocerebellar ataxia type 6 and familial hemiplegic migraine. Epilepsy and familial hemiplegic migraine might be caused by the same genetic variant.
In this patient, the CACNA1A variant was the misleading variant. The father was not affected. The EEG abnormalities, as well as the episodes with loss of tone, were due to the hypoglycemia.
According to the genetic report, the de novo variant in MEN1 (p.Lys238fs) was classified as probably pathogenic. After enucleation of the insulinoma, the patient was symptom free. Anti-epileptic medications could be stopped.

Conclusions: Mendeliome analysis has proven its utility in genetic diseases. Genotype-phenotype correlations are extremely important in order not to misdiagnose.

Keywords:
CACNA1A, MEN1, phenotype, genotype

EPNS21-162 Poster only
Genetics

A Neurodegenerative Syndrome In Differential Diagnosis Of Cerebral Palsy: Juvenile ALS

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Objective: Cerebral palsy (CP) is defined as "a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain" by the international consensus. There are three predominant CP syndromes: spastic, dyskinetic (choreoathetoid and dystonic) and ataxic. Infants with CP could have additional clinical findings which can be seen in various childhood onset metabolic or neurodegenerative diseases. Thus, both metabolic and neurodegenerative diseases which have slow progression could be misdiagnosed as CP. Amyotrophic lateral sclerosis (ALS) is a severe neurodegenerative disorder as a result of the degeneration of upper and lower motor neurons and characterized by progressive muscle weakness and wasting throughout the entire body. ALS patients who have been reported age at onset less than 25 years are classified as Juvenile ALS (JALS). JALS patients can present with clinical features similar to dystonic CP.

Methods: We conducted a retrospective chart review of all patients with an ICD-10 code associated with CP referred to Antalya Research and Training Hospital Pediatric Neurology clinic from January 2016 to January 2020. Patients who had hypoxic ischemic encephalopathy, prematurity, hyperbilirubinemia, asphyxia, MRI findings consistent with CP were excluded. Remaining patients' metabolic screening tests and genetic testing algorithm were conducted. Each variant was evaluated according to the ACMG criteria.

Results: 435 patients were reviewed, and 93 patients meet the inclusion criteria. After genetic testing, 54 pathogenic variants were detected, and 2 patients from two unrelated families had ALS2 gene variants. Then we evaluated their families and presented these patients as case reports.

Conclusions: Genetic testing for patients whose clinical findings do not fully meet the CP criteria may contribute to the follow-up and treatment of patients by preventing misdiagnosis.

Keywords:
Childhood onset neurodegenerative disorders, Juvenile ALS, ALS2, cerebral palsy, global developmental delay

EPNS21-164 Poster only
Genetics

PROGRESSIVE MYOCLONIC EPILEPSY TYPE 2B (LAFORA DISEASE) IN A 13-YEAR-OLD BOY WITH A NOVEL PATHOGENIC VARIANT IN THE NHLRC1 GENE

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Objective: Autosomal recessive Progressive Myoclonic Epilepsy Type 2B (Lafora type, MIM#254780, ICD-10:G40.3) is an extremely rare, fatal neurodegenerative disease caused by biallelic pathogenic or likely pathogenic variants in the NHLRC1 gene. It is characterized by sudden adolescent onset recurrent seizures (usually myoclonic) and gradual progressive neurological impairment, mostly cognitive deficits.

Methods: The proband, a 13 year-old male, is the second child of consanguineous Afghani parents, presenting with a history of a 2-year history of drug-resistant epilepsy (quadriple therapy: valproic acid, levetiracetam, topiramate and clobazam) accompanied by disrupted behavior, slurred speech, and auditory and visual hallucinations. The electroencephalogram (EEG) was abnormal with slow wave activity and multifocal paroxysmal spikes. Brain MRI and complete laboratory work up (blood, urine, CSF) excluded infectious, immunological, endocrine and metabolic disorders. Treatment by ethosuximide, midazolam, methylprednisolone and ketogenic diet had a small clinical impact. After two months of hospitalization, the seizures were partially controlled with levetiracetam, ethosuximide , clobazam and risperidone and the patient was discharged

Results: Whole Exome Sequencing (WES) identified the NHLRC1:c.583delG variant in homozygosity. The variant, predicted to result in a truncated protein p.(Asp195Ilefs*37) is a novel variant characterized as pathogenic according to the criteria of American College of Medical Genetics-ACMG (PVS1, PM2,PP3). Subsequent segregation analysis with targeted Sanger sequencing revealed a normal sequence for the sister and the expected heterozygosity for the variant in both parents.

Conclusions: Genetic lesions are common causes of epilepsy and with the advent of Next Generation Technologies prompt differential diagnosis may be offered to provide valuable information towards better therapeutic decisions and improved management of patients.

Keywords:
progressive myoclonic epilepsy, Lafora disease, NHLRC1 gene

EPNS21-201
Genetics

Poster only

The Impact of Exome Sequencing in Child Neurology Practice: A Single Center Experience.

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Objective: This study aims to assess the diagnostic impact of exome sequencing (ES) within a large and heterogeneous cohort of neuropediatric patients.

Methods: For this retrospective data analysis we enrolled 197 neuropediatric patients who were referred to our clinic between 2013 and 2021. The patients showed a broad spectrum of childhood-onset neurological symptoms and were priorly undiagnosed. All patients underwent ES (in most cases singleton analysis) to obtain a possible genetic diagnosis. ES was performed using Illumina HiSeq technology using Agilent All Exon or Clinical Research enrichment protocols at an average depth of 60-fold. Bioinformatic analysis was accomplished by an in-house programmed pipeline combining different state-of-the-art protocols and algorithms. Pathogenic and likely pathogenic variants were confirmed by PCR and conventional DNA-sequencing. If possible, segregation analysis in family members was performed.

Results: We obtained a causal genetic diagnosis in 111 out of 197 cases (56.3%) through ES. The cohort consisted of 117 male and 80 female patients with a mean age of 8.5 years (range 0-19.1 years). The patients were assigned to subgroups based on their primary symptoms: neuromuscular disorder (NMD; n=78), intellectual disability (ID; n=49), movement disorder (MD; n=42), inborn error of metabolism (IEM; n=17), and other (OTHER; n=11). Different diagnosis rates were observed within these subgroups (NMD 51.3%; ID 61.2%; MD 47.6%; IEM 76.5%; OTHER 72.7%). Some genes were found to be more prevalent in our cohort (*RYR1*, *ANO5*, *PRRT2*).

Conclusions: Our results emphasize the importance of ES as a key and early diagnostic tool in pediatric neurology by now, as we achieved a genetic diagnosis for a high percentage (56.3%) within a heterogeneous cohort. ES should be considered early to abbreviate the child's diagnostic process and render specific therapeutic options possible.

Keywords:
exome sequencing, next generation sequencing, child neurology

EPNS21-2012 Oral or poster
Genetics

Biallelic variants in CRIPT cause Rothmund-Thomson syndrome and genome instability with excessive cellular senescence

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Objective: Rothmund-Thomson syndrome (RTS) is characterized by poikiloderma, sparse hair, small stature, skeletal defects, cancer or cataracts, resembling premature aging. RECQL4 and ANAPC1 are disease genes associated with RTS in over 75% of cases, but in the remaining patients no causative genetic alterations are detected. We describe two individuals with a clinical diagnosis of RTS who both have homozygous variants in the CRIPT gene (OMIM#615789).

Methods: CRIPT patients (including three published patients) were systematically compared to RTS. Patient-derived fibroblasts were available from one patient. Senescence markers, mitotic progression, and sensitivity to chemotoxic agents in live-cell imaging were analyzed in comparison to RECQL4-deficient cells.

Results: All five CRIPT patients fulfilled the RTS diagnostic criteria. While neurological impairment is an inconsistent finding in RTS, all CRIPT patients displayed developmental delay. Using computational gestalt analysis of patient photographs, CRIPT individuals showed greatest overlap with RTS individuals. Histologic analysis of CRIPT patient skin revealed poikiloderma and increased expression of senescence markers (p53, p16, p21). Knockdown of CRIPT in fibroblasts resulted in significantly upregulated ß-galactosidase activity. RECQL4- and CRIPT-deficient fibroblasts showed no chromosomal aberrations, normal mitotic progression, unaltered numbers of mitotic errors and appropriate cell cycle arrest after nocodazole treatment. In a viability screen, both cell types were sensitive to the chemotoxic agent potassium bromate.

Conclusions: CRIPT is reported as a third causative gene in the RTS-spectrum of disorders associated with a more severe neurological phenotype. At the cellular level, RECQL4- and CRIPT-deficient cells both displayed excessive senescence and impaired genome maintenance, suggesting shared mechanisms leading to the clinical phenotypes.

Keywords:
Rothmund-Thomson Syndrome, novel disease gene, developemental delay, premature aging

EPNS21-203 Oral or poster
Genetics

Recognizing KIF1A related disorders: lessons from 2 patients

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Objective: KIF1A related disorders (KRD) are a relatively new neurological diagnosis, first described in 2011. KRD are described as causing a broad range of neurodisability, involving both the central and peripheral nervous systems. Traditional 'localization of the lesion' diagnostic approaches may be insufficient. Neuroimaging may be normal or non-specific. This presentation will highlight salient clinical features in 2 patients who presented to our centre.

Methods: A retrospective case note review and comparison with current literature was performed.

Results: The children presented with mildly delayed walking, global developmental delay, hypotonia and paroxysmal blank episodes. Patient 1 struggled with stairs, had an abnormal gait and frequent falls. He subsequently developed lower limb spasticity, brisk lower limb reflexes, lumbar lordosis and scoliosis. Patient 2 had hypermobility with low muscle tone and lower limb reflexes were initially normal. On follow-up, there were lower limb pyramidal signs evolving with tightness around both ankles, brisk tendon reflexes and extensor plantar responses.

MRI brain in patient 1 at age 2 suggested reduced volume of the cerebellum and mega cisterna magna. This was unchanged when repeated at age 5 years. Patient 2 had a normal MRI head at age 4 years and at 5 years.

Patient 1 was diagnosed with KIF1A related disease at age 10 following exome sequencing. Similarly, patient 2 was diagnosed following exome sequencing at age 7 years. There was no family history of this condition in either patient.

Conclusions: The clinical findings in these 2 patients are in keeping with the literature reports of KRD with developmental delay, hypotonia and hyperreflexia. Pyramidal signs become more prominent with age. Exome testing has been invaluable in arriving at a correct diagnosis and should be considered early in children with unusual neurological signs. Familiarity with this relatively new neurological disorder may direct clinicians to more targeted genetic testing at an earlier age.

Keywords:
KIF1A related disorders (KRD)

EPNS21-2036 Oral or poster
Genetics

An Algorithm that Identifies Drugs in Clinical Use as Potential Therapies for Developmental Disorders.

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Objective: With the approaching era of individualised therapeutics and with the evolving drive to use existing pharmacological agents in a broader range of conditions, there is a widespread intellectual appetite for identifying such agents. We set out to develop an algorithm to identify such agents for further experimental and potential clinical use in a wide range of developmental disorders.

Methods: All developmental disorders (gene, type of mutation involved and likely consequence) were extracted from the Developmental Disorders Genotype To Phenotype (DDG2P) database. These were then cross-referenced with data from the Open Targets platform to identify drugs that had passed phase 3/4 clinical trials that would work in an opposing direction of action to the mutation. The resulting drug-mutation pairs were then manually curated to determine likely bioavailability at the anatomical site implicated in the disease in question. Finally, drugs with an established Orphan designation in other diseases were identified as potential novel therapies.

Results: 2589 mutation-disease pairs were extracted from DDG2P. Of these, 323 had drugs that were known to have an effect on the 'normal' gene product in question. In total, 2674 drug-mutation pairs were identified. 560 of these were drug-mutation pairs with an opposing direction of effect and were bioavailable at the anatomical site implicated in the disease. Of these, 76 had been trialled clinically in the condition in question and 484 were novel drug-mutation pairs (109 of which had orphan status for other diseases).
A sub-analysis of 11 severe disorders due to activating mutations was performed, and this pipeline resulted in the ascertainment of 20 novel drug-target pairs that could be clinically trialled in these conditions.

Conclusions: This algorithm successfully identifies drugs that are already in clinical use for other diseases as potential experimental and therapeutic agents in developmental disorders. In part, this algorithm will be implemented into DECIPHER.

Keywords:
Neurodevelopment, genetics, genomics, developmental disorders, pharmacogenomics, pharmacology, drugs

EPNS21-2050 Oral or poster
Genetics

Evaluation of Genetic Etiology in Slovene Patients with Cerebral Palsy

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Objective: Cerebral palsy (CP) is a permanent movement or postural disorder resulting from non-progressive impairments of the developing brain. Studies suggest that up to 30% of CP cases may be of genetic origin. The aim of our study was to search for genetic etiology of CP in a national cohort of children.

Methods: In Slovenia, children with CP, born in 1996 or later, are included in the Slovenian National Registry of Cerebral Palsy. We use the CP definition used by the Surveillance of Cerebral Palsy in Europe. In this cross-sectional study, all children in the registry, born between years 2003-2016, were invited to participate. All children who responded to our invitation were examined by a pediatric neurologist. Blood was drawn for genetic testing. Whole exome sequencing was performed and a gene panel of over 100 genes associated with the CP spectrum disorders was evaluated. The study is still recruiting participants.

Results: So far, 46 children without a previously known genetic diagnosis were examined - 25 boys and 21 girls. Of all children, 87% had spastic, 10.9.% had dyskinetic, and 2.1% had ataxic CP, of which 32.6% of children were classified as GMFCS IV or V. One child had a positive family history for CP. One child reported progressive deterioration of neurological functions. Three children had dysmorphic features. On genetic analysis, 1 patient (2%) had a homozygote pathogenic variant in SPAST gene, 7 (15%) had a likely pathogenic variant, 15 (33%) had a variant of uncertain significance and will need further family segregation, and 23 (50%) children had a negative genetic report.

Conclusions: This is the first national study evaluating possible genetic etiology of CP in Slovene children. So far, 46 children have been evaluated, one had confirmed genetic diagnosis and in 48% further genetic testing is warranted. Establishing genetic nature of CP where possible can contribute to early disease recognition and possible targeted treatment of these patients.

Keywords:
cerebral palsy, genetic, whole exome sequencing, spasticity, targeted treatment

EPNS21-2075 Oral or poster
Genetics

PIK3CA-Related Overgrowth Spectrum Disorders. Treatment with Sirolimus.

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Objective: Presentation of patients on PIK3CA-Related Overgrowth Spectrum (PROS) and monitor treatment with mTOR inhibitor Sirolimus.

Methods: This prospective study describes the outcome after treating patients with PROS with mTOR inhibitor Sirolimus. A protocol with low-target Sirolimus levels was used, with frequent blood sampling and Magnetic Resonance Imaging (MRI) studies every six months. Three patients had Isolated Lymphatic Malformations (ILM), two patients presented Fibroadipose Overgrowth with Hemihyperplasia and Multiple Lipomatosis (FAO-HHML), one patient with Capillary Malformation of the Lower Lip, Lymphatic Malformation of the Face and Neck, Asymmetry and Partial/Generalized Overgrowth (CLAPO). Genetic testing was positive for mosaic mutations in the PIK3CA gene in two FAO-HHML and one CLAPO patient.

Results: In ILM, patients have observed a significant decrease in the size of the lesions. In one case of a gigantic congenital cervicothoracic lesion, sclerotherapy was performed at 18 months in combination with Sirolimus that started at three months with excellent results. An ILM of the left abdominal wall in a 10-year-old boy subsided after a 12-month treatment with Sirolimus. A large intra-abdominal ILM in a 7-month female infant responds after 1-month treatment.
The FAO-HHML group included two three-year-old females. Treatment was started at 18-24months. Both had a similar response, consisting of softening of the tissue and a functional improvement of the limb. No reduction of lesion size was noted, and both patients are now treated with selective PIK3CA inhibitor.
CLAPO syndrome patient was treated due to worsening her hemihypertrophy on her genitalia. No improvement in size was noted.

Conclusions: ILM patients show an excellent response to Sirolimus treatment, while on the other conditions, a slight improvement was noted mainly on the functional level.

Keywords:
PIK3CA, PROS, ILM, Sirolimus

EPNS21-2076 Oral or poster
Genetics

Expanding phenotype in a new mutation of CUL4B gene - Cabezas type variant?

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Objective: CUL4B-variants are associated with intellectual disability, X-linked, syndromic 15(Cabezas type); males may present intellectual disability, seizures, gait abnormalities, behavioral problems, macrocephaly, short stature, obesity, hypogonadotrophic hypogonadism, and variable dysmorphic features. We present a male patient with a new variant of the CUL4B gene with a milder phenotype compared to those already described.

Methods: A careful personal and family history followed by clinical, neurological, psychological and genetic evaluation of the patient were performed. Brain MRI 1.5T was performed. Genetic testing included array Comparative Genomic Hybridization(aCGH) followed by Whole Exome Sequencing targeting all protein coding exons, exon-intron boundaries (±20 bps) and selected non-coding, deep intronic variants, coupled with Deletion/Duplication(CNV) Analysis.

Results: A 8-year-old male patient, from healthy parents and unremarkable history presented with global developmental delay, intellectual disability(IQ=50), underdeveloped speech(2.5 year-old level). Fair hair and skin, large ears with abnormal helix, anteriorly oriented, strabismus (operated), kyphosis, slight toe abnormalities, joint hyperextensibility and ataxia were associated. Obesity, short stature, microcephaly were absent. Brain MRI was negative. aCGH was negative. Whole Exome Sequence analysis identified a hemizygous nonsense variant CUL4B c.1105C>T, p.(Arg369*), a stop codon, loss of function variant. Currently, this variant has not been described in the medical literature.

Conclusions: This variant generates a premature stop-codon in exon 8 predicted to lead to loss of normal protein function(established disease mechanism). Therefore, although not yet described, this should be classified as pathogenic. Comparing to the already published cases, it is unusual that this case shows a milder phenotype, not meeting all the clinical criteria for Cabezas syndrome. Genetic testing of the mother and genetic counseling should be performed.

Keywords:
cul4b, cabezas, speech delay, intellectual disability

EPNS21-232
Genetics

Oral or poster

A Worldwide Study of CTNNB1 Genotype and Phenotype: Preliminary Results

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Objective: CTNNB1 Syndrome is a severe neurodevelopmental disorder caused by disruption of the CTNNB1 gene on chromosome 3p22.1. Our study's aim was to establish the phenotype and genotype-phenotype correlations. Currently, there is no known cure for CTNNB1 Syndrome, however gene therapy is being devised concurrently with this study.

Methods: Patients and/or their caretakers met online with a doctor who guided them through an online survey. We collected their medical and family history, as well as the results of genetic and other diagnostic testing. The parents were guided through several diagnostic tests for autism spectrum disorder, speech and motor development, sleep, visual function, eating and drinking ability, and behavior. With the study still ongoing, we expect to have even more participants by the time of the conference. ClinicalTrials.gov - Identifier: NCT04812119.

Results: We interviewed 32 children with CTNNB1 Syndrome from 12 countries, 18 male and 16 female. The youngest child was 8 months old, while the oldest was 20 years old. The most common type of mutation was a frameshift mutation (18 children). The most commonly affected exons were exons number 7 and 9 (6 children each). We established a typical CTNNB1 facies. Most children showed autistic traits. Sixteen children exhibited speech problems; 16 were unable to speak. Fourteen children exhibited sleep problems, 17 had eating and/or drinking problems. Thirty children were reported to have manual ability problems, while all 34 had problems with their gross motor function - 6 were wheelchair dependent. Central hypotonia was reported in 33 children, while peripheral hypertonia was reported in 27 children. Twenty-six children exhibited hyperekplexia. Auto-aggression was reported in 22 children.

Conclusions: Preliminary results show a typical phenotype in children with CTNNB1 Syndrome as well as correlations between different genotypes and phenotypes. The gene in question shows promise for good response to genetic therapy.

Keywords:
CTNNB1 sydrome, neurodevelopmental disorders, genotype-phenotype correlation

EPNS21-240 Oral or poster
Genetics

Long time polysomnographic sleep and breathing evaluations in patients with a CDKL5 disorder

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Objective: In children with refractory epilepsy in the first three months of life and severe developmental delay, atypical Rett syndrome, due to a mutation in the CDKL5 gene, should be considered. As with Rett syndrome, children with CDKL5 syndrome have sleep (90%) and breathing disorders (50%). The sleep disorders have a major impact on caregivers and are difficult to treat. Since the developmental delay improves over time, we assumed the sleep disturbances might diminish as well. In neurodevelopmental disorders such as Rett syndrome and Angelman, sleep and breathing disorders are chronic and persist in adulthood. The prognosis of these aspects in CDKL5 children is unknown.

Methods: We retrospective evaluated changes of sleep and respiratory disorders in a small cohort of Dutch CDKL5 patients, over 5-10 years, using video-EEG and/or polysomnography (3 x 24h), and a parental questionnaire, the Sleep Disturbance Scale for Children (SDSC).

Results: Sleep disturbances persisted during the study period. In all patients long sleep latency, frequent arousals (not related to apneas/seizures) and low sleep efficiency were present and stayed as such. This was in accordance with the SDSC, which showed disorders of initiating and maintaining sleep (DIMS), and in some sleep wake transition disorders (SWTD). In the girls total sleep time (TST) was short (except one) and persisted. Time in bed (TIB) was normal for the age group 2-8 years, but prolonged in the old age. Low/ absent REM sleep continued to be present.
During sleep no apneas occurred. During wake, central apneas due to episodic hyperventilation, diminished over time and remained clinically present in one adult CDKL5 girl.

Conclusions: Sleep disturbances were present and persisted, similar to classic Rett syndrome. They have a major impact on the CDKL5 families. The decreased REM sleep and sporadic breathing disturbances in wake may indicate failure of brainstem respiratory centres.

Keywords:
CDKL5 disorder, sleep disorders, breathing disorders, polysomnography, EEG, long time, prognosis, clinical evaluation

EPNS21-253 Poster only
Genetics

Coffin- Siris syndrome in a girl with neurodevelopmental delay, dysmorphic features and growth hormone deficiency due to p.(Gln467Argfs*64) mutation in the ARID1B gene

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Objective: Coffin-Siris syndrome (CSS) (MIM #135900), is an extremely rare genetic multisystemic disorder characterized by aplasia or hypoplasia of the upper phalanx of the fifth finger, moderate to severe cognitive and/or developmental delay and characteristic facial features (thick lashes, hypertrichosis of the trunk, sparse hair).

Methods: A female child was referred at the age of twenty-one months for neurodevelopmental delay, dysmorphic features and an early onset scoliosis. Brain MRI revealed hypoplasia of the corpus callosum. At the age of five, she had an episode of generalized tonic-clonic seizures and treatment with valproic acid was started a year later. The patient was addressed for short stature evaluation at the age of 9 years 8/12 showing a remarkable growth retardation (height:124,3cm<3thcentile, weight:29,65Kg,25thcentile, growth velocity rate:4.1cm/year(< 2SDS). Hormonal investigations revealed growth hormone deficiency (GHD) in two stimulation tests. Recombinant human growth hormone (rhGH) was started that resulted in a significant improvement of the growth velocity up to 5,4cm/ year (>90-97th centile). The patient is under treatment until now and presents a nice growth response. Surgical correction of her scoliosis at the age of 12, has improved her growth status.

Results: Because of the combination of dysmorphology, epilepsy and intellectual disability, Next Generation Sequencing (NGS) was performed. Nucleotide change c.1392_1402del, p.(Gln467Argfs*64) was identified in ARID1B gene at heterozygotic state associated with the Coffin-Siris Syndrome.

Conclusions: CSS remains a rare cause of developmental delay and despite its phenotypic heterogeneity molecular diagnosis is essential in revealing additional comorbidities, such as growth hormone deficiency, that need to be carefully evaluated and timely treated. Appropriate therapies for this population are needed to optimize growth potentials.

Keywords:
Coffin-Siris syndrome, Growth hormone deficiency

EPNS21-274 Poster only
Genetics

CDKL5 developmental and epileptic encephalopathy: evidence for progressive brain atrophy

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Objective: The clinical phenotype of CDKL5 deficiency disorder (CDD) is has been well defined during time, while neuroimaging has not been systematically analysed.

Methods: We report a brain MRI retrospective study on 82 brain MRIs of a cohort of 43 patients with CDD. Data on structural abnormalities of grey and white matter, delayed myelination, presence of supratentorial and/or cerebellar atrophy were collected. Two paediatric neuroradiologists reviewed the MRI scans while blinded. For a subgroup of five patients, a quantitative MRI analysis was performed and compared with 15 sex and age matched controls.

Results: In 30 out of 37 of patients (81%,) MRI was normal within the first year of life. Twelve patients (52%) performed a second MRI which revealed a supratentorial atrophy (involving both grey and white matter) at the median age of 3.1 years (IQR 2.0-8.7 years), associated with cerebellar atrophy in 8 (median age of 6.2 years, IQR 3.1-11.8 years). The neuroradiological evaluation of all available images (n=35) from 22 patients confirmed the previous finding: 20/22 patients had a normal MRI in the first year of life and seven patients developed a mild supratentorial atrophy with frontal predominance during the second year of life. Cerebellar atrophy was seen in six of 11 patients.
Quantitative analysis detected a volumetric reduction of the whole brain volume, including both the white and cortical grey matter, with a reduction of surface area, mainly over the temporal regions.

Conclusions: Although most of CDD patients had a normal brain MRI in the first year of life, both the macroscopic evaluation and the quantitative analysis detected a brain volume reduction involving the grey and white matter during the disease evolution. These results might be due to the possible role for CDKL5 in spine development and synapse morphogenesis. Further prospective studies on a larger cohort of patients might confirm this data.

Keywords:
CDKL5, Brain atrophy, Epilepsy, Genetic Epilepsy

EPNS21-307 Oral or poster
Genetics

The Effect of Swimming Exercise, Low-Lavel Laser or Combinations on Degeneration, Inflammation, Oxidative Stress, and Utrophin and Irisin Protein in Duchenne Muscular Dystrophy Mice Model

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Objective: The aim of this study was to investigate the effects of low-lavel laser therapy (LLLT) on muscle degeneration, oxidative stress, and utrophin and irisin protein levels, in order to reduce the side effects or increase the benefits of swimming exercises, which have previously shown to be beneficial in the Mdx mouse model.

Methods: In this study, 20 Mdx mice were divided into four groups; sedentary and placebo LLLT (SK), sedentary and LLLT (SL), thirty-minute swimming exercise (Eg), and thirty-minute swimming exercise and LLLT (EgL). After eight weeks of swimming exercise, total oxidant capacity, total antioxidant capacity, utrophin and irisin protein levels were measured by ELISA in muscle tissue. Skeletal, diaphragmatic and cardiac muscle histopathological scores, skeletal and cardiac muscle myocyte diameters were determined under the light microscope.

Results: While irisin protein levels were elevated in group SL compared to SK, it was determined that total oxidant capacity, oxidative stress index, heart muscle histopathological scores decreased and irisin protein levels increased in both exercise groups (Eg and EgL) ($p<0.05$). In addition, in the EgL group, an increase in rotarod and utrophin protein levels, and a reduction in muscle and diaphragm muscle histopathological scores were observed ($p<0.05$).

Conclusions: It was determined that the application of swimming exercise in the Mdx mouse model increased the irisin protein levels in the skeletal muscle, while reducing the oxidative stress levels, degeneration in the heart muscle, inflammation and cardiopathy. When LLLT was applied combined with exercise, muscle strength, skeletal muscle utrophin protein levels increased, and skeletal and diaphragmatic muscle degeneration and inflammation is reduced. In addition, it was determined that only LLLT application increased the level of skeletal muscle irisin protein levels. More studies are needed on irisin, LLLT and exercise mechanisms.

Keywords:
duchenne, mdx mice, exercise, low-lavel laser therapy, irisin

EPNS21-330 Poster only
Genetics

Renal angiomyolipoma in children and adolescents with tuberous sclerosis complex: a single centre experience

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Objective: To present a single centre experience of long term follow up and management of renal angiomyolipoma in children and adolescents with tuberous sclerosis complex (TSC).

Methods: 29 patients (13 male and 16 female) with a confirmed TSC diagnosis are being followed up in our Paediatric Neurology Department. All our patients undergo annual renal imaging to assess for the progression of angiomyolipoma and renal cystic disease.

Results: Median age of the patients was 15 years (IQR range 9 to 18). 31% (9/29) of the participants had renal AML. Mean age at the time of AML diagnosis was 8.2 years. All patients had multiple and bilateral AML. Renal AML was treated with an mTOR inhibitor (everolimus) in 7 patients with a mean treatment duration of 14 months. No adverse events were noted in our cohort. Two patients were treated with everolimus due to renal AML, whereas the rest were undergoing treatment for TSC-associated SEGA and AML. Only 5 patients had a repeat renal imaging following commencing everolimus. The participant with the largest AML (125cm3) experienced a reduction in the size of AML by >50% following 6 months of treatment with everolimus. The patient who was treated with everolimus due to renal AML had no response in 24 months compared to three patients who were treated for a combination of SEGA and AML and exhibited a 50% reduction in the volume of AML from baseline.

Conclusions: Renal involvement is a common feature of TSC. Ongoing surveillance is necessary to monitor progression of known lesions and emergence of new ones. mTOR inhibitors are safe and effective in reducing the volume of renal AML in the adult population. Its efficacy in the treatment of renal AML in paediatric patients is yet to be determined in longitudinal prospective studies.

Keywords:
Tuberous sclerosis complex, renal angiomyolipoma, mTOR inhibitor, everolimus

EPNS21-331
Genetics

Oral or poster

Phenotypic Spectrum of STXBP1 Gene Mutations - A Case Series

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Objective: STXBP1 variants are commonly associated with early-onset epileptic encephalopathy (EOEE). They are also reported in patients with movement disorders with and without epilepsy.
We hereby describe 4 cases of STXBP1 mutations with three different phenotypic presentations.

Methods: Case Series

Results: Patient 1: A male infant with no significant perinatal history presented at the age of 2 days with mixed types of epileptic seizures. Up until his current age of 4 years, his seizures continued to be refractory to various treatment modalities including anti-epileptic drugs (AEDs), ketogenic diet and vagus nerve stimulator (VNS). He has global development delay (GDD).
Patient 2: This boy presented at the age of 2 months with infantile spasms that were responsive to vigabatrin and valproate. He is now 5 years old and is off AEDs. He has GDD, a dyskinetic movement disorder and intellectual disability (ID).
Patient 3: Aged 2 months; this boy presented with infantile spasms. He became seizure-free with steroids, vigabatrin and levetiracetam. At his current age of 7 years, he is globally delayed, has autistic features, ataxia, and ID.
Patient 4: This girl was first seen aged 11 years. She had ID and ataxia but with no history of seizures. She was also diagnosed with attention deficit hyperactivity disorder.

Conclusions: The clinical presentation of STXBP1 mutations is variable ranging from EOEE to isolated movement disorders. Although STXBP1 gene mutations are detected in severe epilepsy patients, others can have movement disorders as the primary feature without seizures. Ataxia, tremors, ID and neurodevelopmental disorders are also seen.
Response to AED therapy is variable. An estimated 20% of patients require more than one AED and approximately 25% are refractory to therapy.
Almost all patients, with or without epilepsy, have a degree of neurodevelopmental impairment and intellectual disability with language and social skills impairment.

Keywords:
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EPNS21-349
Genetics

Oral or poster

Two distinct phenotypes in patients with RHEB-related mTOR-pathy - whether the localization of variants in Switch domains of RHEB protein matters?

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Objective: Three published cases of RHEB-related disorders are associated with missense variants located in regions encoding Switch I/II domains in RHEB protein (Reijnders 2017). We present the fourth case of a 8-year-old boy of Polish origin carrying de novo heterozygous missense variant c.100T>C (p.Ser40Pro) in the RHEB gene in comparison to the previously published phenotypes grouped according to their association with Switch I or II domain of RHEB protein.

Methods: The presented patient was qualified for the WES analysis under the program of cerebral palsy re-diagnosis in the Warmia-Mazury Region (North Poland) in 2019-2020. WES analysis was performed using Illumina platform and verified by Sanger sequencing. Analysis of variant segregation in family confirmed de novo status of RHEB variant identified in proband. Classic syndromes
associated with clinical signs observed in patient and caused by chromosomal rearrangements were excluded. Patient's phenotype was compared to the published cases (Reijnders 2017), taking into account the functional division into cases caused by changes located in the Switch I (group 1) or Switch II domain (group 2) of RHEB protein.

Results: The presented patient, together with two published patients, was placed in the group 1 and the third published patient in the group 2. Phenotype observed in the group 1 was more complex and severe with exclusive occurrence of dynamic muscles tone evolution from generalized hypotonia to spastic tetraparesis, neuromuscular scoliosis, hip dislocation, gastro-oesophageal reflux, episodes of hyperventilation and heart arrhythmias. Seizures occurred in patients in both groups with diffuse EEG epileptic abnormalities (including hypsarrhythmia) and some drug resistance in group 1.

Conclusions: RHEB-related disorders could be considered a new mTOR-pathy in which the localization of the variant in a specific Switch domain in the RHEB protein determines the severity of clinical presentation and the scope of therapeutic management.

Keywords:
RHEB gene, Switch domains, mTOR pathway

EPNS21-350
Genetics

Oral or poster

Extrapyramidal presentation of KCNH5-related epileptic encephalopathy - further delineation of phenotypic spectrum of disease.

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Objective: The KCNH5 gene encodes a voltage-gated potassium channel. Its pathogenic variants have been associated with isolated epileptic encephalopathy in only one published case (Veeramah 2013). We present a second case of a 5-year-old boy of Polish origin carrying de novo heterozygous missense variant c.1394G> A (p.Gly465Glu) in the KCNH5 gene in order to extend the phenotypic spectrum of KCNH5-related disorders.

Methods: The presented patient was identified in a group of 22 patients with pyramidal-extrapyramidal form of cerebral palsy and concomitant epilepsy, qualified for the WES analysis under the program of cerebral palsy re-diagnosis in the Warmia-Mazury Region (North Poland) in 2019-2020. WES analysis was performed using Illumina platform and verified by Sanger sequencing. Analysis of variant segregation in family confirmed de novo status of KCNH5 variant identified in proband. Classic syndromes associated with clinical signs observed in patient and caused by chromosomal rearrangements, changes of methylation patterns or triplet expansion were excluded.

Results: Our patient was born at term via uneventful vaginal delivery, from pregnancy complicated by mother's well-controlled hypothyroidism. Since birth he presented with generalized hypotonia with brisk deep tendon reflexes in lower limbs, mild ptosis, weak crying and sucking, poor eye contact, severe limbs tremor and myoclonus. First hemiclonic seizures with epileptic forms in interictal EEG were appeared at 5 months of age, with good response to valproic acid monotherapy. Brain MR scan was normal. The delay in psychomotor development was observed with unassisted sitting at 24 mo, walking on widened basis with truncal ataxia at 36 mo, speech expression at the level of single syllables at 24 mo.

Conclusions: The presented case indicates the need to consider KCNH5-related epileptic encephalopathy as a more complex disease with possible extrapyramidal presentation. Full phenotypic synopsis of disease needs identification of subsequent patients.

Keywords:
KCNH5 gene, epileptic encephalopathy, extrapyramidal symptoms

EPNS21-366
Genetics

Poster only

Clinical spectrum associated with biallelic INPP4A variants in neuropediatric patients

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Objective: Pontocerebellar hypoplasia (PCH) is a clinically and genetically heterogeneous group of inherited neurodevelopmental disorders, characterized by prenatal onset of pontine and cerebellar hypoplasia, microcephaly, developmental delay, and other neurological features. We aimed to find the genetic cause in a patient with a severe neurodevelopmental disorder and brain MRI findings fitting PCH.

Methods: Clinical history of the 27-month-old patient was recorded from the patient's file and brain MRI scans were retrospectively analyzed. Whole-exome sequencing was performed in the patient followed by segregation of the causative variant in the patient's parents and healthy twin sister. Genetic and clinical findings in the patient and previously reported patients harboring pathogenic variants in INPP4A were compared.

Results: The 27-month-old patient presented with severe developmental delay, progressive microcephaly, PCH, truncal hypotonia, limb spasticity, and myoclonic epilepsy. We detected the homozygous INPP4A variant c.2840del [p.(Gly947Glufs*12)] in the patient that segregated with the disease in the family. INPP4A encodes inositol polyphosphate 4-phosphatase that is highly expressed in the central nervous system and important for glutamate excitotoxicity and cell proliferation. Our patient and eight reported patients from three families carry homozygous nonsense or frameshift variants affecting different INPP4A transcript variants and show a phenotype ranging from mild intellectual disability to a severe developmental disorder with microcephaly, seizures, and PCH.

Conclusions: Biallelic INPP4A pathogenic variants underlie a spectrum of neurodevelopmental phenotypes, ranging from developmental delay to severe PCH. The location of the pathogenic variant and the affected INPP4A transcript(s) likely determine the clinical outcome.

Keywords:
INPP4A gene; pontocerebellar hypoplasia; microcephaly; developmental delay; myoclonic epilepsy; exome sequencing;

EPNS21-373 Oral or poster
Genetics

Trio-exome-sequencing reveals genetic mutations associated with childhood epileptic encephalopathies

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Objective: To describe a cohort of patients with epileptic encephalopathies (EE), without known etiology, and to investigate the associated genetic mutations by trio-exome-sequencing (proband and parents).

Methods: Multicenter study in which patients aged 0 to 14 years with a diagnosis of EE of unknown etiology were selected, carrying out a retrospective descriptive study by review of medical records (phase 1), telephone contact for inclusion (phase 2), anamnesis, physical examination and extraction of blood sample from the patient and their parents (phase 3) to perform a trio-exome-sequencing test (phase 4).

Results: 72 patients from two tertiary hospitals with a diagnosis of EE without known cause were selected. 33 of them were excluded in the first 3 phases of the study for diverse causes -mainly absence of consent or difficulty obtaining blood samples from proband or parents.
Of the 39 patients who completed the first 3 phases of the study: 15 patients presented with epileptic spasms, 6 patients with Dravet spectrum EE (prior negative for SCN1A), 5 cases of myoclonic epilepsies, one patient with Ohtahara syndrome, and 12 difficult-to-classify cases. All of them presented with cognitive impairment of varying degrees, being more severe the more refractory was the epilepsy.
In phase 4, 23 trios were excluded due to poor quality of the DNA sample. Of the 16 trios analyzed, 11 pathogenic mutations were identified related to the clinical features: SCN2A, SCN9A, KCNQ2 (in 2 patients), LRPPRC, CACNA1A, GNAO1, PUM1, ARID2 and RAD21.

Conclusions: The yield of exomic sequencing for the identification of mutations in EE was 68.75% in our sample (11/16), revealing different mutations associated with EE as SCN2A, SCN9A, KCNQ2, LRPPRC, CACNA1A, GNAO1, among others. Cryptogenic EEs represent a heterogeneous electro-clinical group, being up to 30% difficult to classify in our sample (12 cases). Trio-exome-sequencing could only be performed in 22.2% (16/72) of the cohort because of various difficulties in the process.

Keywords:
exome, epileptic encephalopathy, exome sequencing, child epilepsy, genetics

EPNS21-419 Oral or poster
Genetics

Ribosomal polymerase disorders: an important cause of developmental and epileptic encephalopathy with myoclonic seizures

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Objective: To describe the epilepsy phenotype associated with ribosomal polymerase disorders, POLR1A and POLR3B encode protein subunits of ribosomal polymerase I and III respectively. Pathogenic variants in both genes are associated with a spectrum of neurodevelopmental disorders. The epilepsy phenotype has not been previously described in detail.

Methods: We gathered details of genetic findings and epilepsy phenotypes for two patients with POLR1A-associated neurodevelopmental disorder (NDD) and five with POLR3B-associated NDD. All diagnoses were made by Whole Exome/Genome Sequencing. Clinicians were asked to complete proformas detailing seizure types, EEG characteristics, MRI findings, developmental progress, and any comorbidities.

Results: In both cases of POLR1A, and all five cases of POLR3B, variants were de novo, missense, absent from healthy population databases and predicted pathogenic. Both patients with POLR1A variants initially presented infantile spasms and subsequently developed resistant myoclonic and drop seizures. They had severe developmental impairment, microcephaly and mild hypertelorism. EEG demonstrated hypsarrhythmia at presentation and remained markedly abnormal with multifocal high amplitude spike/slow wave activity, despite trials of multiple treatments. All POLR3B patients presented with myoclonic seizures at 6-18 months. Two developed drop seizures. Electroencephalograms demonstrated generalised epileptiform abnormalities, with spike-wave and polyspike-wave discharges. Seizures were intractable in all cases. Additional features were: global developmental delay (5/5); ataxia (3/5); microcephaly (2/5); and subtle dysmorphic features (3/5).

Conclusions: The epilepsy observed in POLR1A and POLR3B disorders is consistent with a Developmental and Epileptic Encephalopathy (DEE). Initial seizures are likely to be spasms in POLR1A and myoclonic in POLR3B. Epileptologists should be aware of these phenotypes and these genes should be included in epilepsy gene panels.

Keywords:
Epilepsy, Genetic, Ribosome, Polymerase, Spasms, Hypsarrhythmia

EPNS21-423 Poster only
Genetics

THG1L disease - a new evolving cause of epileptic encephalopathy

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Objective: The phenotype of THG1L (tRNA-Histidine Guanylyltransferase 1-Like) related disorder in patients homozygous to a missense mutation, c.164T>C p.(Val55Ala), was previously reported to include cerebellar and pyramidal signs, mild to moderate cognitive impairment and cerebellar atrophy. We report a more severe phenotype in two siblings due to a novel variant in the gene.

Methods: Quatro whole genome sequencing was carried out, followed by segregation analysis of the family.

Results: Two siblings of mixed Jewish descent presented in the first weeks of life with profound developmental delay, progressive microcephaly and epilepsy. Epileptic syndrome was consistent with epilepsy of infancy with migrating focal seizures, followed by modified hypsarrhythmia with clinical focal seizures and epileptic encephalopathy thereafter. Repeated brain MRI showed progressive cerebellar atrophy, mild cerebral atrophy and a thin corpus callosum. Genetic testing revealed that they were compound heterozygous to the known p.(Val55Ala) mutation and a novel c.392C>T, p.(Ser131Phe) variant in the THG1L gene. Both mutations fully segregated with the disease in the family. The THG1L gene encodes a mitochondrial guanyltransferase that adds GMP to the 5' end of tRNA(His). In addition, it forms complexes with mitofusins to enhance mitochondrial fusion. Mitochondrial t-RNA(His) activity was normal in patients' fibroblasts.

Conclusions: Based on the normal Mitochondrial t-RNA(His) activity and previous studies of the role of mitofusins and mitochondrial fusion in development and maintenance of the cerebellum, we hypothesize that the pathomechanism of THG1L dysfunction in our patients is related to disturbed mitochondrial fusion. The discovery of a new THG1L mutation leading to such devastating phenotype is of paramount importance for clinicians and genetic counseling.

Keywords:
THG1L, epileptic encephalopathy

EPNS21-425 Oral or poster
Genetics

Tremor and frontal epilepsy secondary to gain-of-function mutation in SCN8A: a case report

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Objective: SCN8A mutations are quite rare and produce different clinical manifestations. The most frequent is epilepsy. Other clinical manifestations are developmental delay and movement disorders.

Methods: We introduce the case of a 14 year-old patient who has tremor and seizures. Genetic test indicated a gain-of-function mutation in SCN8A.

Results: A Chinese adolescent, who was adopted at the age of 16 months (familiar history unknown) came to our center for the first time at the age of 12 due to tremor and nocturnal generalized tonic-clonic seizures beginning at 3 years of age. It is predominantly resting and postural tremor, also kinetic. It mainly affects the eyelids, tongue and upper limbs. It is associated with trunk ataxia and mild intellectual disability.

Blood tests (metabolic and thyroid test), cerebrospinal fluid (neurotransmitters), urine test (including SAICAR and biotinidase tests), cranial magnetic resonance imaging (MRI) and electroencephalogram were performed in other centers without pathological findings. In our center, we repeated a blood test and an extended neurophysiological study (electroencephalogram, somatosensorial evoked potentials, electromyogram) which were normal. The first genetic test, array-CGH 60 k, was normal. Lastly, epileptic encephalopathies gene panel revealed a gain-of-function mutation in SCN8A.

She was admitted to the intensive care unit twice because of increased disabling tremor. Currently, 3 years later, she is clinically stable from both epilepsy and tremor. Her treatment consists on carbamazepine, zonisamide, and propranolol.

Conclusions: The clinical variability produced by SCN8A mutations should make us include it in the differential diagnosis of epileptic-dyskinetic disorders. Thus, genetic testing is essential for an accurate diagnosis.

Keywords:
SCN8A, Epilepsy, Tremor, Epileptic-dyskinetic disorders

EPNS21-439 Oral or poster
Genetics

A Rare Cause of Recurrent Febrile Encephalopathy in a Child: The Expanding Spectrum of ATP1 A3 Mutations. A Case Report.

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Objective: ATP1A3 mutations have been recognized in infants and children presenting with a diverse group of neurological phenotypes, including Rapid-onset Dystonia Parkinsonism (RDP), Alternating Hemiplegia of Childhood (AHC), and Cerebellar ataxia, Areflexia, Pes cavus, Optic atrophy, and Sensorineural hearing loss (CAPOS). A new phenotype of fever-induced paroxysmal muscle weakness and encephalopathy (FIPWE) in patients with ATP1A3 mutations at c.2267G>A has been described most recently in few cases. Here we report the clinical presentation and management of an additional case with an ATP1A3 mutation at c.2267G>A p residue 756H. The patient is presenting with fever-induced paroxysmal muscle weakness and encephalopathy.

Methods: Case Report

Results: This 18-month-old boy was born term with normal birth history. He had normal development until 4 months of age, when he presented with two episodes of generalized seizures, central hypotonia, areflexia and developmental regression during a febrile illness. He made a gradual recovery as the febrile illness resolved. He had similar episodes during most of his subsequent febrile illnesses. The sequencing of his whole exome, identified a de novo mutation at ATP1A3 c.2267G>A pathogenic variant (p.Arg756His). During a subsequent febrile illness at the age of 14 months, aggressive management of his fever was done. Currently, at the age of 2 years, the patient is maintaining a steady developmental progress. But he is still delayed.

Conclusions: ATP1A3 mutations related disorder like FIPWE have been increasingly implicated in fever related encephalopathies. Recurrent encephalopathy with unclear etiology warrants targeted sequence of ATP1A3 gene. High index of suspicion and awareness of such unique clinical condition is required to make this rare diagnosis. In such cases, aggressive management of febrile illness may be helpful in alleviating the symptoms.

Keywords:
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EPNS21-452 Oral or poster
Genetics

1Q21.1 MICRODELETION SYNDROME HETEROGENEOUS PHENOTYPE, INCOMPLETE PENETRANCE AND/OR VARIABLE EXPRESSION. A CASE SERIES

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Objective: The 1q21.1 region is flanked by repetitive sequences, favoring rearrangements, such as microdeletion(1q21.1d) and microduplication(1q21.1D), characterized by dysmorphic facial features, intellectual disability and microcephaly(1q21.1d) or macrocephaly(1q21.1D). Moreover, for 1q21.1d it has been described an increased risk for schizophrenia versus an autism spectrum disorder(ASD) in 1q21.1DUP. The molecular causes of the neurological phenotypes are unknown, some genes have been proposed. A repetitive region of domains DUF1220 related to neural progenitor proliferation and brain size evolution between species is harbored in 1q21.1. We evaluate the phenotype of 1q21.1DEL patients. To find a phenotype-genotype correlation we propose to unravel the molecular basis using innovative sequencing tools.

Methods: Individuals with 1q21.1d, studied by microarray chromosome analysis(CMA), are included. Data about general and cranial growth, psychomotor development, cognitive-behavioral phenotype, and neuroimaging(MRI) is recruited. CMAs were reviewed and, for some patients, long read sequencing has been performed.

Results: Among the 16 individuals, the 12 index-cases show facial dysmorphic traits, microcephaly (<-3DS), feeding disturbances, psychomotor retardation and other neurodevelopmental disorders(ASD). MRI shows a preserved architecture. Most are inherited conditions, with learning difficulties or minor neuropsychiatric disorders in carrier parents. CMA showed 10 type I, 3 type II and 3 atypical deletions.

Conclusions: 1q21.1d is a recurrent cause of non-syndromic psychomotor retardation. Routinely CMA studies in neurodevelopmental disorders have increased the diagnosis. Cognitive alterations seem mild but global. Carrier parents show milder phenotype but positive symptoms. We suggest using rather highly variable expressivity than incomplete penetrance for 1q21.1d. Innovative techniques that allow to determine the number of repetitions of DUF1220 will allow to clarify its relationship with the phenotype.

Keywords:
1q21.1; intellectual disability; neurodevelopmental disorders

EPNS21-466 Oral or poster
Genetics

Dominant and recessive paroxysmal movement disorders associated with loss-of-function variants in JPH3

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Objective: JPH3 encodes junctophilin-3, a brain-specific cell adhesion molecule. Triplet repeat expansions in JPH3 have been reported in Huntington-like disease 2, an adult-onset neurodegenerative disorder. Loss-of-function variants in mice are associated with motor function deficits in both the homozygous and heterozygous state - milder in the latter. Recently, a single individual with homozygous loss-of-function of JPH3 and a paroxysmal movement disorder has been reported. We describe an additional individual with a homozygous variant and also a less severely affected family with autosomal dominant inheritance of a heterozygous variant in three generations.

Methods: Whole-genome sequencing was performed in a cohort of well-phenotyped patients with paroxysmal movement disorders believed to be genetic in origin. Known genetic were excluded by use of a broad "megapanel" of relevant genes, followed by gene-agnostic analysis. In silico prediction tools helped predict impact of candidate variants.

Results: A homozygous frameshift variant in JPH3 (c.1310del; p.Arg437Leufs*34) was identified in a teenage girl from a consanguineous family who had a clinical diagnosis of alternating hemiplegia of childhood. In a family with three generations affected to varying degrees by a paroxysmal movement disorder and mild neurodevelopmental impairment, a heterozygous nonsense variant (c.1014C>G; p.Tyr338*) in JPH3 was found.

Conclusions: Our findings corroborate the single case report of an autosomal recessive phenotype associated with loss of function of junctophilin-3. The discovery of a similar, milder, autosomal dominant phenotype bears out pre-existing findings in an animal model. JPH3 variants should be considered in children with paroxysmal movement disorders of unknown origin. These cases illustrate the possibility of different types of dysfunction of the same gene - that is, toxic protein accumulation resulting from triplet repeat expansion versus loss of function - causing different diseases.

Keywords:
JPH3; junctophilin-3; paroxysmal dyskinesia; alternating hemiplegia of childhood

EPNS21-505 Poster only
Genetics

Clinical, cytogenetic and molecular findings in patient with Pallister-Killian syndrome

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Objective: Pallister Killian syndrome (PKS) is a rare genetic disorder caused by tissue-limited mosaicism tetrasomy of the short arm of chromosome 12, which usually presents as an extra isochromosome 12p. Clinical features include distinct facial anomalies, other systemic abnormalities with variable developmental delay and intellectual impairment. Some PKS patients also have seizures.

Methods: We present clinical and genetic findings of PKS patient diagnosed and followed up in our hospitals compared with previously published cases.The diagnosis was confirmed by karyotype analysis of fibroblast cultures and In situ hybridization with chromosome 12-specific DNA, which revealed the i(12p).

Results: Our patient is a girl born in April 2021 from a regular controlled pregnancy of young unrelated parents. After birth, craniofacial dysmorphia, hypotonia, mild conductive hearing loss and nystagmus were observed. Initiated neuropaediatric and genetic processing led to the diagnosis of Pallister Killian sy. During the follow-up, she developed progressive myoclonic epilepsy that required polytherapy adjustment.

Conclusions: The wide phenotypic spectrum of PKS in conjunction with the mosaic distribution of the i(12p) makes PKS often an underdiagnosed disorder. Since additional chromosome is usually absent in karyotypes obtained from cultured peripheral lymphocytes, clinical recognition with buccal mucosal cell analysis ,skin biopsy and fibroblast chromosome examination is of most importance.

Keywords:
child, Pallister Killian sy, epilepsy

EPNS21-543
Genetics

Oral or poster

SIGMA-PMM2: A plasma microRNAs signature for cerebellar atrophy due to PMM2-CDG

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Objective: PMM2-CDG is the most frequent congenital disorder of glycosylation. It causes cerebellar atrophy with a cerebellar syndrome, leading to long-term disability. Patients may also show extraneurological symptoms.

Despite clinical symptoms present early cerebellar atrophy is unstoppable and irreversible. Different strategies of treatment are under development and the early diagnosis of this disease could have the potential to improve the quality of life of the patients. miRNAs play a key role in the neurological transcriptional networks and are more stable in plasma than other RNAs, which makes them particularly interesting for the early detection of cerebellar diseases. The goal of this study is to find a non-invasive plasma-based miRNA signature to differentiate PMM2-CDG patients from other patients with cerebellar atrophy (CA) and healthy controls (HC).

Methods: Plasma was isolated from 21 PMM2-CDG patients, 12 CA and 46 HC and divided in two cohorts for the training and validation. The concentration of different miRNAs in plasma was assessed using next generation sequencing. Using machine-learning methods, we built three different signatures with a combination of miRNAs.

Results: After evaluating the sensitivity and specificity of the different signatures, we observed that one of the models showed promising precision detecting PMM2-CDG in the training cohort and the validation cohort.

Conclusions: This is the first study proposing the detection of plasma miRNAs as a non-invasive method for the early detection of PMM2-CDG and offering a non-invasive diagnosis for children with presymptomatic neurological disease. If miRNA are useful biomarkers not only in the diagnosis but also in the monitoring and prognosis of PMM2-CDG deserves further studies. In addition, the increase or decrease or certain circulating miRNA may suggest underlying mechanisms that are unknown in this rare condition.

Keywords:
PMM2-CDG, disorder of glycosylation, biomarkers, presymptomatic neurological disease

EPNS21-548 Oral or poster
Genetics

Do the classical Cornelia de Lange Syndrome criteria suit for BRD4 gene deletions?

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Objective: Cornelia de Lange Syndrome (CdLS) is an heterogeneous neurodevelopmental disorder characterized by a distinctive facial phenotype and frequent somatic comorbidities. Mutations in BRD4 have been recently described leading to a non-classical phenotype or a mild atypical form, and microdeletions including BRD4 have been scarcely reported. We describe a patient with the shortest deletion reported to date, and review the literature in order to explore the usability of the international criteria and artificial intelligence dysmorphologic platforms for the clinical diagnosis of BRD4 deletions.

Methods: Dysmorphological, neurological and psychometric evaluation were performed. Chromosomal microarray (CMA) study was performed in genomic DNA. All reported patients in the literature with overlapping deletions were reviewed and, when possible, consensus criteria for CdL and Face2Gene evaluation were applied

Results: Our 3-year-old patient had a global developmental delay, IQ calculation based in non-verbal tests resulted below the mean. Dysmorphic features, despite mild, fulfilled the classical CdL criteria. A de novo interstitial deletion was identified in the band 19p13.12 of ~ 234Kb that includes the BRD4 gene. The review of the 12 reported patients showed that despite all presented 3 major criteria and almost all present a clinical score compatible with classical CdL, Face2Gene only suggested CdL with a high score in three of them. Congenital diaphragmatic hernia as major criteria was never reported and hand oligodactyly/adactyly, was described in two cases.

Conclusions: Dysmorphologically, our patient phenotype was mild and CdL was not suspected until having the CMA result, as it seems for the other reported patients. In fact, most of them were not recognized by Face2Gene. Interestingly, in our patient some similarities were found among her behavioral phenotype and the classic CdL. We present the smallest mutation reported so far, supporting the relevance of BRD4 gene in the overlapping deletions.

Keywords:
Cornelia de Lange Syndrome, mutation, Face2Gene evaluation, Chromosomal microarray study

EPNS21-560 Oral or poster
Genetics

Gonadal mosaicism in two siblings with Coffin Siris syndrome associated with ARID1B mutation: Second report in the literature.

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Objective: Coffin-siris syndrome (CSS) is an autosomal dominant disorder with distinctive features and genetic heterogeneity. It caused by a heterozygous mutation, most commonly a de novo pathogenic variant in the BRG1(BRM)-associated factors complex genes. The majority of documented pathogenic mutations to date have arisen in a sporadic, de novo manner except only one report of inheritance of a germline mosaic ARID1B mutation.

Methods: In this study, we evaluated 5 and 8 years old male siblings from a non-consanguineous Turkish family. They presented with growth retardation , mental retardation and dysmorphic features including sparse hair; macrocephaly, frontal bossing, small low-set ears, long face, small mouth, long philtrum, depressed nasal root, high palate, hypoplastic nails and short palpebral fissure. Older patient only could speak single word , the other sibling could not speak . On laboratory investigation , hemogram, biochemical and thyroid function tests , ammonium, lactate, urine and plasma amino acids, urine organic acids, echocardiography, chromosome analysis , were normal. MRI showed partial corpus callosum agenesis.

Results: Whole exome sequencing (WES) analysis identified a novel heterozygous ARID1B mutation (c.5737C>T; p.Q1913*) in the both of two affected children. Further family testing by targeted Sanger sequencing showed that this mutation was absent in peripheral blood samples obtained from both parents and unaffected siblings. Therefore, we propose that the most likely explanation for this situation is that one of the parents is a gonadal mosaic for this mutation.

Conclusions: To the best of our knowledge, this is the second report of a gonadal mosaicism inheritance of an ARID1B variant leading to CSS recurrence.

Keywords:
ARID1B; Coffin-Siris Syndrome; gonadal mosaicism; whole-exome sequencing

EPNS21-57
Genetics

Oral or poster

Genetic causes of cerebral palsy

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Objective: Cerebral palsy (CP) is the most frequent cause of motor impairment in children. Recently, genetic factors have gained importance in the aetiology of CP, and yet research regarding this subject is still scarce. We performed diagnostic genetic investigations in a large cohort of patients with CP, aiming to gain a better insight into the genetic causes of CP.

Methods: Our cohort existed of 650 patients, of whom 273 were excluded because they met at least one exclusion criterion, being (1) prematurity < 30 weeks postgestational age, (2) history of perinatal asphyxia, (3) unavailability of parental DNA for trio analysis and (4) parental refusal. Genetic investigations were performed in the 377 remaining patients comprising of (1) Single Nucleotide Polymorphism array to exclude chromosomal anomalies and (2) a whole exome sequencing based gene panel consisting of 200 genes associated with CP (-mimics). When no genetic diagnosis could be found, a genome-wide analysis on the exome data was performed.

Results: Results were available for 358 patients. Genetic analyses are still ongoing in 19 patients. A genetic diagnosis could be established in 153/358 patients, resulting in a diagnostic yield of 42.7%. However, it must be noted that the diagnostic yield was biased because of the inclusion of CP patients with an evident syndromic phenotype. Excluding this group of patients decreased the genetic diagnostic yield to 10.6% (38/358 patients). Recurrent variants were observed in KIF1A (7/153 patients, ~4.6%), COL4A1 (4/153 patients, ~2.6%) and RNASEH2B (2/153 patients, ~1.3%). Several other genes were mutated in a single patient e.g. AP4S1, GNAO1, KIDINS220, TUBA1A etc.

Conclusions: Genetic investigations in our CP cohort, excluding patients with a syndromic phenotype, demonstrated a diagnostic yield of 10.6%. These findings illustrate the significant contribution of genetic mutations in CP, highlighting the importance of genetic testing in this particular population.

Keywords:
cerebral palsy, whole exome sequencing

EPNS21-633 Oral or poster
Genetics

Novel lysosomal positioning defects due to bi-allelic mutations in BORCS7 causes a neurodegenerative disease presenting as hereditary-spastic paraplegia.

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Objective: Two multimeric endosomal complexes are known as the regulator for the lysosomal function and mobility, BLOC-1 and BORC. One of the core subunits of the BORC complex is BORCS7, a 106 amino acid protein with a C-terminal coiled coil domain. A mutation in BORCS7 (p.Q87*) in mice displayed impaired motor performance in several tests at 5 weeks of age, accompanied by morphologic abnormalities within the spinal cord with similarities to human Hereditary Spastic Paraplegia (Snouweart, 2018). No mutations in human BORCS7 have been reported until now.

Methods: We recruited an 8-year old boy presenting seizures and spasticity, severe global delay with the inability to speak. Muscle biopsy resembled a severe neurogenic atrophy. To unravel the underlying etiology, we performed Exome Sequencing. Data analysis and variant filtering was performed with Varbank 2 according to an autosomal recessive inheritance.

Results: Genomic analysis revealed the first homozygous stop mutation in BORCS7 (c.247C>T, p.Q83*) in this patient, confirmed by co-segregation analysis of the family. Thus is the first report in human of BORCS7 mutations and defines a novel neurodegenerative disease.

Conclusions: We are experimentally working hypothesis is that the found nonsense mutation in BORCS7 will disrupt the binding to the other subunits of the BORC complex. Thus, a missing core component of the complex, as BORCS7 was reported, will not be able to function as a regulator of the lysosome positioning in neurons.

Keywords:
Lysosome, Cellular transport, Neurodegeneration

EPNS21-640 Poster only
Genetics

Whole genome sequencing for the diagnosis of severe epileptic encephalopathies - a case of FOXP1 and NAA15 genes pathology in girls with Lennox-Gastaut syndrome

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Objective: A significant number of genetic diseases have been diagnosed in recent years, but research is ongoing. Diagnosis of complex epileptic epilepsies, including Lennox-Gastaut syndrome, is important in seeking treatment. Because the significant frequency and different types of seizures impair the quality of life of patients.

Methods: ILAE Classification of the epilepsies (2017)
Long-term video EEG monitoring and during night sleep
Magnetic resonance imaging 1.5 and 3 T
Next-generation sequencing (NGS) - epileptic panel
Whole genome sequencing (WGS)
Examination by a neurologist, medical psychologist and speech therapist

Results: A 6-year-old girl went to the examination with the main complaints about the presence of different types of seizures: drop attacks, tonic, atypical absences and cognitive impairment with speech underdevelopment. She was ill from 6 months, when epileptic spasms first appeared and gradually other attacks appeared. Valproate, levetiracetam, topiromax, lamotrigine, clonazepam, rufinamide,Vigabatrin, hormones are not effective in therapy. During EEG recording was dominated by a slow spike-and-wave pattern (1.5-to 2.5-Hz) medium and high amplitude. Metabolic examination revealed no pathology. On MRI 3 T - minor hypoxic changes. Given the negative result during next-generation sequencing (panel on epilepsy 183 genes), the patient passed a complete genomic sequencing. FOXP1 gene (associated with mental retardation with/without signs of autism, autosomal dominant type of inheritance, US) and NAA15 gene (associated with mental retardation (autosomal dominant type of inheritance, US) were detected.

Conclusions: Diagnostic search for severe epileptic encephalopathies is important to determine the cause and develop treatment of patients. Case studies in different countries are important for collecting patient data. This patient is referred for PET CT and undergoes pre-surgical training.

Keywords:
epileptic encephalopathies, long-term video EEG monitoring, whole genome sequencing

EPNS21-659 Oral or poster
Genetics

Expanding phenotype of TOR1A mutation - a case presentation

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Objective: Biallelic mutations in TOR1A gene have been recently described as a cause of severe arthrogryposis multiplex congenita and developmental delay. Additional features include microcephaly, dysmorphic face, and failure to thrive. In this abstract we report a new case with distinctive phenotype suggestive of TOR1A mutation associated with multiple hernias.

Methods: Our patient is the first child from healthy, unrelated parents. The pregnancy was complicated by polyhydramnios, fetal akinesia, and arthrogryposis. On delivery, baby required resuscitation due to bradycardia, cyanosis, and respiratory depression. and mechanical ventilation has been started. On examination, severe arthrogryposis has been noticed, with reduced spontaneous movements, increased muscle tone, dysmorphic facial features, umbilical and inguinal hernias. Her development was severely delayed. She experienced repeating spasms of abdominal wall muscles which together with regurgitation and vomiting resulted in weight loss. Upper endoscopy showed sliding hiatal hernia. At the age of two months, the patient received open fundoplication and gastrostomy using upper midline incision. Bilateral Spigelian hernias reoccurred twice, at the level of the umbilicus and bellow, at 6 and 11 months respectively, requiring surgery both times. She died at three years. Sepsis was the immediate cause of death.

Results: All metabolic work up was normal. Neuroimaging showed brain atrophy. Molecular genetic analysis for microdeletion syndromes was negative. Whole exome sequencing performed at 4 months of age revealed a homozygous nonsense variant in Exon 5 of TOR1A (c.862C > T, p.Arg288). This finding enabled genetic counselling of the affected family that led to prenatal testing in order to give birth a healthy child.

Conclusions: We are adding our data to the current knowledge base for phenotype spectrum associated with TOR1A mutation and highlight the importance of early diagnosis with the possibility of prenatal testing in every further pregnancy.

Keywords:
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EPNS21-660 Poster only
Genetics

PRECISE BREAKPOINT DETERMINATION ON THE CDKL5 GENE BY OPTICAL GENOME MAPPING IN A GIRL WITH DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY

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Objective: Pathogenic variants in the CDKL5 gene are responsible for an X-linked dominant severe neurologic disorder characterized by intractable seizures and severe global and intellectual developmental delay. We present a case of a 9-year-old girl with early-onset epileptic encephalopathy since the age of 3 months, having the following karyotype analysis: 46,X,t(X;2)(p22;p25.1)dn. Chromosomal microarray analysis (CMA) and whole exome sequencing did not reveal any other pathogenic alterations.

Methods: Optical genome mapping (OGM) was used to determine the precise breakpoints on chromosomes 2 and X. Ultra-long molecules of gDNA were isolated from peripheral blood according to the manufacturer specific extraction protocol, followed by tagging and optical image analysis processing in the Saphyr instrument of Bionano Genomics. A de novo genome assembly was used to identify SV (>500bp), while depth of coverage was used to find CNV (>500kbp). The whole experimental procedure took place in the Bionano Genomics hub laboratory in France.

Results: OGM specified the precise breakpoints of the reciprocal translocation 46,X,t(X;2)(p22.13;p25.2) and revealed a breakpoint on Xp22.13 that interrupts the CDKL5 gene, which is likely to disrupt proper gene function.

Conclusions: OGM provided important insight into the girl's phenotype revealing CDKL5 disruption due to a balanced de novo reciprocal translocation [46,X,t(X;2)(p22.13;p25.2)]. OGM has been considered as a next generation cytogenomics tool unraveling complex genetics events where karyotype and CMA have limitations. Our case, further supports that those newer technologies can identify precise genomic variants, permitting genotype-phenotype correlations which further increase the percentage of the diagnostic yield.

Keywords:
CDKL5, Optical Genome Mapping, chromosomal translocation, break points

EPNS21-674 Oral or poster
Genetics

CLINICAL SPECTRUM OF CACNA1A MUTATIONS

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Objective: To describe the clinical spectrum of CACNA1A mutations in affected children.

Methods: We made a retrospective and descriptive study of patients with mutation in CACNA1A gene. We performed a systematical review of medical records and we collected clinical data, genetic studies, treatment received and magnetic resonance.

Results: We found 3 patients with heterozygous mutation in CACNA1A. Patient 1 is a 14 year old boy who had been followed-up since he was 10 years old because of episodic ataxia type 2, mild intellectual disability and attention deficit hyperactivity disorder. He responded partially to acetazolamide treatment. His father had the same mutation and was also affected by episodic ataxia type 2.
Patient 2 is a 10 month old girl who was admitted to hospital at 9 months old for having pluricotidian tonic upward gaze episodes that started at 4 months old. She had delayed neurodevelopment, with impossibility for cephalic support and sitting at 12 months old. Electroencephalogram and polysomnography were normal. The paroxystic episodes were mildly reduced after receiving trihexyphenidyl.
Patient 3 is a 5 year old boy who was admitted to hospital for right hemiplegia, fever and decrease state of consciousness. He had had previous episodes of left hemiplegia after minor trauma that resolved in 20-30 minutes, so he had been misdiagnosed of focal epilepsy. Magnetic resonance revealed edema of the left cerebral hemisphere and electroencephalogram showed slowed brain bioelectric activity. He recovered in three days. Subsequently he had cognitive impairment and motor clumsiness in addition to several episodes of hemiplegia after having fever or minor trauma.

Conclusions: Mutations in CACNA1A involve a wide clinical spectrum, from intermittent episodes to neurodevelopmental-delayed disorders. Better categorization of CACNA1A mutations will lead to better knowledge of clinical manifestations and will allow a more accurate forecast to be established.

Keywords:
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EPNS21-700 Oral or poster
Genetics

SPAST variant: beyond the known phenotype and inheritance pattern

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Objective: We report 4 individuals with a severe neurological disease who harbor biallelic variants in SPAST

Methods: Mutational analysis was performed by genomic DNA studies (gene panel or WES trio) in patients and parents samples. Human spastin hexamer model in complex with substrate peptide (6pen) has been used as template. PyMol2 software has been used for visualization. Spastin has been localized and quantified in patient's derived fibroblasts and compared to healthy controls as well as those with classical phenotype (dominant inheritance). Functional studies were performed by confocal microscopy: (1) immunofluorescence labeling spastin, tubulin and nucleus, (2) in in vivo studies to see plasma membrane and quantified mitochondria morphology by ImageJ software (NIH, Bethesda, MD, USA)

Results: Four patients showed with spastic tetraparesis and intellectual disability. Brain MRI was abnormal in 2/4 individuals, showing cerebellar atrophy and white matter hyperintensity, respectively. A motor neuronoaxonal impairment was identified in peripheral nerve studies. Progressive swallowing difficulties and motor regression was observed in the older patients. In silico analysis predicted high impact on the protein structure. Confocal microscopy studies revealed fluorescence intensity differences of SPAST in the sample of individuals with biallelic variant compared to healthy control. Aberrant plasma membrane prolongations and indirect signs of mitochondrial apoptosis were found in the cells of patients

Conclusions: This is the first report of individuals with biallelic variants in SPAST. The phenotype observed is relatively homogeneous and much more severe than those reported in individuals with monoallelic variants in SPAST. Our findings widen the etiological possibilities under the so call Cerebral-palsy-mimics. Functional experimental studies were essential to unravel and better understand the biological mechanisms of this expansion of phenotype.

Keywords:
SPAST, Hereditary spastic paraplegias, inheritance pattern.

EPNS21-168 Oral or poster
Inflammatory Disease of the CNS

Acquired Demyelinating Diseases: A Single Center Experience

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Objective: Acquired demyelinating diseases are inflammatory disorders of the central nervous system. They can occur either as a monophasic disease or a multiphasic one with relapses. In this retrospective study, we aimed to determine the clinical, laboratory and imaging findings, treatment and follow-up of the patients with acquired demyelinating disease.

Methods: Outpatients and inpatients who applied to Ankara City Hospital Pediatric Neurology Department between January 2020 and September 2021 were included.

Results: A total of 45 children (31 girls and 14 boys; female/male: 2,2/1) with a mean age of 14 ±1.1 years were included. The most common complaints of the patients were paresthesia, vision problems and weakness, respectively. At least one relapse was seen in 11 patients. The diagnoses were multiple sclerosis (29 patients), optic neuritis (5 patients), MOG antibody-associated demyelinating disease (4 patients), radiological isolated syndrome (3 patients), transverse myelitis (3 patients) and acute disseminated encephalomyelitis (1 patient). IgG index was measured in 36 patients and was high in 80.5% (n=29) of them. Oligoclonal Band positivity was found in 57.1% (20/35) of the patients. The mean follow-up period of the patients was 1.5 years (1 month to 8 years). During the follow-up period only patients diagnosed with transverse myelitis developed neurological sequelae.

Conclusions: Demyelinating diseases are increasingly common in childhood and require rapid diagnosis and treatment. Long-term follow-up of these patients is important in terms of clarifying the diagnosis and planning the treatment.

Keywords:
demyelinating disease, child, multiple sclerosis

EPNS21-173 Oral or poster
Inflammatory Disease of the CNS

Anti-glycine receptor antibody mediated progressive encephalomyelitis with rigidity and myoclonus with concurrent brucella infection

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Objective: Progressive encephalomyelitis with rigidity and myoclonus (PERM) is a rare immune mediated variant of Stiff Person Syndrome. We describe a case of anti-glycine receptor mediated PERM with evidence of concurrent brucella infection.

Methods: A 11 year old boy presented with acute history of painful back spasms for a week triggered by touch or change in posture. He progressively became encephalopathic, with frequent myoclonus which were spontaneous and induced by tactile stimulus. MRI spine showed longitudinally extensive myelitis involving the central grey matter. MRI brain showed hyperintensities in the claustrum bilaterally with diffusion restriction. Cerebrospinal fluid showed lymphocytic pleocytosis, cultures and viral studies were negative. Video-EEG showed diffuse encephalopathy with no electrical change during the reported myoclonus. The child did not respond to initial treatment with intravenous methylprednisolone and immunoglobulin. He responded to 5 cycles of double volume plasma exchange. He was treated with rituximab and maintained on oral mycofenolate mofetil. Brucella titres were rising in his serum, but were negative in the CSF, hence he was given prolonged antibiotics for neuro-brucellosis.

Results: He made a steady recovery and was discharged 2 months after initial presentation with on-going neurorehabilitation. Serum samples were positive for anti-glycine receptor antibodies, serum and CSF were negative for other autoimmune encephalitis antibodies. Follow up after a year showed normal cognition, but worsening scoliosis. He has not relapsed, however has mild hyperekplexia in the morning and remains on symptomatic treatment with baclofen and clonazepam.

Conclusions: PERM is rare in children and symptoms are due to disruption of the inhibitory glycinergic pathways in the brainstem. Prompt recognition and aggressive immunomodulation is key to successful management.

Keywords:
Progressive encephalomyelitis with rigidity and myoclonus (PERM), anti-glycine receptor antibodies, brucella

EPNS21-178 Oral or poster
Inflammatory Disease of the CNS

Prolonged dystonic episodes with reversible basal ganglia changes in a child with N-methyl-D-aspartate receptor (NMDAR) encephalitis

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Objective: NMDAR encephalitis has a recognisable phenotype with encephalopathy, hyperkinetic limb movements and seizures in children. MRI brain can be unremarkable or variable, with changes in the hippocampus being commonly reported. We report a 4 year old with NMDAR encephalitis who presented with prolonged dystonic episodes with symmetrical hyperintensities in the basal ganglia, who responded favourably to aggressive immunomodulation.

Methods: A 4 year old girl presented with progressive mutism over 7 days. She subsequently started having episodes of paroxysmal sudden stiffening and dystonic posturing of her limbs with uprolling of her eyes, lasting for 10-30 minutes, which were initially managed as epileptic seizures with no improvement. These were associated with tachycardia, sweating, lingual tremor and blepharospasm. EEG showed slow background and no clear electrical correlate to the episodes.

Results: MRI brain scan showed symmetrical hyperintensities in the basal ganglia with diffusion restriction. CSF showed no pleocytosis and was positive for NMDAR antibodies. Serum anti-dopamine receptor antibodies were negative. Ultrasound abdomen showed no tumours.

The child received intravenous methylprednisolone and immunoglobulins with no significant improvement. She was tried on rituximab, but developed serum sickness. She responded to two pulses of cyclophosphamide and was maintained on mycofenolate. She made a steady improvement and was discharged after 3 months. Follow up evaluation 6 months later showed normal neurological examination with perseverant speech, which improved with rehabilitation. Follow up MRI showed complete resolution of the previous MRI changes.

Conclusions: This report signifies a pure basal ganglia encephalitis like presentation of NMDAR encephalitis with prolonged dystonic episodes, which is rare in children. Profuse basal ganglia changes which are reversible are not common either. This case adds to the expanding phenotype, both clinical and radiological, of NMDAR encephalitis.

Keywords:
NMDAR encephalitis, basal ganglia, MRI, dystonia

EPNS21-200 Oral or poster
Inflammatory Disease of the CNS

Pathogenic variant in Toll-like receptor 3 (TLR3) in twin girls with a viral encephalitis - don't forget to screen for primary immunodeficiencies (PID)

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Objective: We describe MCDA twins with encephalitis and a pathogenic variant in TLR3.

Methods: = obj

Results: At the age of 8 months girl 1 was admitted to the ICU with encephalitis, hepatitis and pleural effusion, after a brief febrile illness. MRI of the brain showed extensive bilateral diffusion restricted lesions, including in the thalami, the cerebellum and the corpus callosum. CMV PCRs were positive, ganciclovir and Megalotect were started. She recovered within 3 weeks and was discharged on IV immunoglobulins (IVIG) and ganciclovir.
At the age of 12 months her sister, girl 2, was admitted to the ICU after a brief febrile illness because of encephalitis with tonic clonic seizures, hepatitis, myocarditis and pericarditis. The respiratory panel was positive for parecho/rhino/entero- and coronavirus NL63. CMV PCRs were negative. The brain MRI showed abnormalities similar to those of her sister. She recovered with supportive therapy and received levetiracetam and IVIG.
At the age of 14 months, girl 1 developed RSV bronchiolitis and acute hepatitis. A concentric left ventricular hypertrophy was detected on ultrasound, but she recovered. Girl 2 also developed an RSV infection and presented with cardiogenic and hypovolemic shock with massive capillary leak. She received antibiotics, steroids, IVIG, inotropes, vasopressors and was placed on ECMO, but unfortunately died 24 hours after admission.
A clinical exome sequencing identified a pathogenic heterozygous variant in TLR3 in both sisters (c.1660C>T, P554S). TLR3 deficiency causes susceptibility to herpes simplex encephalitis and severe influenza pneumonia due to a defective type I interferon (IFN) response. As girl 1 had no IFN stimulated gene induction, a low dose of INF-beta was administered at the age of 15 months. A few hours after administration she developed cardiogenic shock and died despite maximal resuscitation therapy including ECMO. RSV was still positive on the bronchoalveolar lavage.

Conclusions: Always consider PID in case of a severe encephalitis.

Keywords:
Encephalitis, TLR3, TLR3 deficiency, primary immunodeficiencies

EPNS21-2004 Oral or poster
Inflammatory Disease of the CNS

Effect of natalizumab treatment on the rate of No Evidence of Disease Activity in young adults with multiple sclerosis in relation to pubertal stages

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Objective: Approximately 40% of young-onset multiple sclerosis (MS) patients experience breakthrough disease, which carries a high risk for long-term disability, and requires using therapies beyond traditional first-line agents.
Despite the increasing use of newer disease-modifying treatments (DMTs) in this population, data are not available to guide the need for escalating DMTs and there is a scarcity of data on the effects of natalizumab in children and young adults with active disease.

Methods: A retrospective, two-year follow-up study comprised patients
treated at 5 regional medical centers (MCs) representing the main hospitals treating MS in Israel.
We performed analysis of the rate of No Evidence of Disease Activity (NEDA), tolerability, and safety of natalizumab in a multi-center cohort of 36 children and young adults with highly active MS. All patients had active disease and initiated treatment with natalizumab.

Results: To examine a possible effect of age on the outcome of treatment, outcomes were also analyzed by pre-pubertal (n = 13 children aged 9-13 years) and pubertal subgroups (n = 23 young adolescents aged 14-20 years).Mean patient age (±SE) at treatment initiation was 15.2 ± 0.5 years. The NEDA-3 status of the pre-pubertal group was 92% in the first and second year and in the pubertal group - 96% in the first year and 92% in the second year.
Natalizumab reduced the number and volume of brain lesions in both pre-pubertal and pubertal groups.
Treatment was well-tolerated, only 8 patients (22.2%) had adverse events during the 2-year study period.

Conclusions: Natalizumab appears to be highly effective and well tolerated
in young patients with MS, with a high proportion of patients
achieving NEDA-3 after two years of treatment.
our findings, support the efficacy of natalizumab in suppressing disease progression in the entire neuroaxis and its possible use as a first-choice treatment in young patients
with MS

Keywords:
young-onset multiple sclerosis, Pre-pubertal, Pubertal, Natalizumab

EPNS21-224 Oral or poster
Inflammatory Disease of the CNS

Childhood Primary Angiitis of the Central Nervous System

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Objective: By reporting two cases of childhood primary angiitis of the central nervous system (cPACNS), we like to raise awareness and suggest further treatment options in therapy-resistant disease.

Methods: Retrospective case description.

Results: Case 1
A 3-year-old boy presented with acute right-sided hemiplegia. Stroke work-up showed active CNS vasculitis in branches of the left arteria cerebri media on magnetic resonance angiography (MRA). He was treated with methylprednisolone 20mg/kg/day (5 days) and aspirin. Secondary causes of vasculitis and stroke mimics were excluded. Corticoids were tapered over 3 months. Because of progressive large vessel vasculitis on follow-up MRA, we started monthly infusion of cyclophosphamide (CFM) for 6 months, followed by 18 months of maintenance therapy with mycophenolaat mofetil (MMF). Despite treatment, MRA showed progressive lesions without clinical symptoms. Rituximab and monthly immunoglobulins (IVIG) were added to the treatment with MMF. Regression of active vasculitis was obtained after 9 months. Rituximab will be continued over a period of 2 year.
Case 2
Another 3-year-old boy presented also with acute right-sided hemiplegia. Medical history revealed varicella at the age of 1. High dose corticosteroids and aspirin were started. Steroids were tapered over 6 weeks. New vasculitis lesions were seen at 3 months after initial presentation. High dose corticosteroids was repeated, followed by slow tapering. Three months later he presented with a new acute ischemic stroke. Treatment with monthly CFM was started and is currently ongoing.
Both patients had a good clinical recovery of their stroke.

Conclusions: cPACNS is a rare entity within CNS vasculitis, which requires fast recognition and aggressive treatment to prevent further damage. The recently published treatment guidelines by Beelen et al facilitate more standardised care. Based on our case, we suggest add-on treatment with Rituximab and IVIG to the combination of corticosteroids and MMF in therapy-resistant disease.

Keywords:
CNS vasculitis, cPACNS, stroke, Rituximab, cyclophosphamide

EPNS21-237 Poster only
Inflammatory Disease of the CNS

THREE YEAR OLD BOY WITH MOGab MENINGOENCEPHALOMYELITIS

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Objective: MOGAD is an acquired demyelinating inflammatory disease with presence of MOG antibodies. It includes conditions such as MS, NMOSD, ADEM and a variety of atypical and overlapping syndromes.

Methods: A 3 year old boy presented to our hospital with headache, slightly altered consciousness, altered gait, bladder and bowel dysfunction. The Neurological Examination revealed neck stiffness, increased reflexes in all extremities and clonus in both ankles. Due to the patient's young age, sensory deficits could not be assessed. Parents reported high fever approximately a month before and again 10 days prior, which lasted until 24 hours before the child's hospitalization. During hospitalization the child remained afebrile, but his neurological condition deteriorated, especially cognition and walking difficulty.
At first, blood tests showed elevated WBC that returned to normal on the 3rd day of hospitalization. Extended CSF analysis revealed only WBC: 57/mm3 and positive MOGabs (>1/20).
Brain MRI showed an abnormality at the right globus pallidus and leptomeningeal enhancement. An MRI of the cervical spinal cord was performed, which revealed an augmentation of the spinal cord at A3-A6 level, as well as leptomeningeal enhancement. With confirmation of the diagnosis the patient received i.v treatment with methylprednisolone and his condition started to improve.

Results: Six months later the patient's parents reported no symptoms, but the neurological examination continued to reveal mild pyramidal signs. An MRI scan of the brain and cervical spinal cord were normal. MOGabs though remained positive.

Conclusions: MOGabs are a relatively new biomarker in demyelinating diseases of the CNS. They are present in a wide spectrum of conditions and seem to influence disease prognosis and therapy. The exact spectrum of MOGAD is not yet conclusively established and it seems to differ in adult and pediatric patients.

Keywords:
MOG, MOGabs, NMOSD

EPNS21-238 Poster only
Inflammatory Disease of the CNS

Unusual adverse event of Interferon-b in a 14 year old MS patient

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Objective: Interferon-b is a first-line medication for multiple sclerosis. It is typically administered in newly diagnosed patients and has also been approved for administration in children. Although Interferon-b induced retinopathy is a well-known adverse event in HCV patients, IFNb has rarely been associated with retinopathy. There have been published less than 15 case reports of IFN### induced retinopathy in adult MS patients.

Methods: We present a 15 year old female that was diagnosed with multiple sclerosis at the age of fourteen. She was firstly admitted to our clinic due to diplopia and also mentioned paresthesias and episodes of instability the previous year. A head MRI-scan was performed, as well as blood and CSF analysis that were diagnostic for MS. The patient was administered intravenous methylprednisolone for 5 days and then started treatment with IFN-b 22mcg escalated to 44mcg. Two months later, on a regular ophthalmological examination, the patient presented cotton wool spots in the retina of both eyes, although asymptomatic. An OCT was performed and the diagnosis of IFNb induced retinopathy was made.

Results: Taking into account the clinical and radiological signs as well as the relative bibliography, it was decided to discontinue IFNb and the patient was switched to other treatment.

Conclusions: The IFNb induced retinopathy is a rare adverse event that to our knowledge has never been described in a pediatric patient before. The pathogenesis is unknown and the patients usually present with symptoms. Our patient was asymptomatic and the retinopathy was found incidentally.

Keywords:
Multiple Sclerosis, Interferon b, adverse event, retinopathy

EPNS21-239 Oral or poster
Inflammatory Disease of the CNS

Clinical features, Investigations and Outcomes of Paediatric Limbic Encephalitis: a multicentre study

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Objective: Report the paediatric presentation, clinical course, and outcomes in Autoimmune limbic encephalitis (LE). LE is a rare neuro-inflammatory condition which presents with memory deficits, seizures, and psychiatric disturbances associated with medial temporal lobe imaging changes.

Methods: Six tertiary centers in the UK and Ireland identified children with LE < 18 years old between 2008 and 2021. Clinical, diagnostic, and radiological data were recorded from the medical files. The modified Rankin Scale (mRS) at presentation and follow-up were reported.

Results: Twenty-five children were identified, with a median age at onset of 11 years (IQR 8, 14) and median follow-up of 24 months (IQR 18, 48). All children presented with seizures; of which 15/25 (60%) required intensive care for status epilepticus. Short-term memory deficit (n=20) was the next most frequent complaint. Behavioural change (n=19), additional cognitive difficulties in reasoning or processing speed (n=16), and visual/auditory hallucinations (n=6) were also reported. All cases had typical bilateral mesial temporal changes in all, of which 8/25 (32%) were asymmetrical. Extra-limbic changes with claustrum involvement were reported in 9/25 (38%). Neuronal anti-NMDAR antibodies (n=2), synaptic anti-GAD (n=2) and paraneoplastic antibodies anti-Hu (n=2) were detected in 6 cases. Steroids was administered in 23/25 (92%), intravenous immunoglobulin (IVIg) in 14/25 (56%) and plasma exchange in 7/25 (28%). Rituximab was administered in 15/25 (60%). After a minimum six-month follow-up, 12/25 (48%) had refractory seizures and 15/25 (60%) had memory impairment. Five children (20%) had mRS scores 3 or higher.

Conclusions: LE was associated with significant morbidity and adverse outcomes in this paediatric cohort. Additional extra-limbic radiological findings in the context of clinical features should also be considered within the LE phenotype.

Keywords:
Autoimmune limbic encephalitis, Adolescent, Child, Disease Severity

EPNS21-243 Poster only
Inflammatory Disease of the CNS

Immune-modulatory therapy in pediatric small fiber neuropathy

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Objective: Small fiber neuropathy (SFN) is increasingly suspected in patients with pain of uncertain origin even though most pediatric cases remain undiagnosed. Although up to 50% of SFN cases may be idiopathic, the sparse data available in children point to metabolic, toxic, infectious and autoimmune causes. The latter justifies a trial with immune-modulatory therapy in well-defined patients.

Methods: The data of two adolescents diagnosed with SFN in whom we suspected an underlying autoimmune etiology and who were treated with immune-modulatory therapy were collected retrospectively.

Results: The first patient is a previously healthy 13-years-old female who presented with suddenly started burning pain in hands and feet. Extensive etiological work-out showed as only clue for a possible underlying autoimmune etiology anti-GM2 and anti-GAD65 antibodies. The second patient is a girl known with eczema. She presented at the age of 14 years with burning pain all over the body following a severe eczema flare. In both patients, clinical examination revealed no abnormalities and conventional pain medication did not provide any relief. Diagnosis of SFN was confirmed with skin biopsy through epidermal nerve fiber density assessment. Assuming an underlying autoimmune etiology immune-modulatory therapy was started. The first patient was treated with intravenous immunoglobulins, prednisolone and mycophenolate mofetil. She became pain free within one month and remains pain free after cessation of medication. The second patient was treated with prednisolone and mycophenolate mofetil. Pain score was reduced after one week from 10/10 to 2-3/10 but remains at this level until last follow-up one year later, still under mycophenolate mofetil treatment.

Conclusions: The diagnosis of SFN should be considered in children with an otherwise unexplained pain syndrome. A thorough investigation is required to reveal the underlying disorder. If an autoimmune etiology is suspected immune-modulatory therapy is indicated.

Keywords:
Small fiber neuropathy, pain, autoimmune, immune-modulatory therapy

EPNS21-255 Poster only
Inflammatory Disease of the CNS

Should epileptic seizures as a first presentation be considered part of diagnostic criteria for relapsing remitting multiple sclerosis (MS) in children?

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Objective: Seizures are rarely described as the first presentation of both paediatric and adult-onset MS

Methods: We describe 2 patients from 2 tertiary paediatric neurology centres (Great Ormond Street Hospital,London and Dana-Dwek Children's Hospital, Tel Aviv) <18 years who presented with seizures before a confirmed demyelinating event with radiological evidence of dissemination in time and space.

Results: Patient 1, 12y.o female, with type 1 diabetes mellitus presented in status epilepticus following an unwitnessed generalized tonic-clonic seizure (GTCS).She represented 8 months later following a further GTCS and was started on anti-seizure medication.EEG was unremarkable and neuroimaging showed multiple periventricular white matter lesions.CSF oligoclonal bands were positive and she had negative serum MOG and AQP4 antibodies.She subsequently presented with ataxia, left-sided weakness and paraesthesia with new supratentorial and spinal lesions on repeat neuroimaging.She was admitted for treatment with intravenous methylprednisolone with good clinical response and is awaiting to start ocrelizumab for highly active MS. Patient 2, 14y.o. male, with a history of chronic otitis media complicated by cholesteatoma was found on neuroimaging to have multiple cortical and subcortical T2 lesions.He was asymptomatic with no focal neurological signs.CSF OCBs were positive with negative serum MOG and AQP4 antibodies.Twelve months later, he presented with a focal-onset seizure, lasting ten minutes with acute onset left sided visual loss and confusion, with interictal EEG showing generalised regular spike and wave activity.He did not have any further clinical events and serial MRI showed evidence of new intracranial lesions fulfilling revised 2017 McDonald criteria for MS.

Conclusions: This case series highlights that epileptic seizures can be the first presentation in paediatric MS patients prior to typical demyelination symptoms manifesting, and there is potential for including them in the future diagnostic criteria.

Keywords:
Multiple Sclerosis, RRMS, Seizures

EPNS21-342 Oral or poster
Inflammatory Disease of the CNS

Blood count parameter analysis in pediatric MOG-antibody-associated disorders

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Objective: MOG-antibody-associated disorders (MOGAD) are acquired demyelinating syndromes of the central nervous system clinically presenting with acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), transverse myelitis (TM) or neuromyelitis optica spectrum disorders (NMOSD)-like phenotypes. Blood count parameters might reflect disease activity and be useful to help distinguishing MOGAD, MS and NMOSD patients.

Methods: We evaluated differences regarding complete blood count, neutrophil-to-lymphocyte (NLR), platelet-to-lymphocyte (PLR) and monocyte-to-lymphocyte ratio (MLR) between the above-mentioned groups at different points in time (clinical attack, acute treatment, remission).

Results: Blood parameters of 243 pediatric patients with a total of 713 points in time (pt) were included in our study. 67 patients had MOGAD (202 pt), 11 aquaporin-4 antibody (AQP4-ab)-positive NMOSD (76 pt), 58 MS (219 pt), 45 seronegative ADEM, ON or TM (100 pt), 23 other inflammatory neurological disorders (OIND, 63 pt) and 39 were healthy controls (HC, 53 pt).
We found elevated thrombocytes, leukocytes and neutrophils in children with monophasic MOGAD during acute attack. During acute treatment, leukocytes, neutrophils and NLR increased in all groups except for MOGAD, and MLR in AQP4-ab-positive NMOSD and seronegative ADEM/ON/TM patients. At the end of the acute treatment, all these parameters decreased in all groups, but between acute attack and remission only in the MOGAD group. Only MOGAD patients had higher thrombocytes during acute attack than in remission. During remission, NLR, PLR and MLR in AQP4-ab-positive NMOSD patients were significantly elevated compared to MOGAD patients.

Conclusions: Our analysis showed differences in thrombocyte, leukocyte and neutrophil count as well in NLR, PLR und MLR between evaluated groups and timepoints. Therefore, blood count parameters could support clinicians' interpretations of disease activity and possibly discriminate between different disease entities.

Keywords:
MOGAD, ADEM, MOG-antibodies, blood count parameters, serum biomarkers

EPNS21-364 Poster only
Inflammatory Disease of the CNS

Dancing eyes: evolution and treatment - experience from a tertiary care university hospital

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Objective: Opsoclonus-myoclonus syndrome (OMS) is a rare disease characterised by symptoms like opsoclonus, myoclonus, ataxia, and encephalopathy. Aetiology is either paraneoplastic or idiopathic (autoimmune). The treatment aims to reduce the number of lymphocytes, cytokines, and the production of autoantibodies. Main therapeutic options are dexamethasone, immunoglobulins, cyclophosphamide and rituximab.
We will present the experience of our clinic regarding the evolution and treatment of OMS.

Methods: We conducted a retrospective observational study targeting 17 patients admitted to our clinic during 2011-2021. Patients were observed over 6 to 24 months. We recorded demographic, clinical, imaging and laboratory data. The patients were divided into 2 groups depending on the presence/absence of neuroblastoma. We used the Mitchell-Pike scale to evaluate the patients. We analyzed the relationship with SARS-COV2 infection. Statistical analyses were performed using SPSS 28.0.

Results: Six patients were lost from the record: 5 of them due to lack of compliance, 1 of them died. For 4 patients the symptoms subsided, and 7 patients still have active disease. No correlation between the onset symptoms severity and the presence/absence of neuroblastoma has been observed. For those that had paraneoplastic aetiology, the excision of the tumor does not ensure remission of the disease; further treatment is required. Of those who were diagnosed during the SARS-COV2 pandemic, 4 patients were confirmed positive: 1 before the onset of OMS symptoms, and 3 of them after: symptomatology relapse during the infectious episode for the latter ones.

Conclusions: The evolution and treatment of patients with OMS are long-lasting, regardless of the aetiology of the disease, in most cases requiring the administration of a combined treatment: immunosuppressants and immunomodulatory agents. Taking into account the fact that our analysed group is small, we need additional studies for a proper evaluation of the treatment response.

Keywords:
opsoclonus-myoclonus syndrome, dexamethasone, cyclophosphamide, rituximab, neuroblastoma

EPNS21-379 Oral or poster
Inflammatory Disease of the CNS

Baricitinib treatment in Aicardi-Goutières Syndrome types 6 and 7

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Objective: Aicardi-Goutières syndrome (AGS) is a monogenic interferonopathy. JAK1/2 inhibitors block type I interferon signaling. We present two patients treated with Baricitinib from our center.

Methods: Clinical data was collected from medical reports.

Results: Patient 1
15-month-old girl admitted in our clinic with progressive neurodevelopmental delay. No relevant medical or family history. At 6 months of age, parents noticed increasing difficulty in sitting assisted and poor movements to reach objects. On examination, she had axial hypotonia and lower limbs dystonia. There were no multisystemic abnormalities. Genetic analysis identified de novo heterozygous IFIH1 mutation, disclosing the diagnosis of AGS type 7. Baricitinib was started, under laboratory monitoring. No medical complications are reported. Currently at five months of treatment, lower limb dystonia is less severe and fine motor skills of the hands are considerably better.
Patient 2
18-months-old boy admitted in our unit for psychomotor regression. No relevant medical or family history. At 12 months of age, he started to lose motor skills, such as crawling and sitting unassisted and presented periods of irritability. On examination, spastic and dystonic tetraplegia was observed. Genetic analysis identified de novo heterozygous ADAR1 mutation, disclosing the diagnosis of AGS type 6. Prednisolone 10 mg/kg/day was started, with clinical improvement. Corticosteroids were gradually discontinued and switched to Baricitinib. No medical complications are reported. Currently at seven months of treatment, periods of irritability have ameliorated and he has better movement coordination.

Conclusions: Baricitinib may reduce the symptoms of AGS by blocking interferon activation, as suggested by phase I and ongoing phase II trials. We have observed improvement of motor key milestones in both patients, highlighting the potential impact of early treatment in mitigating the disease progression.

Keywords:
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EPNS21-409 Oral or poster
Inflammatory Disease of the CNS

A Protocol for Evaluation and Treatment of Children with Acute Autistic/Psychotic Regression

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Objective: We wish to describe 16 children with autistic or psychotic regression, suspected as part of autoimmune encephalitis, and to suggest a protocol for evaluation, treatment, and follow-up.

Methods: This is a retrospective study describing children with suspected autoimmune encephalitis due to abrupt neuropsychiatric symptoms.
Differentiating between an autistic regression and behavioral and communicative regression as part of autoimmune encephalitis is very challenging. We will present the clinical history, supportive diagnostic testing, including plasma and cerebrospinal fluid investigations, MRI, PET/SPECT, EEG, and genetic testing results, as well as treatment protocols used in our clinic, and the clinical impact of the medications.

Results: Preliminary results- twelve children received IVIG and steroids. Six of them had an improvement, with two children showing a remarkable recovery. One child did not benefit from this treatment, but was later diagnosed with SHANK3 mutation. Another child was diagnosed with a mass in the right caudate, and had a significant but temporary improvement.
Four children received rituximab, but in non of them a significant improvement was noticed. Four children received tocilizumab, with a positive effect in one of them.

Conclusions: Early diagnosis is extremely important in children with acute autistic or psychotic regression because treatment with immunomodulatory therapy may improve prognosis in cases of autoimmune encephalitis. Refining the protocol for evaluation, treatment, and follow-up based on clinical experience is highly needed. By sharing cases from our clinic we wish to expand our knowledge with hope to better diagnose and treat autoimmune encephalitis.

Keywords:
regression, autoimmune encephalitis

EPNS21-41 Poster only
Inflammatory Disease of the CNS

A Pediatric Case of Myelin Oligodendrocyte Glycoprotein Antibody-positive Acute Disseminated Encephalomyelitis

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Objective: Anti-myelin oligodendrocyte glycoprotein antibodies (MOG-ab) are associated with acute disseminated encephalomyelitis, neuromyelitis optica spectrum disorder, optic neuritis, and myelitis in children.

Methods: A four-year-old female patient with influenza B infection was admitted with severe headache and fever.

Results: Cranial magnetic resonance imaging showed subcortical T2/FLAIR hyperintensities in bilateral occipital areas, left postcentral gyrus and right precentral gyrus. MOG-ab and Immunoglobulin G index were found positive, while the oligoclonal band was negative. Steroid treatment was given with the diagnosis of MOG antibody-positive acute disseminated encephalomyelitis. In the follow-up, her complaints improved rapidly, the lesions on magnetic resonance imaging regressed to a great extend. MOG ab measured 6 months later was negative.

Conclusions: Considering that pediatric patients with positive MOG antibody will have a recurrent disease course, an individualized treatment regimen should be planned according to the severity and frequency of the attacks.

Keywords:
myelin oligodendrocyte glycoprotein antibodies, acute disseminated encephalomyelitis

EPNS21-414 Poster only
Inflammatory Disease of the CNS

Glycine receptor antibodies in pediatric patients with facial nerve palsy

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Objective: Peripheral facial nerve palsy (FNP) is a common disorder and most often remains without detectable cause despite appropriate investigation. This idiopathic form is almost exclusively associated with a restitutio ad integrum within a few weeks due to speech therapy and, in case, oral prednisolone therapy. Appropriately, an inflammatory genesis is obvious.
Cranial nerves are also affected in other inflammatory disorders, e.g. multiple sclerosis or progressive encephalomyelitis with rigidity and myoclonus (PERM), a variant of the stiff person spectrum disorders, which are associated, among others, with antibodies against the glycine receptor (GlyR-abs).

Methods: To evaluate a possible pathogenic importance of GlyR- and other antineuronal antibodies in patients with peripheral FNP, we evaluated serum and CSF samples with tissue- (TBA) and live cell-based assays (CBA) for antineuronal and GlyR-abs.

Results: The included 49 patients had a median age of 11 (range 2-17) years, 26 were girls, 23 boys. 44/49 had an idiopathic FNP, 5/49 neuroborreliosis. In the TBA, 2/123 samples (62 serum, 61 CSF) showed a positive staining pattern, which was not corresponding to the staining pattern of GlyR-abs. A further sample showed a positive astrocyte staining, therefore we did a live CBA for GFAP-abs, which was negative.
With the live CBA, one sample of a 17-year-old male patient with idiopathic FNP was very weak positive with a titer of 1:40, which is considered without clinical relevance.

Conclusions: We could not detect relevant titers of GlyR-abs in pediatric patients with peripheral FNP. Further investigations regarding the etiology of idiopathic FNP are necessary.

Keywords:
facial nerve palsy, glycine receptor antibodies, antibody-mediated, cell-based assay

EPNS21-430 Oral or poster
Inflammatory Disease of the CNS

Prospective study of a series of pediatric patients with multiple sclerosis treated with fingolimod

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Objective: Multiple Sclerosis (MS) occurs in less than 1:100,000 children per year with an average age of onset of 12 years. MS typically follows a relapsing remitting course, with a recurrence rate twice to three times higher than in adults, thus resulting in earlier disability and mainly concerning the cognitive functions. Our purpose is to describe the clinical, laboratory and MRI characteristics of pediatric MS cases under monotherapy with fingolimod.

Methods: A cohort of 6 patients (M/F: 4/2) systematically monitored and treated with fingolimod with a treatment duration up to 4 years is described thoroughly.
Data were retrieved from the medical records of a tertiary hospital in the last four years, from the date fingolimod was officially licensed in Greece for the treatment of pediatric MS. Documentation of clinical, laboratory and neuroimaging findings, as well as course and follow-up of individual cases is reported.

Results: Patients included: 1) a 17-year-old male with seven episodes of optic neuritis and no relapse for 3 years after treatment initiation, 2) a 16-year-old boy with a relapse under interferon, who is asymptomatic 15 months after starting fingolimod, 3) a 15-year-old female with tumor like MS and clinical and radiological improvement, 4) a 12-year-old girl with dissemination of demyelinating lesions in space and time and improvement after 15 months of treatment, 5) an 18-year-old and a 13-year-old patient with neuroimaging deterioration 6 months after starting treatment.

Conclusions: The efficacy and safety of fingolimod is emphasized as a first or second line treatment option in pediatric MS in daily clinical practice.

Keywords:
Multiple sclerosis, fingolimod, cohort, series,Pediatric patients, First-choice therapy

EPNS21-46 Oral or poster
Inflammatory Disease of the CNS

Subacute Sclerosing Panencephalitis (SSPE) outbreak in Tunisia

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Objective: Identify the characteristics of Subacute Sclerosing Panencephalitis (SSPE) in a pediatric Tunisian cohort.

Methods: Retrospective study held in the Department of Pediatric Neurology over one year [2020-2021]. All children diagnosed with SSPE according to the Dyken's modified criteria were included.

Results: Five patients were included. Measles infection was contracted at a mean age of 5.8 months [5-7 months] before reaching the age of vaccination. The mean age of onset was 2.28 years [1.1-2.9 years]. First clinical manifestations were walking instability and negative myoclonus in all patients, associated to irritability in 3 cases. During clinical course, all patients developed psychomotor regression. Neurological examination at a mean age of 2.5 years showed: Epileptic seizures (3 cases), ataxia (2 cases), dystonia (2 cases), parkinsonism (2 cases), and dysautonomia (2 cases). Brain MRI was normal in 1 case, and showed demyelinating lesions in 4 cases, associated with lesions of the cerebellum pedunculi and the pons sparing the corticospinal tract in 3 cases. Electroencephalogram showed periodic activity in 4 cases. Cerebrospinal fluid analysis revealed the presence of oligoclonal bands and a positive IgG serology for measles in all cases. All patients underwent immunoglobulin cures (1 to 6 monthly cures) and 2 received Isoprinosine. All patients were bedridden within 1 to 2 months of evolution.

Conclusions: In this cohort, patients contracted measles during an outbreak in 2019 before reaching the age of vaccination, thus developing SSPE at an early age. This finding is in accordance with literature as it is reported that the younger measles is contracted, the earlier SPEE is developed, with a fulminant course. Demyelination on MRI sparing the corticospinal tract could be suggestive of diagnosis. Therapeutic strategies are limited and our patients did not show improvement under treatment. Vaccination strategies should be enhanced to prevent this fatal complication.

Keywords:
Subacute sclerosing panencephalitis;

EPNS21-556 Poster only
Inflammatory Disease of the CNS

Diagnosis and treatment of multiple sclerosis in adolescents with confirmation of positive oligoclonal bands in the cerebrospinal fluid

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Objective: Multiple sclerosis (MS) is an inflammatory, autoimmune, demyelinating disease of the central nervous system, which leads to neurological deficits throughout life. Pediatric-onset multiple sclerosis (POMS), early-onset MS, or juvenile MS often occurs as a progressive-recurrent. It is important to make a correct diagnosis in time with the beginning of pathogenetic therapy.

Methods: Diagnostics:
McDonald Criteria 2017.
Neurological examination and anamnesis.
Immunogram (subpopulations of T- and B-lymphocytes, Ig G, Ig A, Ig M), circulating immune complexes.
Antibodies to neuroantigens.
Lumbar puncture with the study of oligoclonal bands.
Virological examination, vitamin D.
Examination of the eye fundus (optical coherence tomography).
Magnetic resonance imaging tests.
Electroencephalography, electroneuromyography.

Results: We diagnosed multiple sclerosis in children over 14 years of age using the McDonald ?riteria 2017, which included the determination of oligoclonal bands in the cerebrospinal fluid. Some patients were admitted with primary-progressive form, some with exacerbation or remission for differential diagnosis. According to MRI, scattering in space and time was diagnosed. We often diagnosed immunogram abnormalities and immunodeficiency, increased antibodies to neuroantigens, vitamin D deficiency, DNA to EBV. All had positive oligoclonal bands in the cerebrospinal fluid. Patients have the opportunity in our hospital to receive free pulse therapy with methylprednisolone and courses of intravenous immunoglobulin. Plasmaphoresis was performed in 1 patient with a primary progressive course, and she also received pulse therapy with methylprednisolone and glatiramer acetate.

Conclusions: Patients were diagnosed according to the latest criteria, and against the background of therapy, we received a reduction in neurological deficits in adolescents. Due to the multidisciplinary nature of the hospital, we perform plasmaphoresis if necessary and rehabilitation.

Keywords:
Pediatric multiple sclerosis, Oligoclonal bands in children,

EPNS21-606 Poster only
Inflammatory Disease of the CNS

Tolosa-Hunt syndrome in pediatric age: a complex differential diagnosis

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Objective: Tolosa-Hunt syndrome (THS) is a rare syndrome caused by idiopathic granulomatous inflammation of the cavernous sinus, characterized by orbital pain associated with ipsilateral cranial nerves' paralysis. While considered a benign condition, frequent relapses require prolonged immune-suppressive therapy.

Objective: to highlight how THS differential diagnosis is complex but mandatory

Methods: Case report description

Results: S., a 10-year-old boy, with an history of left orbital pain associated with diplopia, eyelid ptosis and exophthalmos recently received a THS diagnosis. Brain MRI documented a discrete amount of pathological, presumably inflammatory, tissue in the anterior portion of left cavernous sinus; cerebrospinal fluid analysis (cytology, culture, viral molecular analysis) was negative and a prompt symptom resolution after initiating steroid therapy (1,5mg/Kg/day, with tapering in 1 month) was reported. Ten days after steroid suspension S. presented a severe symptom and sign relapse. An extensive differential diagnosis was performed. Infectivological (IGRA-TB test, syphilis and lyme serology) and rheumatological (Antinuclear, anti-DNA, anti-Sm, antineutrophil cytoplasmic antibodies) analysis were negative. Normal dermatological and cardiological evaluations and angiotensin converting enzyme dosage excluded sarcoidosis; negative total-body MRI and lymph node ultrasound ruled out neoplasms. Steroid therapy was restarted at an increased dosage (2mg/Kg/day) with a slow tapering in 5 months with stable remission.

Conclusions: Tolosa-Hunt syndrome is a diagnosis of exclusion. A scrupulous diagnostic work-up and a close clinical and radiological follow-up are essential to confirm THS diagnosis and to rule out other potential serious etiologies (oncological, vascular, infectivological, rheumatological causes). Moreover, the lack of pediatric international guidelines makes therapeutic approach uncertain, particularly in cases of rapid relapse.

Keywords:
Tolosa Hunt Syndrome, inflammatory disease, ophthalmoplegia

EPNS21-623 Oral or poster
Inflammatory Disease of the CNS

Myelin oligodendrocyte glycoprotein (MOG) antibody associated encephalitis presenting at a young age with seizures and movement disorder

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Objective: To describe the case of a 1 year old boy with MOG-antibody associated encephalitis

Methods: Case report and literature review

Results: A 13-month-old boy with previously normal development presented with a new onset generalized tonic clonic seizure and a short history of fever and upper respiratory tract symptoms.A CT head was normal and he was treated for presumed infective meningoencephalitis. The following day he developed a left focal motor seizure with secondary generalization evolving to status requiring intubation and ventilation.Initial MRI revealed widespread bilateral T2 high signal and restricted diffusion with predominance of the posterior cortex and relative sub-cortical sparing,together with involvement of the deep grey matter,not in keeping with ADEM.His EEG was slow with left focal epileptiform discharges,a basic metabolic screen was normal,and CSF revealed mild pleocytosis and raised protein with negative infection markers and a normal lactate.He was commenced on anticonvulsants and steroids with good seizure response. He developed a left side predominant hyperkinetic movement disorder, treated with Gabapentin,clonidine,and his prednisone course extended to a total of four weeks with good response.Repeat neuro-imaging revealed reduction in cortical swelling with bilateral new high T2 signal in the left striatum,and MOG antibodies were detected in the CSF with negative NMDAR antibodies.At time of discharge at 4 weeks his seizures were controlled,he had some spasticity in the right upper limb and was sitting with support(mRS 2).

Conclusions: MOG-antibody associated encephalitis is a more recently described entity in children which is steroid-responsive. https://doi.org/10.1212/NXI.0000000000000731.Our case highlights the phenotypic variability of this condition,with young age of onset, presence of movement disorder,and cortical imaging features with restricted diffusion.MOG-antibody testing should be considered in all children presenting with features of encephalitis.

Keywords:
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EPNS21-645 Poster only
Inflammatory Disease of the CNS

A boy with anti-Ma2 antibodies presenting with myasthenia-like syndrome.

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Objective: Ma2 antibody-associated encephalitis is a paraneoplastic brain disease, presenting as limbic, diencephalic or brainstem encephalitis. It is usually associated with testicular germ-cell tumor or lung cancer, however, in a minority of patients no primary tumor is detected. Here, we report a case of a child with Ma2 antibodies presenting with myasthenia-like syndrome.

Methods: A previously healthy 8-year-old boy presented with subacute bilateral ptosis with no significant diurnal fluctuation, hypernasal voice and weakness after exertion. Single fibre electromyography revealed marginal postsynaptic dysfunction compatible with ophthalmic myasthenia, while anti-AChR and anti-Musk antibodies were negative. Based on the above, the patient was started on pyridostigmine, showing initially partial response. Due to subsequent deterioration with increasing proximal muscle weakness, opthalmoplegia, and upper limb jerks, further diagnostic workup was performed, including brain MRI, lumbar puncture, metabolic panel and genetic panel for congenital myasthenic syndromes, which was normal. With the clinical suspicion of autoimmune-mediated brainstem disease, IVIG was administered, followed by methylprednisolone pulses, with subsequent gradual improvement of patient's symptoms.

Results: Paraneoplastic screen revealed high title of Ma2/Ta antibodies (anti-PNMA2). Extensive screening for neoplastic diseases was performed, including PET scan, and was negative. Methylprednisolone pulses leaded to initial resolution of symptoms, but the patient showed relapse few months later. A course of oral steroids was administered leading to complete resolution of symptoms. To date the patient remains asymptomatic, with regular oncological follow up, while Ma2 antibody title remains positive.

Conclusions: Though paraneoplastic syndromes are rare in children, Ma2 antibodies should be included in the diagnostic workout of brainstem disease, as apart from immunosuppressive therapy, regular oncology follow up is required.

Keywords:
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EPNS21-667 Poster only
Inflammatory Disease of the CNS

ADOLESCENT WITH ACUTE ENCEPHALITIS BECAUSE OF/WITHIN THE SARS-COV-2 CONTEXT

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Objective: Our objectives are to perform a differential diagnosis of the central nervous system acute pathologies in the paediatric patient, including the Coronavirus disease within the current context of the pandemic, learning to detect warning neurological signs, and knowing which treatment to apply.

Methods: To describe neurological complications in relation to SARS-COV2 disease.

Results: Adolescent of 12 years of age with no significant medical history shows a case of acute headache, bradypsychia and visual hallucinations. Admitted for evaluation of positive SARS-Cov-2 PCR. EEG carried out shows a diffuse slowing of the background activity and temporal spike wave discharges along with acute encephalitis. CSF with pleocytosis (leukocytes 445/L, 99% mononuclear cells) and high CSF protein concentrations (146 mg/dL). An infectious (CMV, HSV-1 and 2, HHV-6, PEV, VZV, bacteria) and autoimmune study (oligoclonal banding, anti-MOG and anti-NMDAR antibodies) as well as a serial brain and medullary MR-angiography are requested, no pathological findings. Final diagnosis is acute encephalitis because of/within the SARS-Cov-2 context. Initial treatment starts with corticoids bolus 1 g/24h up until 5 days and acyclovir 800 mg/24h up until 21 days. Complete resolution of symptoms within 48 hours of initial treatment, with no worsening symptoms displayed up until now. Normal EEG results apparent 6 months after.

Conclusions: The encephalitis diagnosis because of/within the COVID context is a diagnosis of exclusion. The pathogenic mechanism is unknown but believed to have a combined origin due to (infectious and autoimmune) processes-without having been linked to the presence of anti-SARS-CoV-2 antibodies. Because of this suspicion, it would be interesting to perform a combined treatment of acyclovir for 21 days and corticoids bolus initially, and afterwards in decreasing doses. The RMN does not have a reason to show changes. The EEG can take up to 6 months to show normal results.

Keywords:
encephalitis, SARS-COV-2, childhood

EPNS21-672 Oral or poster
Inflammatory Disease of the CNS

Chronic Inflammatory Demyelinating Polyneuropathy in Children - A Diagnostic and Therapeutic Challenge

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Objective: Polyneuropathies in the paediatric population impose a diagnostic and therapeutic challenge. We describe a previously healthy, 15-year-old girl who presented with sudden onset of sharp pain and burning sensation in her right leg. Symptoms deteriorated over the next 2-3 hours with complete motor and sensory function loss in the right leg. There were no other associated symptoms, along with an unremarkable past medical history.

Methods: In-depth investigations were requested. From baseline bloods, immunological work-up and lumbar puncture tests, up to cranio-spinal neuroimaging and EMG. In addition, a multi-disciplinary team approach was taken in this case.

Results: After reviewing the clinical picture in conjunction with EMG results, it has been concluded that our patient experienced findings suggestive of CIDP. She was treated with oral steroids, intravenous immunoglobulins (IVIG), and although she improved, symptoms relapsed a few weeks later. Over the course of 3 months, she required multiple courses of IVIGs in addition to gabapentin for symptomatic control of limb pain. She continues to be monitored with regular follow-up.

Conclusions: 1) To discuss the broad differential diagnosis in such presentations, 2) the increase in polyneuropathies in the paediatric population, 3) to look further into guidelines of different treatments, approaches, and the different response to treatments.

Keywords:
Chronic inflammatory demyelinating polyneuropathy, CIDP, steroids, IVIG

EPNS21-676 Oral or poster
Inflammatory Disease of the CNS

Acute necrotizing encephalopathy (ANE)

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Objective: To analyse the clinical, radiological characteristics and genetic implications of a peculiar inflammatory encephalopathy.

Methods: Signs and symptoms, radiological changes and DNA results of 7 members in 4 families are described.

Results: Patient 1 had seizures at age 2 mos, encephalopathy with bithalamic haemorrhage and necrosis at age 5 mos, liver failure at 18 mos and infection-triggered seizures, encephalopathy with symmetrical subinsular and brainstem changes at 2.5 yrs. He recovered with sequelae. His 7 yo maternal half-brother had infection-triggered seizure, encephalopathy, symmetrical capsula externa, putamen, temporal lobe, pons and mamillary body lesion. Both had elevated CSF protein levels.
A girl had infection-related episodes of encephalopathy, high CSF protein and bithalamic necrosis, brainstem involvement at 1 and 2 yrs of age. As a child, her father had influenza-associated "encephalitis" with high CSF protein, and even his mother underwent "encephalitis" in infancy.
In a 3rd family a girl had infection-associated encephalopathic episodes with high CSF protein and similar MRI changes. His paternal uncle died of febrile encephalopathy at age 6 yrs.
The dominant inheritance pattern raised suspicion of RANBP2 gene mutations in these families. Direct sequencing found homozygous pathogenic variants in all affected family members, the healthy mother of patient 1 and his brother, and the healthy father in the 3rd family.
A 2 yo boy in a 4th family had similar clinical course and typical MRI changes but proved negative on expanded genetic tests.

Conclusions: Acute necrotizing encephalopathy with symmetrical haemorrhagic deep grey matter, especially thalamic and also temporal and brainstem lesions is associated with viral infections, manifests with increased CSF protein, and part of the cases is caused by autosomal dominant RANBP2 mutations with incomplete penetrance. Beyond avoiding and prevention of infections, methylprednisolone pulse therapy of the acute episodes is recommended.

Keywords:
acute necrotizing encephalopathy, ANE, RANBP2, elevated CSF protein, thalamic necrosis

EPNS21-677 Oral or poster
Inflammatory Disease of the CNS

Case series of a steroid sensitive fulminant demyelinating disease with negative antibodies.

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Objective: We report a challenging case series of two children with a fulminant demyelinating disease from two different countries but sharing similar brain biopsy findings, imaging and response to treatment.

Methods: A 9-year-old girl with a background of mild developmental delay presented with a five day history of nausea and abnormal eye movements followed by right sided weakness and urinary retention. MRI showed extensive leptomeningeal enhancement and high signal change in mesencephalon ,pons and medulla oblongata as well as lesions from T9 to conus. Brain biopsy showed macrophage infiltration with areas of demyelination and axonal preservation.

The 2nd case we report is that of a 14 year old boy with a social communication disorder presenting with a three day history of headache and lethargy and nausea. He deteriorated with an inability to walk, urinary retention. He developed encephalopathy and respiratory compromise.

MRI showed white matter demyelination with peripheral brain stem involvement and cord lesions.
His brain biopsy showed similar results.

Both children had visual affection. They also had a cerebrospinal fluid lymphocytic response and positive oligoclonal bands.

Results: Both children showed an initial good response to pulse steroid therapy with Methylprednisolone intravenously and deterioration with the switch to oral Prednisolone and the dose being tapered down. They also both had a partial or no response to intravenous immunoglobulin given. There was a good clinical response following the 2nd course of Methylprednisolone administered to both children.

Cases were trialled with Rituximab and plasma apheresis with minimal clinical response.

Conclusions: We report on a fulminant demyelinating disease that was a clinical challenge for management and not fully fitting the diagnostic criteria or investigation findings for ADEM ,infection or multiple sclerosis with negative antibodies but responded nicely to high doses of pulse steroid therapy.

Keywords:
demyelination ,steroid -sensitive, oligoclonal bands

EPNS21-695 Oral or poster
Inflammatory Disease of the CNS

Acute disseminated encephalomyelitis in paediatric age: a multicentre retrospective study

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Objective: Acute disseminated encephalomyelitis (ADEM) is defined as acute onset of encephalopathy in association with variable multifocal neurologic deficits and correlated to typical demyelinating lesions on brain MRI. However, its diagnostic criteria are not exhaustive and data about treatment and prognosis are still inconsistent.
We analysed the demographic, clinical and neuroradiological features of paediatric ADEM patients and evaluated treatments and long-term outcomes.

Methods: It is a multicentre retrospective observational study. We included patients aged less than 18 years, who fulfilled the diagnostic criteria for ADEM and were admitted between Jan 2005 and June 2021, in nine centres (8 in Italy and 1 in UK). Univariate analyses were used to compare monophasic with relapsing ADEM.

Results: One hundred twenty-five patients were enrolled (mean age of onset 7.1 ± 3.6 years). The most reported clinical features during the acute phase were ataxia, pyramidal signs and fever. The prognosis was substantially favourable (severe neurological sequelae only in 1.6%). Sixteen patients (12.8%) manifested relapsing demyelinating disease. Compared to patients with monophasic ADEM, those relapsing had increased oligoclonal bands (OCB) in CSF at onset (37.5 vs 7.7%, $p < 0.05$) and first-line therapy started later (13.5 vs 6.3 days, $p > 0.05$). No differences between groups were found about dosage and duration of therapy. Finally, behavioural problems were more common in relapsing patients (31.3% vs 5.5%, $p<0.05$).

Conclusions: We describe the largest paediatric case series of ADEM to date. The results confirm findings in literature and add several aspects of clinical relevance: starting earlier therapy might prevent relapses; presence of OCB in CSF at onset and development of behavioral problems at follow up may herald a chronic course.

Keywords:
Acute disseminated encephalomyelitis; relapsing demyelinating disease; long-term outcomes

EPNS21-699 Poster only
Inflammatory Disease of the CNS

Acute Disseminated Encephalomyelitis in Pediatric Patients: 20-year single-center experience in Serbia

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Objective: Acute disseminated encephalomyelitis (ADEM) is the most common demyelinating disease in pediatric patients. We aimed to evaluate the clinical profile of children with ADEM and to discern prognostic factors for disease outcome.

Methods: A 20-year retrospective-prospective study was conducted in a cohort with diagnosis of ADEM.

Results: Study included 36 patients, with range of follow-up period of 6 to 120 months. More than a third of patients had back and limb pain or abdominal visceral pain, which highly correlated with MRI findings of myelitis. Abnormal brain CT findings (oedema or hypodense lesions) were evident in 22.2% of patients, and this was associated with higher EDSS, quicker progression of the disease and longer hospitalization. Median value EDSS was 0 at the most recent follow-up visit (after 6-120 months). EDSS ranged from 0 to 2.5 was verified in 29 (80.6%) of patients, while 3 (8.3%) patients scored from 7 to 9.5. Highly significant difference was established for the most recent EDSS between patients treated before the IPMSSG published consensus criteria 2007 (a retrospective study cohort) and those after published criteria (a prospective study cohort).

Conclusions: We found that poor prognostic factors for the disease outcome previous infection as a disease trigger, findings of brain edema or hypodense CT lesion in the first days of disease, higher values of CSF protein, corticosteroid therapy delay. Children diagnosed with epilepsy after ADEM had more extensive lesions on the brain MRI. ADEM remains a serious disease in children, but with a good prognosis in majority of patients, illustrated by 80.6% rate of complete or near-complete recovery.

Keywords:
encephalomyelitis, demyelination, children, adolescents, prognosis

EPNS21-140 Oral or poster
Metabolic Disorders

CLPB Mutation Presenting with Hyperekplexia

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Objective: Objective:
CLPB (casineolytic peptidase B) deficiency is a rare autosomal recessive condition characterised by neurological involvement, neutropenia and 3-methylglutaconic aciduria. We describe a case of a severe phenotype presenting at birth with hyperekplexia and respiratory insufficiency.

Methods: Methods:
A male neonate was born at 32 weeks gestation to first-cousin parents by C-section due to antepartum haemorrhage and abnormal fetal movements. From birth, he had no respiratory effort, requiring mechanical ventilation. He had microcephaly, exaggerated reflexes, significant hypertonia and abnormal seizure-like movements, felt to be in keeping with hyperekplexia. Investigations included an MR brain demonstrating abnormal myelination, blood tests showing marked neutropenia and urine organic acids demonstrating persistent moderate excretion of 3-methylglutaconic acid. Given the constellation of clinical and biochemical findings, a diagnosis of CLPB deficiency was suspected, and mutation analysis was directed specifically towards a pathogenic variant in CLPB, which was identified in a homozygous state. Discussions surrounding his poor prognosis took place with his family and he unfortunately passed away at seven months of age.

Results: Results:
CLPB deficiency is a rare autosomal recessive condition characterised by neurological symptoms and neutropenia. In the most severe phenotype, symptoms begin at birth and include respiratory insufficiency. 3-methylglutaconic aciduria provides a clue to the diagnosis. Those presenting with neonatal-onset phenotypes usually die within the first few months of life.

Conclusions: Conclusions:
Neonates who present with hyperekplexia should be examined and investigated for absence of voluntary movement, respiratory insufficiency and neutropenia. Urine organic acid analysis should be performed in these cases. Early diagnosis is important to facilitate appropriate discussions with patients' families, given the fatal outcome of neonatal-onset phenotypes.

Keywords:
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EPNS21-166 Oral or poster
Metabolic Disorders

Infantile onset of severe mitochondrial encephalomyopathy with fatal outcome due to pathogenic variants in NARS2 gene: a case report

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Objective: Pathogenic variants in NARS2 gene have been linked to various clinical entities, commonly involving the central nervous system. Only 17 patients with NARS2 genopathy have been described in the literature recently with variable clinical picture and outcome. We present a clinical case of severe mitochondrial encephalomyopaty due to compound heterozygous state: c.749G > A (ACMG criteria PS4_Mod, PM2, PP2, PP3)/c.921_921+5delGGTAAT (PVS1, PM2).

Methods: Case report

Results: A five months old boy was first admitted to intensive care unit (ICU) due to focal refractory epileptic status (RES). He was born to a non-consanguineus parents and his prior medical history was unremarkable. Computer tomography (CT) scan, magnetic resonance imaging (MRI) and the results of cerebrospinal fluid investigations on admission were normal, metabolic laboratory investigations revealed elevated lactate (3,0 mmol/L). ES was successfully treated with continuous infusion of midazolam. After this different forms of focal seizures reemerge. Electroencephalogram (EEG) mostly showed focal epileptic discharges with diffuse slowing of background activity. Different antiseizure medications were gradually introduced: levetiracetam, oxcarbazepin, clobazam, topiramate and vitamins. In spite of this, he was hospitalized in ICU six times in seven months due to RES, the most severe at the age of 11 months, when ketamin was used. He developed psycho-motor regression, feeding difficulties and extra-pyramidal signs. Brain MRI at the age of 11 months revealed global cerebral atrophy and MR spectroscopy showed elevated levels of lactate. During the time of last RES ketogenic diet was started. Seizure frequency and the need for hospitalization significantly reduced. He died nine months after his first seizure due to heart failure following pneumonia

Conclusions: Our patient had a severe course of mitochondrial encephalomyopaty with fatal outcome due to compound heterozygous state in NARS2 gene not yet described.

Keywords:
NARS2, mitochondrial encephalomyopaty, status epilepticus

EPNS21-170 Oral or poster
Metabolic Disorders

Diagnosing D-bifunctional protein deficiency in patients with normal plasma biochemistry

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Objective: Peroxisomal D-bifunctional protein (DBP) deficiency is an autosomal recessive disorder, which typically presents in the first month of life with seizures, hypotonia and psychomotor delay. Other features include retinopathy, hearing loss, dysmorphic features and varying systemic complications. The HSD17B4 gene encodes DBP, which has 3 catalytic domains; an N-terminal dehydrogenase, a central hydratase and a C-terminal sterol carrier protein-2-like domain. The enzyme is essential for the oxidation of peroxisomal substrates.

Here we report 2 unrelated patients with DBP deficiency, both presenting with neonatal seizures and hypotonia. Interestingly in both cases biochemical analysis revealed normal levels of plasma VLCFA, phytanic acid and pristanic acid, with no diagnosis established for either patient at this point.

Methods: Whole genome sequencing. Trio exome sequencing. Fibroblast studies.

Results: Patient 1 underwent trio exome sequencing identifying compound heterozygous mutations (c586_587insCGGGATCA; pMet200Aspfs Ter) and (c.743G>A; pArg248His) both located in the dehydrogenase domain. This is the first report of these mutations, and we show both are predicted to be pathogenic. Subsequent fibroblast studies revealed normal VLCFA levels, normal C26:0 but reduced pristanic acid beta-oxidation. The hydratase activity was mildly reduced whereas the dehydrogenase activity was not detectable.

Patient 2 underwent whole genome sequencing, identifying a homozygous missense mutation (c.101C>T: pArg35Val), which has been previously shown to be pathogenic.
Subsequent fibroblast analysis showed an increased levels of VLCFA, reduced hydratase activity and undetectable dehydrogenase activity.

Conclusions: This report highlights the importance of fibroblast enzyme analysis and the use of exome or whole genome sequencing in diagnosing DBP deficiency.

Keywords:
Peroxisomal D-bifunctional protein

EPNS21-183 Oral or poster
Metabolic Disorders

Long term follow up of Niemann-Pick type C patients on cyclodextrin treatment

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Objective: Niemann-Pick type C disease (NPC) is a progressive disorder characterized by neuro-visceral manifestations. The clinical spectrum ranges from a fatal antenatal disorder to an adult-onset chronic neurodegenerative disease. The primary objective is to assess 2-hydroxypropyl-beta cyclodextrin (HPBCD) efficacy on the evolution of the disease.

Methods: This is a descriptive and retrospective study including pediatric patients diagnosed with NPC and treated with HPBCD, from 2012 to 2020.

Results: We included 9 NPC patients treated with HPBCD. The median age of first NPC symptoms was 2 years, ranging from newborn to 12 years, whereas median age of NPC diagnosis was 3,5 years. All patients were previously treated with miglustat. Treatment with HPBCD was started at different moments in the course of the disease. The median age for the first administration was 5 years. The intravenous route was previously used in 3 patients and intrathecal administration in all of them. Clinical assessments using the NPC disease Clinical Severity Score revealed stable values in 6 patients, worsening in two and improvement in one case. In terms of disease biomarkers evolution during the follow up (available only in three patients) a reduction of blood-lyso-SM509 and cerebrospinal fluid-chitotriosidase levels were identified in one and two cases respectively. Adverse side effects were reported in three patients and consisted of acute fever related to the drug infusion and chemical meningitis in two patients, resolving without consequences. Stability of Brainstem Auditory Evoked Response was reported in all patients.

Conclusions: These case studies demonstrate that HPBCD is a well-tolerated treatment that can potentially treat systemic and neurologic manifestations of patients with NPC.

While progressive decline is expected in accordance with previously published natural history data, the rate of progression appears to be less than expected. However, further validation with randomized clinical trials is needed.

Keywords:
Niemann-Pick type C, cyclodextrin, blood-lyso-SM509, chitotriosidase

EPNS21-2037 Oral or poster
Metabolic Disorders

Diagnostic performance of a blood test for the early, simple and fast detection of Glut1 deficiency syndrome

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Objective: GLUT1 deficiency syndrome (Glut1DS) is a genetic neurometabolic disease that causes a wide range of neurological symptoms, in children and adults - epilepsy,cognitive impairment, permanent or paroxysmal movement disorders, either combined or in isolation. Glut1DS is a treatable disorder. However, its diagnosis relies on an invasive test, i.e., a lumbar puncture (LP) to measure glycorrhachia, and, sometimes complex, molecular analyses of the SLC2A1 gene. This procedure limits the number of patients able to receive the standard of care. METAglut1 is a simple blood test
that quantifies GLUT1 at the red blood cell surface.

Methods: We performed a multicenter validation study in France, involving 33 centers. We studied two patient cohorts: a prospective cohort, consisting of patients with a clinical suspicion of Glut1DS explored through the reference strategy, i.e., LP and analyses of the SLC2A1 gene; a retrospective cohort that included patients previously diagnosed with Glut1DS. All patients were blind-tested with METAglut1. In case of discordant results, we performed a functional glucose uptake assay with the patient red blood cells.

Results: We analyzed 428 patients in the prospective cohort, including 15 patients newly diagnosed with Glut1DS, and 67 patients in the retrospective cohort. METAglut1 was 80% sensitive and >99% specific for the diagnosis of Glut1DS. Concordance analyses showed a substantial agreement between METAglut1 and glycorrhachia, with a Cohen's kappa coefficient of 0.78. In the prospective cohort, the positive predictive value of METAglut1 was slightly higher than that of glycorrhachia. METAglut1 succeeded to identify Glut1DS patients with SCL2A1 mosaicism and variants of previously unknown significance.

Conclusions: METAglut1 is an easily performed, robust and non-invasive diagnostic test for the diagnosis of Glut1DS, which allows a wide screening of children and adults with atypical forms of this treatable condition.

Keywords:
Glut1 deficiency syndrome; epilepsy; movement disorder; diagnostic performance; blood test; erythrocyte; flow cytometry; glycorrhachia

EPNS21-2059 Poster only
Metabolic Disorders

The fingerprint of traumatic brain injury on D-2-alpha hydroxyglutaric aciduria delayed diagnosis

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Objective: D-2-alpha hydroxyglutaric aciduria is an ultrarare autosomal recessive progressive neurometabolic disorder, characterized by elevated D-2-hydroxyglutaric acid (D-2-HG). Due to the extremely wide phenotype, its extension would allow a prompt diagnosis, adequate management and early establishment of treatment.

Methods: The case of a 9-year-old boy in which we analysed the clinical evolution, neurophysiological, neuroradiological findings. Metabolic testing was also performed and new generation sequencing(NGS) test confirmed the diagnosis

Results: At the age of 11 months he had a traumatic brain injury that complicated with a right fronto-parietal subdural hematoma that required multiple surgeries. Following this he presented a psychomotor developmental stagnation, acquiring independent walking at the age of 2 years and a half and first words at 4 years old. At the age of 5, he began presenting right focal clonic seizures that were aggravated by Carbamazepine. He became seizure-free after initiation of Clobazam and Topiramate. At 7 years he developed a right brachial paresis. The brain MRI showed right hematoma sequelae and unspecific demyelinating areas. Considering the lack of topographic and electro-clinical correlation he performed further investigations. The metabolic disease panel revealed high levels of D-2-HG and the NGS tests confirmed a compound heterozygous mutation in D2HGDH gene, maternal inherited c.853+5G>C, splice site variant and paternal inherited c.773C>T, p.Ser258Leu, missense variant.
During his evolution, he remained seizure-free, with a right brachial paresis and a delay in language development.

Conclusions: The particularity of this case is the misleading association of an acute acquired neurological condition which hid the clinical picture of a slow progressive neurological disease, D-2-alpha hydroxyglutaric aciduria and delayed it's diagnosis. The coexistence of neurological conditions may be taken in account when the performed investigations don't explain the clinical picture.

Keywords:
metabolic, D-2-alpha hydroxyglutaric aciduria, rare disease, traumatic brain

EPNS21-254
Metabolic Disorders

Oral or poster

Neurological symptoms as a first presentation of Wilson's disease

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Objective: A previously healthy 13-year-old girl with a 5-month-history of hypersalivation, dysarthria, tremor, thrombocytopenia, and leukopenia came to our clinic.

Methods: On examination we noticed incomplete closing of the mouth, splenomegaly, slightly weakened hand grip. Magnetic resonance (MRI) of the brain showed abnormal T2 hyperintensity in the basal ganglia, mesencephalon and pons. Abdominal ultrasound indicated diffuse changes in liver parenchyma with circular edges, regenerative nodes, splenomegaly, and suspected portal hypertension, without ascites. Fibrosis was confirmed by liver fibroscan and abdominal MRI, and laboratory findings (lower prothrombin time, levels of coagulation factors and albumin, and bicytopenia). Esophagogastroduodenoscopy revealed esophageal varices grade I and portal gastropathy due to portal hypertension. Kayser Fleischer ring was present.

Results: Low ceruloplasmin levels and positive penicillamine test further confirmed the suspicion for Wilson's disease which was confirmed by genetic testing that showed homozygous H1069Q mutation. There were no signs of renal tubular damage and heart was structurally healthy. We opted for a combined therapy with penicillamine and zinc acetate due to the possible side effect of penicillamine in the sense of further leucopenia. Vitamin D and calcium supplementation was introduced due to reduced bone density. She began copper free diet, high-energy oral nutritional supplement adjusted for patients with liver disease, MCT oil and gastroprotection. So far, the therapy has been efficient with adequate cupriuria and no signs of therapy side effects.

Conclusions: This is a rare example of silent cirrhosis and clear neurological signs as a first presentation of Wilson's disease. A multidisciplinary team is required to monitor possible complications of the disease, side effects of the therapy and offer mental support to the patient and its family.

Keywords:
Wilson's disease, neurological presentation, silent cirrhosis, penicillamine, zinc acetate

EPNS21-264 Poster only
Metabolic Disorders

Clinical course of patients with single large-scale mtDNA deletions and childhood onset anemia

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Objective: To add to our knowledge of the clinical spectrum of patients with single large-scale mitochondrial DNA (mtDNA) deletion and childhood onset anemia.

Methods: Retrospective collection of clinical data from medical records for patients, both living and deceased, with a single large-scale mtDNA deletion from seven mitochondrial disease centers in five countries. Statistical analysis with descriptive methods and Kaplan-Meier survival analysis.

Results: Seventeen patients matching the genetic criterium and with anemia onset before six years of age. Exocrine pancreatic insufficiency was only seen in five patients in this group. Multiple organs were involved in all patients, with the most common non-hematologic ones being skeletal muscle, central nervous system, endocrine, eyes, gastrointestinal system, kidneys, hearing, liver and heart. Psychomotor retardation was seen in ten patients, hearing impairment in nine patients, failure to thrive in eight patients. Eight later developed Kearns-Sayre syndrome. Eleven patients were deceased, with a median age at death of 7.5 years.

Conclusions: The classically described phenotype of patients with large-scale mtDNA deletions and early onset anemia is Pearson marrow-pancreas syndrome, characterized by sideroblastic anemia and exocrine pancreas dysfunction. Only a minority of our patients fulfill the original criteria of Pearson syndrome though. Involvement of other organs than the pancreas is more common. The clinical course vary, but multi-system impact is the rule and life-expectancy is low.
Early onset anemia in patients with large-scale mtDNA deletions is most frequently not associated with exocrine pancreas dysfunction. Better knowledge of the phenotype is helpful for diagnosis and more accurate prognosis.

Keywords:
mitochondrial disease, mitochondrial DNA, mtDNA, large-scale deletions, Pearson syndrome, Kearns-Sayre syndrome

EPNS21-294 Oral or poster
Metabolic Disorders

Neurodegenerative disease after haematopoietic stem cell transplantation in metachromatic leukodystrophy

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Objective: Metachromatic leukodystrophy (MLD) is an inherited white matter (WM) disease with progressive demyelination of both the central and peripheral nervous system, caused by deficient arylsulfatase A (ASA). Hematopoietic stem cell transplantation (HSCT) has been shown to stabilize and even improve WM damage, yet some patients still deteriorate after successful transplantation. We hypothesized that clinical deterioration after treatment might be caused by the grey matter (GM) component of MLD.

Methods: We analysed deep grey matter (DGM) in three treated MLD patients who clinically deteriorated after HSCT, despite unchanged WM on brain MRI. Longitudinal volumetric MRI was used. Histopathological analyses with staining for ASA and sulfatides on brain tissue of three (other) treated and six untreated MLD patients were also performed.

Results: Volumetric MRI performed on patients who showed clinical deterioration with stable WM abnormalities identified progressive atrophy of DGM, specifically of the thalamus.
Histopathology data showed neuronal sulfatide accumulation in untreated patients, most notably in the thalamus. ASA expression in thalamic neurons was not higher in transplanted than in untransplanted patients. Cortical GM of patients treated with HSCT contained substantially less ASA than the WM. Additionally, ASA-expressing donor macrophages were clearly present in the WM while nearly absent in the cortical GM of transplanted patients.

Conclusions: Our findings confirm the GM involvement previously reported in MLD. The current study shows that this involvement may progress alongside stable WM pathology after seemingly successful HSCT treatment, and that this might be caused by a limited effect of HSCT on the GM component of MLD. The clinical deterioration of the analyzed patients illustrates the potential clinical relevance of the GM involvement for MLD.

Keywords:
MLD HSCT Leukodystrophy MRI Pathology White-matter Grey-matter

EPNS21-30 Poster only
Metabolic Disorders

Infantile Pompe Disease (IPD) affects the CNS despite Enzyme Replacement Therapy (ERT)

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Objective: This is a case report of a child with Infantile Pompe Disease (IPD) and their MRI images to showcase some of the central nervous system (CNS) changes reported in literature.

Methods: This patient presented with peripheral muscle weakness at 6 months of age, and was subsequently confirmed to have IPD. Thereafter, he was treated with fortnightly Enzyme Replacement Therapy (ERT; Myozyme) and has remained on it since diagnosis. An MRI head was undertaken at the age of 13 years during investigation of paroxysmal events, which showed extensive symmetrical white matter abnormalities

Results: MR brain sequence images of this patient demonstrated signal changes involving deep white matter i.e. centrum semiovale, subcortical white matter, corpus callosum and basal ganglia.

Neuroimaging abnormalities predominantly consist of white matter changes. In the early stage (starting around 2 years of age), these changes are confined to a periventricular distribution at the level of the centrum semiovale. Later on (from the age of 8), these white matter abnormalities extend to the subcortical areas, corpus callosum, basal ganglia, internal and external capsule. Infratentorial white matter changes can be seen from about 11 years of age.

Conclusions: Although IPD is still seen as mainly a muscular disease, there are growing reports of CNS changes in patients with treated IPD which is now only unmasked with the advent of ERT leading to prolonged survival beyond infancy.
Nevertheless, the impact of CNS glycogen accumulation and correlation between neuroimaging findings on cognitive and neurological development in IPD is unclear. The limited cases reported in literature are linked with significant developmental delay or progressive functional loss even in patients treated with ERT from a young age
Regular neuroimaging surveillance and assessment of neurological/developmental function is warranted in the IPD population to further determine the extent of CNS pathology and clinical impact.

Keywords:
Pompe disease; Neuroimaging

EPNS21-312 Oral or poster
Metabolic Disorders

Solving a puzzle: An infant with developmental delay, epileptic spasms, and petechiae

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Objective: Infantile spasm(IS) is an early onset epileptic encephalopathy with psychomotor impairment and characteristic hypsarrhythmia pattern on electroencephalography(EEG).More than 25 inborn errors of metabolism have been considered etiologic or predisposing factors for IS.

Methods: Herein we report a rare cause of IS in a patient with underlying metabolic etiology.

Results: An 8-month-old boy presented with poor head control and epileptic spasms. He was the third child of consanguineous parents and born at term following an uneventful pregnancy. Physical examination revealed axial hypotonia, orthostatic acrocyanosis, and petechiae located over the extremities. EEG demonstrated a disorganized, high-amplitude background and multifocal, interictal epileptiform discharges consistent with modified hypsarrhythmia. He was treated with levetiracetam and topiramate with partial clinical and electrophysiologic response.Epileptic spasms resolved with im ACTH. Brain MRI showed mild cerebral atrophy and increased T2 signal in the basal ganglia bilaterally. MR spectroscopy demonstrated a lactate peak. Metabolik work-up revealed high serum lactate levels. Tandem mass spectrometry was normal, urine organic acid analysis revealed increased levels of ethyl malonic acid 176,42 mmol/mol/cr(1,7-14,6). Diagnosis of ethylmalonic encephalopathy(EE) was confirmed by molecular genetic analysis (c.554T>G;p.Leu185Arg homozygous ETHE1).

Conclusions: Ethymalonic encephalopathy is an early-onset autosomal recessive severe disorder affecting the brain, gastrointestinal tract, and peripheral blood vessels. Clinical features include neurodevelopmental delay, psychomotor regression, hypotonia, movement disorders, recurrent petechiae, orthostatic acrocyanosis, and chronic diarrhea. Treatment is primarily supportive. Although the data are limited, liver transplantation appears to be an effective therapeutic option that should be considered before irreversible neurological damage occurs.

Keywords:
Ethymalonic encephalopathy, infantile spasm, petechiae, neurodevelopmental delay

EPNS21-322
Metabolic Disorders

Oral or poster

Cerebral creatine deficiency syndromes, are we sufficiently suspicious?

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Objective: Cerebral Creatine deficiency syndromes(CCDS) are inborn errors of Creatine metabolism with nonspecific neurological symptoms. 3 primary CCDS are arginine glycine amidinotransferase(AGAT) deficiency, Guanidinoacetate methyltransferase(GAMT) deficiency & Creatine transporter deficiency(CTD). 118 CTD & 110 GAMT deficiency cases are reported worldwide. Early diagnosis is imperative for treatment and genetic counselling.

Methods: We present case reports of 2 boys with CTD & GAMT deficiency presenting at 1 & 2 yrs of age, diagnosed at 5 & 3 yrs, respectively. Both have Epilepsy & significant speech delay. First line investigations were negative. Urine Creatine metabolite tests proved pivotal in establishing diagnoses.

Results: Case1: 10yr old developed refractory focal onset seizures & Autism traits after first presenting with febrile seizures. Examination revealed microcephaly & mild facial dysmorphism. MRI Brain, array CGH & Epilepsy gene-panel showed no abnormalities. Urine revealed high Creatine & normal Guanidinoacetate(GAA). Cranial Magnetic Resonance Spectroscopy (MRS) showed diminutive Creatine peak. SLC6A8 mutation confirmed CTD. Following Creatine supplementation, reasonable seizure control, improvement in speech, motor skills & Autism behaviours was noted.
Case2: 4yr old presented with motor & speech delay at 2 yrs age, subsequently developed Movement disorder & generalised Epilepsy. Urine revealed low Creatine & elevated GAA consistent with GAMT deficiency. He has good seizure control with Valproate, motor skills improved but significant speech delay persists.

Conclusions: A high index of clinical suspicion in children with unexplained developmental delay (predominantly speech & language) and Epilepsy is crucial for early diagnosis of CCDS. Urine Creatine metabolite analysis, MRS and genetic studies are important investigations. Despite rarity in literature, we diagnosed 2 cases among population of 90,000 children over a 3 year period. Therefore, we suspect CCDS are perhaps underdiagnosed.

Keywords:
Development delay, speech and language difficulties, Autism, Epilepsy, movement disorder, microcephaly, Creatine deficiency, GAMT deficiency, CTD, SLC6A8

EPNS21-328 Poster only
Metabolic Disorders

Diagnostic approach to acute-onset flaccid areflexic paralysis in the landscape of new prospective diagnosis

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Objective: To discuss the possible differential diagnosis in acute onset of flaccid paralysis associated to severe abdominal pain.

Methods: A previously healthy 7-years-old girl was admitted to the emergency room with acute onset of flaccid paralysis associated to severe abdominal pain. Family history revealed consanguinity and atypical chronic inflammatory demyelinating polyneuropathy of undetermined origin in an older brother.
At hospital admission, neurological examination disclosed four limbs and trunk hypotonia, lower limbs areflexia, upper limbs hyperreflexia, lower limbs dysesthesia, mild dysmetria. EMG recorded symmetric axonal motor peripheral neuropathy. CSF findings were normal. Brain MRI detected slight chiasma and optic nerves thickness reduction. Anterior and posterior roots contrast enhancement was detected on MRI of the spine. EEG showed spread theta-delta activity. IgG against SARS-CoV2 were also found on blood sample.
The diagnostic work-up considered infectious, metabolic, toxic, and immune-mediated causes. However, family history suggested the possibility of a genetic condition and a trio-based whole exome sequencing (WES) was performed.

Results: Genetic test revealed a homozygous missense mutation on the gene FDXR, inherited from the healthy parents by both the girl and her older brother. FDXR is a mitochondrial membrane protein implicated in the biosynthesis of iron-sulfur clusters, essential components for the mitochondrial machinery function.

Conclusions: The acute onset of mitochondrial disease with neurological disorders mimicking an acquired inflammatory condition underline the importance to consider mitochondrial disorders in the differential diagnosis of acquired inflammatory conditions.

Keywords:
flaccid areflexic paralysis, mitochondrial disease

EPNS21-356 Oral or poster
Metabolic Disorders

A case of MTO1 mutation associated with hypertrophic cardiomyopathy, epilepsy and high lactate levels

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Objective: Mitochondrial disorders are multisystemic disorders associated with severe dysfunction of oxidative phosphorilation. Infantile hypertrophic cardiomyopathy is a key clinical findings of many mitochondrial disorders.
MTO1(mitochondrial tRNA translation optimization 1) is rare disorder characterized by hypertrophic cardiomyopathy, lactic acidosis and mild to severe global developmental delay/intellectual disability. Clinical findings are very heterogenous. In the literature, approximately 35 patients were described including one Turkish patient. This is the second case from Turkey associated with homozygous mutaion in MTO1 gene (p.R504C)

Methods: 23 year-old-male presented at 15 years old with weakness, difficulty clumbing stair, hypertrophic cardiomyopathy. There was a first degree consanquinity between his parents. Mental development was normal. He could able to walk at 18 months of age. At age of 15, physical examination showed growth retardation, initial findings of retinitis pigmentosa, 2nd degree cystolic murmur. Laboratory investigation revealed; high plasma lactate level, increased plasma alanine and 3-4 times increased urine lactate and pyruvate level. EEG showed generalized spike and wave activity increased during photic stimulation. Brain MRI and MRI spectroscopy were normal. Muscle biopsy revealed ragged red fiber and findings associated with COX deficiency. WES analysis was performed . Now, the patient is 23 year-old , he follow up with stable clinical findings.

Results: A homozygous mutation in MTO1 gene (p.R504C) was observed. Additionally; Sanger DNA sequencing analysis was also performed and this mutation was confirmed. The parents have heterozygous alteration for this mutation.

Conclusions: In childhood , evaluation of the patients with hypertrophic cardiomyopaty for mitochondrial disorders is very important. Hypertrophic cardiomyopathy may be first clinical finding in MTO1 patients similar in our case. There is a clinical and genetic heterogenity in this rare disorder.

Keywords:
MTO1 mutation, hypertrophic cardiomyopathy , epilepsy

EPNS21-359 Oral or poster
Metabolic Disorders

Course of peripheral neuropathy over time in untreated and transplanted patients with metachromatic leukodystrophy

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Objective: Metachromatic leukodystrophy (MLD) is caused by Arylsulfatase A (ASA) deficiency and consequent sulfatide accumulation, resulting in progressive central and peripheral demyelination. Currently, longitudinal and prognostic data on the disease in the peripheral nervous system (PNS) are lacking for both untreated and transplanted patients. The objective of this study was to analyse the time course of peripheral neuropathy in patients with MLD and to examine whether the development over time differed depending on patient, disease and treatment characteristics.

Methods: This retrospective study included adult and paediatric patients in the Amsterdam UMC (n = 54) and University Hospital Tubingen (n = 44) with nerve conduction velocity (NCV) measurements between 1995-2020 (n = 266). As different nerves were measured among patients, we combined NCV measurements of the peroneal and tibial nerve based on Bland-Altman plots. NCV over time and clinical predictor effects were analysed using linear mixed models with a continuous AR(1) correlation structure on time.

Results: A total of 245 NCV data points were analyzed. NCV remained relatively stable over time after diagnosis with MLD, except for those with a late-infantile phenotype ($p = 0.030$), who showed a more severe decline in NCV. Residual ASA activity, the presence of symptoms and MRI abnormalities at diagnosis were not significant predictors. In addition, the course of NCV over time was not altered by treatment with allogeneic hematopoietic stem cell transplantation. Interestingly, NCV was significantly higher in patients carrying a c.257G>A, c.542T>G, or c.608A>G genetic variant ($p < 0.001$).

Conclusions: Peripheral neuropathy in patients with MLD remains stable over time after diagnosis, except for those with a late-infantile phenotype. "PNS-protective" MLD causing genetic variants are associated with preservation of peripheral nerve function. Allogeneic hematopoietic stem cell transplantation did
not have an effect on the course of peripheral neuropathy.

Keywords:
Metachromatic leukodystrophy, peripheral neuropathy, allogeneic hematopoietic stem cell transplantation

EPNS21-400 Poster only
Metabolic Disorders

Infantile-onset Pompe disease: About two case report with different debut and prognosis

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Objective: Pompe disease,or glycogenosis type II,is a rare,hereditary,multisystemic disease caused by glycogen accumulation in lysosomes due to deficiency of acid alfa-glycosidase(GAA).Treatment is based on enzyme replacement therapy(ERT).Its prognosis will depend,among other factors,on the activity of GAA present in pacients(CRIM status)

Methods: We present two cases with infantile Pompe disease(IPD)of different age of debut

First case:15-day-old patient normal motor development and heart murmur. Echo showed significant biventricular hypertrophy,being diagnosed with IPD CRIM-negative and intitiated ERT.She showed progressive improvement of cardiac pathology with adequate motor development.At 2 years she developed high sustained antibodies against enzyme replacement therapy(HSAT),resulting in progressive deterioration. An immunetolerance induction protocol was started,showing a reduction in antibodies with clinical motor improvement.Subsequently, she presented a new progressive worsening,with HSAT and no response to immunomodulatory therapy. Patient's death at 8 years

Second case:13-year-old patient with generalised hypotonia and delayed developmental milestones at 14 months.Biopsy/genetic study compatible with IPD CRIM-positive.ERT was started,doubling the dose and adding Miglustat due to poor response,with no antibodies to this therapy.He is currently stable,with nocturnal NIV and improved muscle tone(no autonomous standing,GMF III),adequate academic performance and no cardiac involvement

Results: Prognosis of IPD will depend mainly on the age of debut and its relationship to the amount of residual GAA activity.Early initiation of ERT increases survival and decreases complications.Gene therapy has shown promising results in experimental models

Conclusions: In our case,first patient presented torpid evolution,with early diagnosis and CRIM-negative status that conditioned the response to treatment.In second patient,the diagnosis was later and evolution slower,with greater response to ERT and CRIM-positive status

Keywords:
Infantile Pompe Disease, CRIM, Enzyme Therapy, Metabolic Disease

EPNS21-424
Metabolic Disorders

Oral or poster

A Novel mutation in the PIGO gene causes hyperphosphatasia and mental retardation syndrome: A Case Report

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Objective: We report an extremely rare case of a female with a novel homozygous variant in the Phosphatidylinositol Glycan Anchor Biosynthesis Class O (PIGO) gene.

Methods: A female infant born at term became had frequent apneas soon after birth, requiring non-invasive respiratory support for few days. Parents are second cousins. Physical examination showed hypotonia however, there was no organomegaly or striking dysmorphic features.
Brain MRI showed Grade II intraventricular haemorrhage. EEG showed encephalopathic pattern with burst suppression. Extensive metabolic workup including new-born screening was normal. At day 21 of life, she developed frequent tonic seizures. Physical examination revealed generalized hypotonia and subtle dysmorphism. She was started on antiepileptics, pyridoxal-5-phosphate, folinic acid and biotin empirically. Seizures improved, however, continued and evolved to infantile spasms at two months of age. Repeat brain MRI showed thin corpus callosum, normal myelination for age. MR spectroscopy showed normal metabolite peaks. Alkaline phosphatase was elevated. At 18 months of age, she was globally delayed, significantly hypotonic, no visual fixation and continued to have seizures. She passed away due to febrile illness.

Results: Exome Sequencing identified a homozygous variant of uncertain significance in the PIGO gene: c.1109A>G; p.(Asn370Ser). Parents were confirmed heterozygote carriers. Functional testing for Glycosylphosphatidylinositol (GPI) biosynthesis showed reduced expression of GPI anchored proteins CD16, CD24, CD55, CD59, CD66b and FLAER on the surface of granulocytes. The flow cytometric analysis confirmed a GPI anchor biosynthesis defect (GPIBD). Therefore, the flow-cytometry confirmed the pathogenicity of the homozygous mutation c.1109A>G.

Conclusions: We describe a novel variant in the PIGO gene: c.1109A>G; p.(Asn370Ser) causing autosomal recessive hyperphosphatasia with mental retardation syndrome type 2. The variant was confirmed to be pathogenic by functional analysis.

Keywords:
PIGO gene, hyperphosphatasia with mental retardation syndrome type 2, Rare disease, Novel mutation

EPNS21-496 Poster only
Metabolic Disorders

Current status after treatment with serine and glycine in a patient with microcephaly and infantile seizures due to 3-phosphoglycerate dehydrogenase deficiency

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Objective: Phosphoglycerate dehydrogenase (PGDH) deficiency is a rare autosomal recessive serine biosynthesis disorder. It is clinically characterized by congenital microcephaly, infantile-onset persistent seizures, and severe psychomotor retardation. With decreased levels of L-serine in plasma and cerebrospinal fluid (CSF), the diagnosis is suspected and confirmed by genetic study. Early diagnosis allows the prevention of progressive central nervous system damage with serine support. Prenatal diagnosis and genetic counseling provide prevention of secondary cases.

Methods: A twenty-four-month-old girl was born to parents who were first-degree relatives with a similar disease in the family. Head circumference at birth was 31 cm (-2.6 standard deviation [SD]). He showed a psychomotor delay. At one month, she developed flexor spasms that were partially controlled with clonazepam. At the 11-month examination, restlessness, microcephaly at 37 cm (-6.6 SD), axial hypotonia, spastic tetraparesis, bilateral nystagmus and cataract were observed. Electroencephalography showed hypsarrhythmia. No specific finding was found in computed tomography and magnetic resonance imaging performed at the age of 1 month. Blood amino acid chromatography (AAC) showed reduced serine and glycine levels, CSF AAC levels showed reduced serine. On these abnormalities, the diagnosis of suspected phosphoglycerate dehydrogenase (PGDH) deficiency was confirmed by genetic studies of the PGDH gene with homozygous mutation. The patient is undergoing supplementation with L-serine and glycine. About one month after starting treatment, seizures decreased significantly.

Results: Early diagnosis, and the initiation of early treatment, may potentially ameliorate some of the neurologic symptoms, including seizures and spasticity.

Conclusions: Early diagnosis improves response to treatment. Therefore it allows prevention of secondary cases, since supplementation of L-serine during pregnancy may prevent the disease expression in an affected fetus.

Keywords:
serine, epilepsy, microcephaly, supplementation

EPNS21-510
Metabolic Disorders

Oral or poster

The potential benefits of therapeutic lactate infusion in children

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Objective: Traditionally, clinicians consider lactate as a waste product of anaerobic glycolysis and a marker of severe hypoxia. Interestingly, in the past decades, research has showed another side of lactate, as an alternative energy fuel for the brain. This fact has the ability to give an new impulse in research of different neurometabolic disorders and could be of use in developing future new treatment options for these diseases. The increasing awareness of the potential beneficial side of lactate, however, is entering the clinic rather slowly. Following this, and realizing that the application of potential novel therapeutic strategies in pediatric populations often lags behind the development in adults, this review summarizes the key data on therapeutic use of intravenous sodium lactate in humans.

Methods: A review of the literature was performed in April 2021, searched databases are Pubmed and Clinicaltrial.gov. By using relevant MeSH and 'Title and Abstract' terms and correction for duplicates, 282 articles were identified. After screening title and abstracts and checking references 33 articles were included, only one of these articles involved children.

Results: 33 articles describe a study protocol to administer lactate in different patient groups. This review gives an overview of all used study protocols and reported side effects in current literature. Additionally it provides a protocol for future studies with infusion of lactate in children with neurometabolic disorders.

Conclusions: Sodium lactate can safely be administrated without major side effects. Additionally, it is demonstrated that lactate can have a positive effect in adult patients with hypoglycemia and traumatic brain injury. Lactate is an energy source for the brain, and there are reasons enough to warrant studies on the potential therapeutic effects of sodium lactate infusion in children with neurometabolic disorders.

Keywords:
Review, neurometabolic disorders, lactate infusion

EPNS21-526 Oral or poster
Metabolic Disorders

Microcephaly is not a feature of GLUT1DS

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Objective: In literature, microcephaly is considered part of the classical phenotype of glucose transporter 1 deficiency syndrome (GLUT1DS), and previous cohort studies reported a prevalence of microcephaly of around 50% in patients with the syndrome, but this was never studied. However, in our clinical experience, it appears that almost none of the patients presenting with GLUT1DS have microcephaly. Therefore the aim of this study is to investigate all data on head circumference and the prevalence of microcephaly in GLUT1DS patients known in our medical center.

Methods: We conducted a retrospective, observational study among a cohort of 66 patients with GLUT1DS, to investigate the prevalence of microcephaly (defined as < 2 SD below the mean).

Results: We analysed the head circumference of 54 patients, and found a prevalence of 11.1 % of microcephaly at some point during childhood. Notably, none of the patients had a head circumference < -3 SD. Furthermore, we learned that the Z-score of 75.9% of the patients was below 0.

Conclusions: This study shows that microcephaly might occur less often than previously thought in patients with GLUT1DS, and that primary or secondary "microcephaly" seems not to be a sign for clinicians to suspect GLUT1DS. However, as a group, these patients seem to have smaller heads compared to healthy individuals and as such, our study suggests that early brain development and brain growth may be compromised in GLUT1DS.

Keywords:
Glucose transporter 1 deficiency syndrome, SLC2A1, microcephaly, phenotype, retrospective study, head circumference

EPNS21-545 Oral or poster
Metabolic Disorders

Recognizing early MRI signs is crucial in diagnosing metachromatic leukodystrophy

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Objective: Metachromatic leukodystrophy (MLD) is a rare lysosomal storage disorder in which sulfatide accumulation leads to involvement of the peripheral and central nervous system. Since in most countries there is no newborn screening for MLD, new patients are mainly identified after they have developed symptoms. Brain MRI typically shows characteristic white matter changes, the diagnosis of MLD will subsequently be genetically and biochemically confirmed. Nevertheless, in the early or presymptomatic (PS) disease stage, the typical MRI changes might not be present with subsequent delay in the diagnosis. This study aims to describe the characteristics of MRI abnormalities at the time of first MRI, related to clinical presentation.

Methods: We retrospectively reviewed brain MRIs of patients with MLD, followed at Amsterdam UMC or Tübingen University Hospital. Included were normal, mildly, or moderately affected MRIs at diagnosis, regardless of whether patients were symptomatic or not. PS patients were defined as having no symptoms (identified through an affected sibling) or an isolated peripheral neuropathy.

Results: We included 50 brain MRIs from 35 late-infantile (LI, 10 PS) and 15 juvenile patients (12 PS). In early symptomatic LI patients, MRI did show first characteristic leukodystrophic changes (always including the corpus callosum) in only 14/25, despite clear CNS symptoms such as pyramidal signs. The other 11 had nonspecific mild T2 hyperintense signal changes. In contrast, 7/12 PS juvenile patients already showed characteristic changes, including corpus callosum involvement.

Conclusions: Patients with LI MLD, even with clear clinical signs of CNS involvement, may have no or mild, nonspecific abnormalities at brain MRI whereas in juvenile patients typical MRI signs are often present already before clinical signs. This might lead to significant diagnostic delay in patients with LI MLD. Thus, clinical signs such as stagnation of development and neurological signs need to guide diagnostic work-up.

Keywords:
Metachromatic leukodystrophy; MLD; MRI

EPNS21-554
Metabolic Disorders

Oral or poster

Cavitating leukoencephalopathy: a recognizable clinical-radiological pattern in patients with early-onset encephalopathy and hyperlactacidemia

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Objective: Cavitating leukoencephalopathy (CL) is an entity characterized by degeneration of the white matter in the brain, and most of the genes involved are related to energy metabolism defects.
The aim of the study is to describe the phenotype and genotype of a group of patients with CL, evaluated at the Metabolic Unit of a tertiary hospital.

Methods: Clinical, radiological, biochemical and genetic data of 4 patients fulfilling CL criteria were assessed.

Results: We describe 4 unrelated patients, 3 boys and 1 girl, age range: 1.2-13 years, consanguinity was present in 2/4 families. Perinatal history was unremarkable. All cases showed a normal neurodevelopment until age 7-12 months. Clinical onset was characterized by severe irritability and metabolic acidosis, followed by the loss of previously achieved developmental milestones. The evolution of the 4 patients showed a global developmental delay with spastic tetraparesis and epilepsy (2/4). Elevated blood and CSF lactate was present in all patients and an abnormal urine organic acids profile was found in one patient. Brain MRI showed diffuse bilateral white matter signal changes with cavities and cystic degeneration involving the corpus callosum, periventricular and subcortical areas. Targeted clinical exome revealed homozygous variants in LYRM7, NDUFS1 (2/4) and CTNND2 genes, which are related to mitochondrial complex-III, mitochondrial complex-I and neuronal development respectively.

Conclusions: CL is a recently described clinical-radiological entity. Our cohort broadens the genetic spectrum of the disease, as the CTNND2 gene had not been previously reported related to CL. The clinical presentation is homogeneous, with an early onset encephalopathy associated with hyperlactacidemia, with progression towards spastic tetraparesis. This clinical-radiological association should guide the work-up and genetic analysis, specially directed to energy metabolism defects.

Keywords:
Cavitating leukoencephalopathy, mitochondrial disorders, hyperlactacidemia

EPNS21-56
Metabolic Disorders

Oral or poster

PEX10 - Peroxisome biogenesis disorders: expanding phenotype. Clinical Case.

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Objective: Peroxisome biogenesis disorders in the Zellweger spectrum are a heterogeneous group caused by mutations in PEX genes, which can manifest a complex and wide spectrum of clinical phenotypes. Consequently, disease diagnosis and medical management are challenging.

Methods: We aim to describe the clinical and genetic features of a seven-year-old boy, with peroxisome biogenesis disorder related to PEX10 mutation.

Results: Second child of Brazilian non-consanguineous couple, unremarkable family history and uneventful gestation, was affected by progressive cerebellar ataxia since 5 years old and learning difficulties. Neurological examination showed mild mental retardation, nystagmus, dysartria, cerebellar ataxia and hypertonic lower limbs, without other pyramidal signs. Serial cerebral MRI exhibited progressive cerebellar atrophy. Extensive laboratory evaluation revealed elevations of C26:0 and C26:1, pristanic, phytanic and pipecolic acids. Sequencing of the PEX 10 gene revealed compound heterozygous mutations: (NM_153818.2) exon 1 c.2T>C (p.M1?) and exon 4 c.815_816delAC (p.H272fs) and both parents were confirmed to be heterozygous carriers. After the diagnosis he started dietary restriction of phytanic acid and supplements of the fat-soluble vitamins, ADEK. Currently, he is still able to walk independently with some difficulty. He also has hepatomegaly de novo and mildly elevated transaminases, without cholestasis.

Conclusions: Our case suggests that peroxisome biogenesis disorders should be considered in the differential diagnosis of autosomal recessive progressive ataxia with early onset. The current guidelines are meant to provide a starting point for the management of these complex conditions. The early diagnosis should prompt evaluation of appropriate treatments, such as bile acid supplementation and dietary restriction of phytanic acid, which have been reported at some extent to be effective in halting disease progression.

Keywords:
PEX10; peroxisome biogenesis disorder; ataxia

EPNS21-561 Poster only
Metabolic Disorders

Electro-clinical diagnosis of retinal dystrophy and early clinical clues in inherited metabolic disorders

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Objective: To describe clinical manifestations pointing to retinal dystrophy in children diagnosed with inherited metabolic disorders (IMDs) with neurological symptoms and retinal dystrophy confirmed by electroretinography (ERG).

Methods: we retrospectively analyzed IMD children evaluated from 2012 to 2021. The minimal data set included family history, age and visual symptoms at onset, clinical and ophthalmological signs, ERG and follow-up.

Results: The cohort includes 12 IMD children: peroxisomal biogenesis disorders (PBDs) (n.2); 5,10-methylene tetrahydrofolate reductase (MTHFR) deficiency (n.1); pyroglutamic acidemia (5-OXO)(n.1), congenital disorder of glycosylation(CDG1A) (n.1) and methylmalonic acidemia homocystinuria (MMHA+HCU) (n.7), including 1 prenatal diagnosis. In IMDs with post-natal diagnosis, the visual symptoms prompting to ERG were low vision in all children and nystagmus with or without photophobia in 6 MMHA+HCU and 2 PBDs. Mean onset age was 5 months. At follow-up all IMDs had visual function deterioration, allowing to blindness in 4 (3 MMHA+HCU, 1 PD). In MMHA+HCU, two clinical patterns were observed: early macular atrophy with visual acuity loss and cone-rod ERG pattern (n.2) and early diffuse retinal pigmentary changes with mild to moderate visual acuity loss, depending on age, and rod-cone ERG pattern (n.5). PBDs and CDG had severe early onset visual loss with rod-cone pattern at ERG. 5-OXO had late onset visual field restriction with mild visual loss and rod-cone ERG pattern. MTHFR deficiency had association with electro-clinical phenotype of early onset rod-cone dystrophy and RPGR genotype

Conclusions: IMDs are genetic conditions with multisystem involvement, including retinal degeneration. Low vision associated to nystagmus and photophobia are early clinical clues. ERG is useful to diagnose and characterize retinal dystrophy, particularly in patients with mild or not pathognomonic fundus changes, ensuring timely rehabilitation programs.

Keywords:
retinal dystrophy, electroretinography, visual acuity, nystagmus, metabolic disorders

EPNS21-562
Metabolic Disorders

Oral or poster

Progressive spastic paraparesis with crystalline retinopathy caused by a de novo mutation in *SPTLC2* causing a shift in substrate specificity of Serine Palmitoyl Transferase towards longer chain acyl-CoA's

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Objective: Presentation of a previously undescribed phenotype caused by a *SPTLC2* mutation.

Methods: An eight-year-old girl presented to the clinic with slowly progressive spastic paraparesis. She had normal intelligence and no dysmorphism. She was small for her age and had a low amplitude tremor in the hands and fasciculations of the tongue. MRI of the brain and the spine were normal but on fundoscopy a crystalline retinopathy was observed. Optical Coherence Tomography (OCT) showed thinning of the retina with loss of Müller cells and presence of small cysts.

Results: By WES we found a de novo mutation in *SPTLC2* coding for a subunit of Serine Palmitoyl Transferase (SPT). SPT catalyzes the first and rate limiting step of ceramide -and thus of sphingolipid- synthesis by joining palmitoyl-CoA and serine. SPT consists of 4 subunits coded by *SPTLC1* and *SPTLC2/3*, *SPTSSA/B* and *ORMDL3*. Mutations in *SPTLC2* were previously described as a cause for hereditary sensory and autonomic neuropathy (HSAN) IC, where a shift in substrate specificity from serine to alanine leads to accumulation of the neurotoxic deoxysphinganine (DoxSA). Recently mutations in *SPTLC1* were described in juvenile ALS without crystalline retinopathy and linked to sphingolipid overproduction. Similar to our case a combination of retinopathy and neurological regression is seen in the Stellar mouse. In this mouse model a missense mutation in Sptssb causes excess synthesis of sphingolipids with a 20-carbon long chain bases (LCB). Unlike patients with HSAN IC, our patient did not have an increase of DoxSA in plasma. Nonetheless, an increase in desoxysphinganine (DosSA) and desoxysphingosine (DosSO) (downstream products of glycine+palmitoyl) were seen. Moreover, similar to the Stellar mouse, the 20-carbon LCB forms of GlcCer, LacCer and Gb3 were increased.

Conclusions: We hypothesize that the *SPTLC2* mutation in our patient causes a shift in substrate specificity of SPT towards longer chain acyl-CoA's, explaining the different phenotype.

Keywords:
SPTLC2, HSP, spastic paraparesis, retinopathy, SPT, Serine Palmitoyl Transferase, Sphingolipid, ceramide

EPNS21-587
Metabolic Disorders

Poster only

The 1st national case of D-2-hydroxygloutaric aciduria 2

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Objective: D-2-Hydroxyglutaric Aciduria (D2HGA) is a rare neurometabolic disorder with a wide clinical spectrum ranging from asymptomatic to severely affected patients with intractable epilepsy, severe hypotonia and developmental retardation,cortical blindness as well as facial dysmorphic features. Associated MRI findings are ventricular enlargement, subependymal cysts, white matter abnormalities and cortical atrophy.

Methods: A 6 months old in vitro fertilized male twin sibling born at the 28th week of gestation, presented with seizures,hypotonia and drowsiness. Episodes of respiratory distress and feeding problems were also reported. The neurological examination revealed borderline macrocephaly, insufficient eye contact and severe developmental delay. EEG was abnormal and brain MRI demonstrated high signal white matter alterations in T2-weighted sequences occipitally,presence of subependymal cysts, moderately increased subarachnoid spaces and delayed myelination. Abdominal U/S showed bilateral pelvicalyceal dilatation and megaureter.

Results: Biochemical analysis was not diagnostic. Subsequent Whole Exome Sequencing (WES) analysis revealed heterozygosity for the pathogenic mutation c.419G>A (p.Arg140Gln) in the IDH2 gene, associated with D-2 hydroxyglutaric aciduria type 2 (D2HGA2). Further molecular testing of both parents was supportive of a denovo mutation. Upon diagnosis, carnitine and B2 supplementation was initiated, while antiepileptic drug therapy with different regimes resulted in a moderately beneficial effect.

Conclusions: D-2 hydroxyglutaric aciduria type 2 is a rare neurometabolic disorder with clinical heterogeneity. Supportive of a diagnosis are increased D-2 hydroxyglutarate levels in urine and a specific constellation of clinical and MRI findings, while definitively confirmative is molecular analysis by means of next generation sequencing. Up to now, there is no specific therapy for patients with D2HGA, while in most patients the prognosis is unfavorable with a truncated lifespan.

Keywords:
D-2-hydroxygloutaric aciduria 2, neurometabolic disorder

EPNS21-595 Oral or poster
Metabolic Disorders

Multimodal parametric MRI-based longitudinal and controlled study of a non-progressive case of aspartylglucosaminuria

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Objective: Intro. Aspartylglucosaminuria (AGU) is a rare inborn error of metabolism that impairs brain development and induces progressive decay over time. Brain MRI abnormalities (mild T2 hypersignal in the white matter, T2/T2* hyposignal in the thalami), have been described but remain poorly characterized. Taking advantage of progress in multimodal and parametric MRI, we propose to clarify these abnormalities by studying a single case matched to controls at 2-year intervals.

Methods: Methods. A yet nonprogressive patient was imaged at 16 and 18 years of age, matched to 3 controls (age, sex), with 3T T1-, T2- and Flair-weighted (3D 1mm isometric), qT1, qT2, qT2* relaxometry, and 64-direction b1500 diffusion (1.8mm isometric) MRI sequences. White matter masks of the lobes and cerebellum, deep gray nuclei and thalami, red nuclei, substantia nigra and pulvinar were obtained on 3DT1 images (VolBrain, probabilistic atlases, FreeSurfer) and parametric maps were estimated in all modalities. The distributions of values in these structures were compared (patient vs. controls and over time) by non-parametric testing.

Results: Results. The patient presented a global brain size reduction particularly marked on the thalami. Apart from a non-significant trend for the pallidi, there was no difference at 2-year intervals. Three multimodal abnormality patterns could be identified: (1) a reduction in qT2*>qT2 associated with an increase in qT1 throughout the deep gray, more significant for pallidi, (2) except in thalami where the reduction in qT2 and qT2* was associated with a significant reduction in qT1 and predominated in pulvinars, (3) a significant increase in qT1 throughout the white matter, sometimes associated with a slight increase in qT2 qT2* without diffusion anomaly (MD, FA).

Conclusions: Conclusion. Our study shows the feasibility of an individual quantitative analysis thanks to the tools available today and raises the question of the histopathological correlates of the 3 patterns of abnormality found during AGU.

Keywords:
MRI, parametric, metabolic disease, aspartylglucosaminuria, quantitative

EPNS21-601 Poster only
Metabolic Disorders

Glutamine treatment in glutamine synthase deficiency

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Objective: To describe a case of glutamine synthase deficiency and the effect of glutamine treatment.

Methods: Case study

Results: The clinical and biochemical course of a girl with glutamine synthase deficiency is described. She is treated with per oral glutamine treatment every 2 hours(with a 6-hour pause during night), gradually increased to a final intake of 1,25 mg/kg/d. So far, now 3 years old, she has been doing quite well. She is seizure free on levetiracetam, moving independently and interacts with other children. Her speech development is delayed, using one-word sentences. There are no signs of involvement of other organs.

Conclusions: Per oral glutamine treatment in the otherwise devastating disorder glutamine synthase deficiency may effectively alleviate symptoms.

Keywords:
GLUL; glutamine synthase deficiency; glutamine treatment;

EPNS21-62 Poster only
Metabolic Disorders

A CASE WITH CONGENITAL DISORDER OF GLYCOSYLATION WITH DEFECTIVE FUCOSYLATION 2 AND NEW MUTATION IN FUK GENE

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Objective: Congenital disorders of glycosylation (CDG) is a group of rare, hereditary, multisystem disorders, predominantly affecting nervous system. There are N- and O- types of glycosylation. Fucosylation, a form of N-glycosylation, involves many enzymes. Until today, type 1 and type 2 fucosylation defects were identified, having pathogenic variants in genes encoding 1,6-fucosyltransferase and fucokinase enzymes, respectively. In this article, a patient with type 2 fucosylation defect will be presented, with hypotonia, developmental delay and blindness and a pathogenic variant that was previously described in two patients.

Methods: Whole exome sequencing (WES) was performed, since the patient had no time to implement diagnostic algorithm for hypotonia etiology.

Results: WES revealed a new pathogenic variant of homozygous c.993_1011del (p.Glu335Hisfs*55) frameshift variant of the FUK gene NM_145059 transcript. She had milder clinical manifestation than reported two patients.

Conclusions: Congenital Defect of Glycosylation should be considered when the clinical findings cannot be explained by other known diseases, particularly in patients with multisystemic, predominantly neurological involvement.

Keywords:
Congenital Defect of Glycosylation, Type2 Fucosylation Defect, Hypotonia, Developmental Delay

EPNS21-624
Metabolic Disorders

Oral or poster

Hamburg iNCL scale: A new tool for the quantitative description of disease progression in infantile CLN1 patients

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Objective: Neuronal ceroid-lipofuscinosis type 1 (CLN1) disease is caused by deficiency of the lysosomal enzyme palmitoyl-protein thioesterase 1 (PPT1). The classic infantile phenotype in CLN1 represents the most rapidly progressive form among all NCL phenotypes.

Methods: N=14 infantile CLN1 patients (4 female, 10 male) were followed longitudinally. Diagnosis was confirmed by genetic and enzyme activity testing. Mean age at symptom onset was 10.8 months (SD 4.2). First symptom was motor developmental delay in n=12 out of the total 14 patients, followed by language developmental delay. Only 1 of the 14 patients ever achieved the ability to walk without support. N=7 patients learned single words with low word count, n=7 patients only attained monosyllables as maximum language function. This low level of maximum developmental function differs significantly from all other NCL phenotypes. Consequently, already established rating scales cannot be applied as these do not meet criteria for scoring the defined level of maximum function. A new adapted rating scale for quantitative description of disease progression in infantile CLN1 patients was developed. Consisting of three main functional domains (gross motor function, fine motor function, and expressive language) and six clinically meaningful categories (communication & interaction, visual attention, irritability & agitation, seizures, sleep, and feeding), function can be scored retrospectively and prospectively.

Results: Our longitudinal data showed that mean age of first regression was 19.7 month (SD 2.1) for gross motor function and 18.5 month (SD 2.0) for expressive language function. Total loss of gross motor function occurred at a mean age of 32.3 month (SD 6.7), total loss of expressive language at mean age of 24.3 month (SD 5.6), respectively.

Conclusions: We have developed a clinical scoring system for infantile NCL patients for robust quantitative description of disease progression. On the basis of our results, effects of future therapies may be evaluated.

Keywords:
NCL, CLN1, infantile phenotype, Battens, PPT1

EPNS21-658
Metabolic Disorders

Oral or poster

Natural history of CLN7 disease: Quantitative prospective assessment of disease characteristics and rate of progression

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Objective: Neuronal ceroid-lipofuscinosis type 7 (CLN7) disease is caused by deficiency of the MFSD8 protein. Affected patients present with a late infantile and variant late infantile phenotype characterised by language developmental delay, psychomotor decline, epilepsy, and vision loss. Data on the natural history of this rare disease are very limited. However, with emerging experimental therapy approaches such as AAV-mediated gene therapies, such data are urgently needed in order to assess treatment efficacy.

Methods: We analysed a cohort of n=12 genetically confirmed CLN7 patients (7 females, 5 males) with regard to age at diagnosis, age at symptom onset, and type of first symptoms. In addition, we followed these patients longitudinally in our NCL clinic to assess progression of disease. Analysis of disease progression was performed similar to ongoing clinical trials in other NCL diseases with late infantile phenotypes using the motor and language domain of the Hamburg late infantile clinical rating scale (ML score) which quantifies the loss of motor and language function on a scale from 6 (normal function) to 0 (no function left).

Results: Mean age at first clear symptom of disease was 45.3 months (SD 17.4). Genetic diagnosis was at a mean age of 73.4 months (SD 22.8). Motor problems were the most common first symptom in n=9 patients, followed by language delay in n=8 patients. Of note, 3 patients presented with vision loss as first symptom which is unusual for late infantile phenotypes in other NCL diseases.

Conclusions: CLN7 disease presents with both, late infantile as well as variant late infantile phenotypes. Therefore, first symptoms might differ, diagnosis is often delayed and disease progression varies from other late infantile NCL phenotypes.

Keywords:
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EPNS21-68 Oral or poster
Metabolic Disorders

Biochemical studies in fibroblasts to interpret variants of unknown significance in the ABCD1 gene

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Objective: Due to newborn screening for X-linked adrenoleukodystrophy (ALD), and the use of exome sequencing in clinical practice, the detection of variants of unknown significance (VUS) in the ABCD1 gene is increasing. In these cases, functional tests in fibroblasts may help to classify a variant as (likely) benign or pathogenic. For these tests to have a better predictive value, a well-defined control and ALD range is crucial, but not yet available. We sought to establish reference ranges for these tests in ALD patients and controls with the aim to help determine the pathogenicity of a VUS in ABCD1.

Methods: Fibroblasts from 36 male patients with confirmed ALD, 26 healthy control subjects and 17 individuals with an uncertain clinical diagnosis and a VUS identified in ABCD1 were included. We performed a combination of tests: very long-chain fatty acids (VLCFA) levels, D3-C22:0 loading test to study VLCFA metabolism and immunoblotting for ALD protein, and established disease and control ranges for these tests.

Results: All ALD patient fibroblasts had elevated VLCFA levels and reduced peroxisomal ß-oxidation capacity (as measured by D3-C16:0/D3-C22:0 ratio in the D3-C22:0 loading test) compared to controls. Of the 17 VUS cases, VLCFA metabolism was not significantly impaired (most test results in the control range) in 6/17, VLCFA metabolism was significantly impaired (most test results in/near the ALD range) in 9/17 and a definite conclusion could not be drawn in 2/17.

Conclusions: Biochemical studies in fibroblasts provided clearly defined control and disease ranges for VLCFA metabolism. In 15/17 (88%) VUS we were able to classify the variant as likely benign or pathogenic. This is of great clinical importance as the insecurity of a possible ALD diagnosis is a major burden for patients and their families. Furthermore, new variants will be detected and the array of functional tests described here will allow the confirmation (and rejection) of ALD diagnosis with more certainty.

Keywords:
peroxisomal disorders, fibroblasts, adrenoleukodystrophy, variants of unknown significance, newborn screening

EPNS21-684 Poster only
Metabolic Disorders

THE ROLE OF TRNA SYNTHETASES MITOCHONDRIALS IN NEUROLOGICAL DISEASES. DESCRIPTION OF CLINICAL PHENOTYPE.

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Objective: Objectives
-The main objective is to describe the biochemical, radiological and clinical phenotype.
-We want to expand our knowledge about these diseases with a bibliographic search to create a classification.

Methods: Methods:
-We carried out a retrospective observational study looking for mutations in genes associated with mt-ARS deficiencies, detected by NGS sequence at the Sant Joan de Déu Hospital from 2010 to 2020.
-We performed a bibliographic review of publications made in Pubmed/Embase of published articles and through references in publications recovered until November 2020 of all patients reported with pathogenic mutations encoding by ARS2 genes.

Results: Results:
-We found 9 patients with mutations in heterozygous status in genes reported to be associated with defects in ARSs (FARS2,RARS2,PARS2,IARS2,WARS2 and DARS2).
-We made a bibliographic review founding 472 pediatric patients.The clinical characteristics were described and have been classified into ranges of prevalence.

Conclusions: Conclusions
-Report our experience in patients with mutations in tRNA synthetases, with the objective of broadening the clinical phenotype.
-Analyze the bibliography to described up to the moment of publication, we created a classification offering the possibility to a diagnostic approach.
- A patient with a FARS2 mutation with an undescribed progressive myoclonic epilepsy phenotype is reported.

Keywords:
tRNA, mitochondia, ARS2

EPNS21-686 Poster only
Metabolic Disorders

Episodic hyperammonemia in a biallelic mutation of TMEM70. A case review.

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Objective: To review an uncommon cause of recurrent hyperammonemia.

Methods: Case review

Results: The patient was the son of non-consanguineous Chilean parents. He was born at 36th gestational weeks with a low birth weight (1.875 g.). He has down-slanting palpebral fissures, curved eyebrows and hypospadias. In infancy he fail to thrive, showed mild hypotonia and moderate developmental delay. At the age of 29 months he presented the first metabolic crisis with no detected trigger, characterized by moderate rise in blood ammonia (385 ug/dl), metabolic acidosis (pH 7.2), mild hyperlactacidemia (77 mg/dl), and hyperketonemia. At 39 months old during a respiratory infection he presented with ammonia elevation of 513 ug/dl, mild metabolic acidosis, mild hyperlactacidemia (44 mg/dl), and hyperketonemia. Analysis of critical samples showed a normal acylcarnitines and aminoacid profile, and normal organic acids and orotic acid in urine. Molecular study determined that the proband was compound heterozygous for two null variants in TMEM70 gene, a splicing aceptor variant (c.317-2A>G) in the maternal allele and a start-loss variant (c.2T>C) in the paternal allele. The patient has nutritional treatment, L-Carnitine, CoEnzyme Q10 and careful monitoring. Since then he has been free of metabolic crises.

Conclusions: Human mitochondrial (mt) ATP-synthase, known as respiratory chain complex V, is the final step to ATP production. TMEM70 mutations are a common cause of nuclear ATP synthase deficiency. The known phenotypes include facial dysmorphism, neonatal hypotonia, hypertrophic cardiomyopathy (HCMP), lactic acidosis and hyperammonemia. We report the case of a five years old boy in which recurrent hyperammonemia was the main clinical manifestation.
Discussion: The presence of episodic hyperammonemia in patients with developmental delay and dysmorphic features should raise the suspicion of ATP-synthase deficit. To the best of our knowledge, this is the first case of biallelic TMEM70 mutation reported in Chile.

Keywords:
Episodic hyperammonemia TMEM70 gene, developmental delay, ATP-syntase deficiency

EPNS21-687 Poster only
Metabolic Disorders

D-bifunctional protein deficiency: a case report

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Objective: D-bifunctional protein (PDB) deficiency is a very rare progressive peroxisomal disease, which affects the metabolism of very long chain fatty acids (VLCFA). This article presents our experience in a patient affected by this rare disease and reviews the forms of presentation, management and evolution.

Methods: Single case from a tertiary hospital with access to extended metabolic study and genetic study of the patient.

Results: This is a 40-week gestational age neonate of consanguineous parents. Admitted for hypoglycaemia, hypotonia, feeding difficulties and multifocal clonic seizures. Phenotype with mild retrognathia, low-set ears, separated nipples and bilateral cryptorchidism. He also had associated hepatomegaly. Absence of visual tracking, global hypotonia with areflexia without clonus. Cranial MRI showed a subtle alteration of the supratentorial white matter, predominantly occipital and frontal, with respect for the cerebellar white matter. Laboratory tests showed evidence of adrenal insufficiency and elevated plasma VLCFA, phytanic and pipecolic acid, polyunsaturated, arachidonic and docosahexaenoic acids with normal erythrocytes. Plasma primary bile and trihydroxycholestanoic acids were elevated. Erythrocyte plasmalogens were slightly low. Suspecting a peroxisomal disease, a targeted gene panel was performed and showed a pathogenic homozygous c.1369A>T (p.Asn457Tyr) mutation of the HSD17B4 gene

Conclusions: The described c.1369A>T defect of PDB causes an identifiable severe neonatal picture which associates hypotonia, seizures, hypoglycaemia, diffuse white matter involvement and elevated VLCFA that can be genetically confirmed

Keywords:
D-bifunctional protein deficiency,peroxisomal disease, metabolic disease

EPNS21-691 Poster only
Metabolic Disorders

NEONATAL MOLYBDENUM COFACTOR DEFICIENCY: ELECTROENCEPHALOGRAPHIC PATTERNS

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Objective: To characterize EEG features in neonates and young infants with Molybdenum Cofactor Deficiency (MoCD), that can lead to early diagnosis of this disease. Literature reports only burst-suppression pattern or encephalopathy with multifocal discharges in the EEGs of patients with MoCD, but to date no specific EEG findings have been described.

Methods: Retrospective search of the EEG database and the metabolic database from 2002 to 2020 at GOSH (UK) and Ferrara (IT). Patents with a confirmed diagnosis of MoCD and at least 1 EEG were included and their EEGs analysed. Ictal and interictal EEG abnormalities were classified according to American Clinical Neurophysiology Society (Tsuchida et al. 2013). Seizures were classified according to the ILAE (Pressler et al. 2021).

Results: Eleven infants with MoCD (6 males) aged 1-120 days were included (7 neonate). In the neonatal period the background activity was abnormal in all with burst-suppression (n=4), excess discontinuity (n=3) and dysmaturity features (n=11). Seizures were recorded in all neonates (n=7) at 1-18 days which were electrographic-only in 6 and electro-clinical in 1 (focal clonic), with high seizure burden and resistant to treatment. Ictal EEG pattern consisted predominantly of rhythmic delta frequencies with recruitment, arising independently from the central regions. Infants outside the neonatal period had lower seizure burden. A unique Delta-crown pattern (high amplitude delta transients with ripples of superimposed fast activity) was observed in 7 patients between 3 and 74 days of life. Delta-crowns were seen over the central regions and frequency increased at times of seizures.

Conclusions: EEG is a valuable biomarker in MoCD. The possibility of MoCD needs to be explored in a neonate with progressive encephalopathy and the typical EEG makers (Burst-suppression or discontinuous background, delta-crown pattern and high seizure burden).

Keywords:
MoCD, EEG, Delta-crown

EPNS21-692 Oral or poster
Metabolic Disorders

Mucolipidosis type II/III: rare diseases that should be addressed in different clinical settings

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Objective: Characterize clinical manifestations of children with MLs II andIII followed at a referral center for neurometabolic diseases, in Barcelona, between 2000-2019.

Methods: Eight patients with ML and their clinical data were analyzed.

Results: 8 patients (ML II=3, ML III alfa/beta=3, ML III gamma=2) were recruited from 7 unrelated families, 2 with parental consanguinity. Predominant clinical presentations were skeletal symptoms. All showed high levels of lysosomal acid hydrolase enzymes in plasma and/or reduced in fibroblasts. MLs II/III was confirmed by identification of pathogenic variants in GNPTAB/GNPTG. ML II patients showed the most severe clinical phenotype and diagnosis was detected sooner, with initial symptoms in early childhood: low weights, joint restriction in upper and lower limbs, scoliosis, coarse facial features, gingival hypertrophy and developmental delay. Both with cardiologic manifestations, only 1 with hypoacusis, craniosynostosis and hepatosplenomegaly, the same who had a fatal outcome at 4, due to cardiorespiratory failure.
In ML III alfa/beta patients, first symptoms were at 2-3 years-old with progressive stiffness, pain in multiple joints and coarse facial features. Other skeletal alterations were increase of kyphoscoliosis and pectus carinatum. Only 1 showed mild cognitive impairment.
ML III gamma patients were sisters from consanguineous parents with subtle coarse facial features, gross motor developmental delay detected at 2 and 4, and developed non-painful joint stiffness in multiple joints. They undergo surgery of bilateral carpal tunnel syndrome.

Conclusions: ML should be considered in cases of joint stiffness. The differential diagnosis of ML II or III is based on age of onset, clinical findings and degree of severity. The early diagnosis especially in ML II is an opportunity to bone marrow transplant, a promisor therapy.

Keywords:
Mucolipidosis, lysosoma

EPNS21-11 Oral or poster
Miscellaneous Topics

IMPACT OF COVID-19 LOCKDOWN ON CHILDREN WITH CHRONIC NEUROLOGICAL DISEASES IN ENUGU, NIGERIA

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Objective: To understand the impact(health,cognitive,economic and psychological)of the lockdown for the COVID-19 pandemic on children with chronic neurological disorders in Enugu, Nigeria

Methods: A focused group discussion of caregivers and children with chronic neurological conditions registered at the paediatric neurology clinic of University of Nigeria Teaching Hospital was conducted.Seven caregiver-patient pairs participated in the discussion.

Results: Access to Quality Health Care Services: There was limited access to consulting physicians in the hospital to review the child's health status, and lack of money to purchase drugs as parents' means of livelihood were disrupted.
Access to Learning and Learning Materials: Findings indicated that children seemed to have forgotten what they learnt in the previous academic period. Some of the children have torn their books, given that learning tutors gave out the books for children to practice at home.
Impacts on the Child's Family Livelihood: The lockdown policy imposed hunger in the households as parents couldn't attend to their various jobs. Households rarely eat recommended daily servings and mix of food. Some of the caregivers lost their jobs, others had their shops and businesses locked down, leading to inability to contribute money for household feeding.
Access and Adherence to COVID-19 Infection Prevention and Control Guidelines: Children had access to cloth face mask. However, children seldom adhere to the use of facemask when necessary. Regular hand washing was common. Only one participant reported availability and use of hand sanitizer.
Psycho-social Consequences: The lockdown of worship centers conferred a sense of anger, frustration, and hopelessness among some of the participants. Caregivers believed they lost social interactions including drinking with friends.

Conclusions: The COVID-19 lockdown had untoward effects in the lives of children with chronic neurologic illnesses requiring the development of well adapted local strategies to mitigate them.

Keywords:
COVID-19, LOCKDOWN, IMPACT, NEUROLOGY, NIGERIA

EPNS21-190 Oral or poster
Miscellaneous Topics

Childhood and Adolescent Sleep Awareness in Caregivers and Health care Professionals: A Community and Hospital Based Survey

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Objective: To develop validated questionnaires to evaluate childhood and adolescent sleep awareness in caregivers (CGs) and healthcare providers (HCPs)

Methods: The study population comprised of CGs (parents of children aged 2 to 18 years attending a public school and of those attending outpatient services at a tertiary care teaching hospital) and HCPs (medical interns and nursing graduates within 1 year of graduation).
The questionnaires were developed and validated by content, face and construct validation. Internal consistency was expressed using Cronbach alpha. Awareness was expressed as proportion of correct responses in the final questionnaire.

Results: The domains of the questionnaires were
a) sleep hygiene (10 items),
b) primary sleep and systemic disorders (25 items) and
c) miscellaneous (4 and 10 items in CGs and HCPs respectively).
The questionnaires were applied on 313 CGs and 175 HCPs (110 medical interns and 65 nursing graduates). The Cronbach alpha for the CGs and HCPs were 0.73 and 0.74 respectively. The kappa agreement between knowledge and practice in CGs was 0.2. The proportion of correct responses in domains a and b were comparable in CGs and HCPs (57.4-77.5%). Both the groups performed poorly on questions related to insomnia, hypersomnia, circadian rhythm disorders, parasomnia and obesity. CGs were poorly aware regarding the impact of sleep on scholastic performance. HCPs performed poorly on basic questions related to theory of sleep.
For consultation of sleep problems, 48% CGs chose pediatricians, followed by neurologists and family physicians (15% each). Only 5% CGs ever talked about their child's sleep to a doctor and only 10% of them were ever enquired by a doctor regarding the same.

Conclusions: Comparable awareness in both CGs and HCPs indicate underexposure of sleep topics in undergraduate curriculum of HCPs, which should be strengthened. CGs need to be sensitized regarding components and importance of appropriate sleep habits in children and adolescents.

Keywords:
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EPNS21-2039 Oral or poster
Miscellaneous Topics

Delphi consensus for the UK guideline for management and surveillance of Idiopathic Intracranial Hypertension in children and young people

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Objective: Idiopathic Intracranial Hypertension (IIH) is associated with headaches and a potential loss of vision. The prevalence may rise with childhood obesity. As there is no strong evidence to support the way IIH is diagnosed or treated, it is important to establish consensus to guide management and identify areas of uncertainty for further research. We conducted a national Delphi consensus process to inform a national guideline for the management of IIH in children and young people.

Methods: The Delphi focused on all aspects of IIH including initial assessments (referral, assessments, laboratory tests, LP, ophthalmology assessments), diagnosis (criteria and terminology) and treatment (including conservative, drug and neurosurgical interventions), follow-up, and surveillance.

General paediatricians, paediatric neurologists, ophthalmologists, opticians, neuroradiologists, and neurosurgeons known to have a clinical interest or experience in IIH were invited to take part.

The charity IIH-UK contributed to represent patients and their families. A priori consensus was defined as 70% agreement.

Results: Recommendations are proposed, based on areas of consensus and relate to aspects of IIH patient management, including: timing of assessment, baseline assessments including investigations, preferred diagnostic criteria, LP and CSF pressure interpretation, use of neuroimaging, structure and function of MDT meetings, ophthalmological assessments, methodology for LP (including local and general anaesthetic considerations), management of diet, acetazolamide and neurosurgical options. (For detail please refer to Table 2)

Conclusions: This new UK consensus for the management and surveillance of IIH provides a realistic and pragmatic approach, based on expert opinion for best clinical care for children and young people with IIH. We hope these recommendations will minimise under and over diagnosis, improve the care offered, and outcomes obtained.

Keywords:
Idiopathic Intracranial Hypertension, Pseudotumor Cerebri Syndrome, Headache, Lumbar Puncture, Acetazolamide

EPNS21-2065 Poster only
Miscellaneous Topics

A Non-Verbal Child Presents irritable: A silent but deadly diagnosis initially undiscoverable?

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Objective: Children with communication difficulties often pose a diagnostic dilemma. This subsequently leads to a loss of lead time and later presentation. We present a case of such medically complex non verbal who presented with nonspecific findings that eventually led to an inconspicuous diagnosis.
Through this case report,we emphasize on the importance of thorough history taking and a detailed clinical examination.

Methods: A 5-year-old nonverbal child with a background of Cerebral Palsy with dystonias, GERD(Peg In-Situ), Epilepsy, Global Developmental Delay, Hydrocephalus with VP Shunt, Chronic Lung disease and Obstructive Sleep Apnoea presented to our day unit. Throughout the past year, he had been on multiple antiepileptic drugs including Levetiracetam, Oxcarbazepine, Sodium valproate- and Diazepam.

The patient had presented multiple times in the span of a few months to the day unit with increased irritability, cough, worsening dystonias and increase in seizure activity. Additionally on this occasion he presented with a high pitched cry and ''Screaming in pain''; Mum wondered if his dystonias were getting worse.

Results: On examination he had conducted respiratory auscultation notes and a tense abdomen, tender with sluggish bowel sounds. Bloods demonstrated hyponatremia, CRP<4 (increased to 134 within 24 hours repeat) , Amylase 1276(30-118), Lipase 794 (13-60), thrombocytosis(554), PT 15 sec. Here we deduced a possible diagnosis of Drug induced pancreatitis and discontinued Oxcarbazepine and Valproate with introduction of new safer drugs, which improved the child's condition.

Conclusions: This was a rare phenomenon of Drug induced pancreatitis, complicated by the communication barriers in non-verbal children. We are reporting this case as a learning point for maintaining a high index of suspicion for possible abdominal morbidities in these patient populations. Good physical examination is useful in such cases, as CT scans need to be avoided for pediatric population due to radiation exposure.

Keywords:
Acute pancreatitis; Seizures; Anti-epileptics; Valproic acid-VPA; Trileptal-Oxcarbazepine

EPNS21-2083 Poster only
Miscellaneous Topics

An Unusual Cause of Gait Disturbance in a 4 Young Child

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Objective: PRKN (parkin) gene is responsible for Juvenile Onset Parkinson's Disease Type. It is a slowly progressive disease, with typical Parkinsonian features incl. bradykinesia, tremor, rigidity. The median age of onset is in the third decade,however cases presenting from 3-81 y. have been described. This case describes a young boy who presented initially with lower limb focal dystonia,he was subsequently diagnosed with heterozygous pathogenic PRKN mutations.

Methods: A 3 y./9 month old boy was admitted with a one week history of lower limb "pain" and gait disturbance.

Results: His medical, developmental and family histories were unremarkable.His cranial and peripheral nerve exams were normal. Gait examination was markedly abnormal. He had abnormal posturing of the left lower limb, was unable to jump or hop, had unsteady tandem gait and was unable to tip toe walk. He was diagnosed with left lower limb focal dystonia. Baseline investigations and imaging were unremarkable. A dystonia genetic panel was sent and demonstrated heterozygous pathogenic PRKN mutations; c.101_102del p.(Gln34fs) exon 2 (present in paternal sample) and c.823C>T p.(Arg275Trp) exon 7 (present in maternal sample), thus confirming a diagnosis of Juvenile Onset Parkinson's Disease and parental carrier status.Currently, the patient demonstrates upper and lower limb dystonia on ambulation, but typical Parkinsonian features have yet to develop 18 months post initial presentation.

Conclusions: It is an unusual case given the extremely young age at presentation and lower limb focal dystonia as presenting feature. Lower limb dystonia has been described as a presenting feature in Juvenile Onset Parkinson's Disease previously in older patients and may remain isolated for years. The treatments for this condition are similar to other forms of Parkinson's Disease. Anti-cholinergic agents have been used to control symptoms with some success in order to delay the commencement of levodopa which can commonly result in dyskinesia and motor fluctuation

Keywords:
gait disturbance, case report

EPNS21-225 Oral or poster
Miscellaneous Topics

Family resilience in CLN3 disease (Juvenile Battens Disease)

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Objective: Family resilience is the capacity of the family to withstand and rebound from stressful life challenges. The aim of the current study was to investigate if the experiences of parenting a child with CLN3 can be related to family resilience theory.

Methods: Semi-structured interviews were conducted with eight parents (five mothers and three fathers) of five children with CLN3. Interview questions focused on the experience of having a child with CLN3 and its relationship with the concept of family resilience. Data was analysed via thematic analysis.

Results: Families described recurring losses following the diagnosis of the child in terms of the child's health and abilities and loss of relationships. The illness caused disruption to the family system and took time from siblings and the couple relationship. The social care system was described as inflexible in relation to progressive disease, while the paediatric health care system was seen as supportive. We found however, that family resilience theory was applicable to the parents' experiences and that it was possible to identify expressions of resilience. Parenting a child with CLN3 can bring together and strengthen the family system through a unified view and insights into what is important. In the current study most parents managed to create meaning in a difficult situation. Additionally, affected families show flexibility and positively adapted to the new situation. With respect to communication and problem solving, open emotional sharing and collaborative problems solving were evident but was not possible in all families.

Conclusions: Whilst CLN3 places a very significant burden on the family system it was possible to identify examples of family resilience. The concept of family resilience may be useful in understanding the experiences of, and supporting families affected by CLN3 and other paediatric neurodegenerative conditions.

Keywords:
children, progressive disease, resilenece

EPNS21-231 Poster only
Miscellaneous Topics

Etiologies of Lumbar Puncture Refusal in Pediatric Patients in Children's Hospital.

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Objective: To assess the misunderstanding regarding LP among parents in Taif city.

Methods: A cross sectional study was done on 687 parents of children who required LP procedure from birth till the age of 18 in Taif Children Hospital from January 2020 to February 2020. Data about participants demographics, ever been asked to take a sample of the cerebrospinal fluid (LP) of the child, circumstances related to this event were collected. For those who were not asked a question of if it was needed to take a sample of the cerebrospinal fluid of one of your children, will you agree.

Results: 15.7% of parents were asked to take a sample of the cerebrospinal fluid of one of their children, of whom, 61.2% agreed, with the average age of the child at the LP being 2.24 ± 3.28 years. A consultant discussed the LP technique to 37.8% of them, and 86.5% and 56.2% said the doctor clarified the nature and complications of the treatment to them. For parents not asked for LP before, 41.4% will not agree to it in the future. For parents who refused LP when indicated and those refusing it in the future, the most common causes were the side effects such as paralysis (60.6%), pain (11.3%) and no trust in HCWs and fear of medical errors (10.9%). For them, the most common sources of refusal were information from friends and relatives (41.2%).

Conclusions: Only 15.7% of parents were asked to collect a sample of their child cerebrospinal fluid, of them 61.2 % accepted. A consultant discussed the LP technique to 37.8% of them, and 86.5% and 56.2% said the doctor clarified the nature and complications of the treatment. The main causes of LP refusal were the side effects such as paralysis, pain, and lack of trust in HCWs and fear of medical errors.

Keywords:
etiologies, LP, refusal, pediatric, Taif, Saudi

EPNS21-26 Oral or poster
Miscellaneous Topics

Effect of lockdown due to COVID-19 pandemic on the children with neurodisabilities

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Objective: The COVID-19 pandemic and the lockdown imposed by most of the governments because of it have affected most of us including children with complex care needs. Because of various reasons like changed routine and social isolation, the physical and psychological health of these children has been affected.

Methods: We selected a cohort of children who usually attend 'Al Noor Training Centre for Persons with Disabilities' which is a specialised center in Dubai, where they usually received regular educational and therapeutic service from the multidisciplinary team members. During the lockdown period due to the COVID-19 pandemic, these children had to stay home and continue their sessions through a tele-rehabilitation program. Any new symptoms in these children were reported by the parents or the interventionist to the research team. These children were assessed by the professionals like paediatric neurologists in able to analyse the new reported symptoms to form an appropriate management plan.

Results: All children had some form of sleep impairment. New onset behavioural problems like aggression, being violent and headbanging were observed in 19 children (79%). 4 (16%) children needed evaluation by psychiatrist while all of them were seen by clinical psychologist. A third of these children were diagnosed to have anxiety. Among them 63% had pre-existing Autistic spectrum disorder. 63% had tension type headache. Two (8%) presented with new-onset seizures which were non-epileptic. New-onset motor tics were observed in 8% while vocal tics were seen in 33% children.

Conclusions: The children with special care needs are also at a higher risk of having a negative impact on their well-being during the lockdown period due to the COVID-19 pandemic and can have added physical and mental health issues. Sleep impairment seems to be the most common issue. Identifying such symptoms in these children can be difficult. But it is important to manage them effectively to mitigate the negative consequence of them.

Keywords:
COVID-19, lockdown, neurodisability, intellectual disability, sleep

EPNS21-273 Poster only
Miscellaneous Topics

Global white matter metabolite ratios predict longitudinal outcome after pediatric TBI

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Objective: The rapid acceleration-deceleration motion in traumatic brain injury (TBI) generates widespread mechanical shearing forces resulting in diffuse axonal injury and downstream metabolic consequences. This mechanism predisposes regions with high axon density (i.e. white matter (WM) to greater burden of injury. Metabolite changes are well described in adult TBI, however less is known about the longitudinal consequences in the pediatric population. The purpose of this study was to evaluate the prognostic ability of global WM and GM metabolite ratios following pediatric TBI and their relationship to 12-month neuropsychological assessments of IQ, attention, and memory.

Methods: We acquired 3D proton magnetic resonance spectroscopic imaging (MRSI) in pediatric patients with complicated mild (cMild), moderate, and severe TBI acutely (6-17 days) and 12-months post injury and compared these findings to age-matched normal developing adolescents. A global linear regression model, co-registering MRSI metabolite maps with 3D high resolution magnetic resonance images was used to identify longitudinal white and gray matter metabolite ratio changes.

Results: Acutely, GM NAA/Cr, WM NAA/Cr and WM NAA/Cho ratios were significantly lower in all TBI groups, compared to controls (ANCOVA, p 0.02). GM NAA/Cho was reduced only in the severe TBI group (p 0.001). At 12 months, all metabolite ratios normalized to control levels in each of the TBI groups (Figure 1). Acute GM and WM NAA ratios were strongly correlated to 12-month assessments of IQ, attention, and memory (Pearson correlation with FDR, $q < 0.001$).

Conclusions: These findings suggest that whole brain GM and WM metabolite ratios reflect longitudinal changes in neuronal metabolism following TBI, which can be used to predict neuropsychological outcome in pediatric patients.

Keywords:
magnetic resonance spectroscopy, pediatrics, traumatic brain injury

EPNS21-276 Oral or poster
Miscellaneous Topics

Outcome of children being referred to Paediatrics A&E as Papilledema in a DGH. Are all these cases reflecting true raised intracranial pressure?

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Objective: We aimed to evaluate the true incidence of papilledema, confirmed by Paediatric ophthalmologist.

Methods: We conducted a retrospective notes review of all paediatric patients aged between 0 and 16 years referred as "papilledema" to Paediatric A&E from August to December,2020

Results: A total of 16 children were included in the study with 10 girls and 6 boys. Mean age was 9 years, ranging from 4-14 years-old.

15 children were referred by ophthalmology to Paediatrics A&E, out of which, 9 children were referred from optometrists and the remaining(6) were identified during routine ophthalmology appointment. One child presented to A&E with headache.

Presenting complaints were: asymptomatic (n=8), headache (n=4), blurred vision(n=2) and 2 with headache and blurred vision. All 16 children had normal neurological examination and had urgent MRI head. 15 MRI scans were normal and 1 child had demyelination which is being jointly managed with regional Neurology unit.

14 children from our cohort were seen in Paediatric clinic and 11 were discharged to further ophthalmology care and 3 are being managed with tertiary hospital.

The remaining 2 children are awaiting clinic appointment but had telephone review.

Till now, 6 of 16 children were seen by Paediatric Ophthalmologist. While 3 children had Grade 1 papilledema and under follow-up, remaining 3 children had normal disc and been discharged.

Conclusions: Majority of children referred as"papilledema" by optometrist, do not have significant pathology on specialist review. Increased referrals for suspicious optic-discs but with normal examination, results in anxiety. We, therefore suggest a pathway where there is a joint neurology and paediatric ophthalmology clinic. All children referred as "papilledema" can be assessed and if confirmed as true papilledema, then we would consider imaging and further tests including LP for CSF pressure.Further follow-up will depend on the aetiology of papilledema. Robust prospective audit will be implemented to evaluate above pathway.

Keywords:
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EPNS21-291 Poster only
Miscellaneous Topics

Neurological deterioration caused by presumed leukodystrophy in a child with cerebral palsy: a case report

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Objective: Genetic mimickers of cerebral palsy had been previously described. Rare phenotypes of developing of progressive disorder in children with pre-existing brain injury are reported sporadically.

Methods: Case report

Results: A boy, 5yo with history of cerebral palsy had been referred due to loss of motor skills, communication, and speech between 3 and 4 y of life.
Born on 30th week of gestation, 1300g, Apgar score 6. First 3 weeks he spent at ICU, 2-3 grade IVH had been diagnosed. His development was delayed: he controlled his head since 12mth, rolled at 2,5y, started to speak at 1,5 y, knew and said all words by 2y, up to 3y speech continued to develop. At 3 years he started to lose phrases and words, concentrated only on cartoons and ignored people. Since age of 4 y his speech reduced to sounds. At presentation the boy does not perform any communication, shows no interest to the play or toys, demonstrates stereotypic movements in hands but can recognize relatives. He has spastic tetraparesis more prominent in legs. No purposeful movements. HC is 51cm.He never had any seizures. MRI performed at 9mth, 3y and 5y showed bilateral gliosis and cysts communicating with ventriculi, thinning of corpus callosum without progression in time.
EEG at 7mths was normal, at 5 years showed multifocal SW discharges in temporal regions, mostly on left. No photosensitivity detected.
Sequence analysis and deletion/duplication testing of the 836 genes (INVITAE) revealed 1 likely pathogenic variant in PLEKHG2. The protein encoded by this gene is a RhoGTPase that can activate CDC42 by promoting exchange of GDP for GTP on CDC42. Defects in this gene have been associated with leukodystrophy and acquired microcephaly with or without dystonia. Several cases had been described in literature. Finally, PLEKHG2-related leukodystrophy had been diagnosed.

Conclusions: Preexisting cerebral injury cannot exclude development of degenerative disease in children. Rare forms of leukodystrophies and their genetic background need further study.

Keywords:
cerebral palsy, leukodystrophy

EPNS21-315 Poster only
Miscellaneous Topics

REVIEW OF PEDIATRIC CASES OF IDIOPATIC INTRACRANIAL HYPERTENSION (IIH)

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Objective: IIH characterized by intracranial hypertension (ICH), confirmed by central spinal fluid open pressure and excluded secundary etiologies. In children, female and obesity are risk factors on post-puberty. The most common symptom is headache and the more frequent signals are optic disc edema (ODE), and cranial nerve impairment. Assessed demographical, clinical, radiological characterisitcs, as prognosis in a IIH cohort.

Methods: Retrospective study of 10 years consecutive pediatric patients medical records based of IIH followed in our center. The survey was based on registers with CID G93.2 (benign intracranial hypertension), with a total of 17 cases. Revised medical records, excluded 6 cases that not fill the Modified Dandy Criteria. Neuroimaging criteria were revised by a neuroradiologist.

Results: From a total of 11 patients, 8 were post-puberty and 7 female. Endocrinological underlying disease were present in 7 patients, 1 presented sickle cell disease, and 1 hemophilia A. Headache as initial symptom occurred in 10 cases, and 6 with vomit; only one one patient was assymptomatic and diagnosis made after a routine ophthalmologic exam. At the initial evaluation all patients presented ODE and 5 sixt nerve palsy. In our cohort 7 patients received acetazolamide; 2 topiramate and 2, none medication. Of those who used acetazolamide, 6 presented metabolic acidosis, although the medication was withdrawal only in 2. Headache with migranous pattern after ICH resolution occurred in 2 patients, but none presented visual sequel.

Conclusions: Although pediatric IIH is infrequent, in front an ICH syndrome, it is important a precocious diagnosis and treatment. Endocrinological underlying disease and female were associated with IIH, as described on literature. Evidence shows that drug teraphy improve headache and avoid progression to visual loss in most cases, also observed in our patients. Studies with a large cohort are requeried to a better evaluation of risk factors and prognosis of IIH pediatric patients.

Keywords:
IDIOPATIC INTRACRANIAL HYPERTENSION, CHILDREN

EPNS21-34
Miscellaneous Topics

Oral or poster

Acute Encephalopathy with EEG intermittent rhythmic discharges as the hallmark of acute SARS-CoV-2 infection in children

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Objective: Neurotropic and neuroinvasive potentials of SARS-CoV-2 virus is a matter of ongoing scientific debate. Few observational studies have reported acute encephalopathy as a neurological manifestations of acute COVID-19 infection in adults. A little is known about epileptogenesis or Electroencephalogram findings in pediatric patients.

Methods: A 17-year-old female presented with 2 weeks history of intermittent headaches, followed by 1 day history of acute change in behavior in the form of prolonged staring, decreased speech, confusion, and alternating periods of agitation and sleepiness. Brain MRI was unremarkable. CSF studies were negative for culture, infectious PCR and autoimmune panels. She tested positive for SARS-CoV-2 PCR with negative IgG. EEG showed remarkable background slowing and frequent frontal intermittent rhythmic discharges. She was managed with high dose steroids with full clinical recovery of all symptoms at discharge, as well as normalizing of subsequent EEG studies.

Results: Neurological symptoms of COVID-19 infection have been reported in about nearly 35% of adult and <20% of pediatric patients. Most reported symptoms are nonspecific including headache, encephalopathy, weakness, and as a part of multisystem inflammatory response syndrome. Natural history and correlation with specific patterns of cortical excitability or epileptic seizures is not known. It is also unclear if there are specific seizure characteristics or EEG patterns in patients with COVID-19 infection and concomitant acute encephalopathy.

Conclusions: Data on neurological sequelae of COVID-19 infection in children are sparse. We report a pediatric patient with a likely COVID-19 infection attributed-encephalopathy & distinct EEG pattern. It is perhaps reasonable to obtain EEG studies in children who test positive for SARS-CoV-2 and report cortical neurological symptoms. Long term follow up of these patients will be helpful to understand clinical significance and implications of such neuro-physiological studies.

Keywords:
COVID-19, encephalopahty, EEG

EPNS21-353 Poster only
Miscellaneous Topics

Idiopathic intracranial hypertension in Emirati Children: A 5-year retrospective review of visual outcome and recurrence risk

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Objective: The purpose of this retrospective study was to evaluate the visual outcome, time to improvement of papilloedema and recurrence rate in Emirati children diagnosed with idiopathic intracranial hypertension (IIH) and identify clinical predictor at presentation.

Methods: A single-center observational retrospective cohort study of children younger than 18 years of age who fulfilled the modified criteria for the diagnosis of IIH between 2015 and 2020

Results: 25 children met the diagnostic criteria for IIH. Mean age of symptom onset was 10.2 years (3 - 16 yrs). M:F 1: 1.2
The presenting symptoms were headache (80%), papilloedema (100%), 6th cranial nerve palsy (24%), and visual field defect (16%).
The common risk factor included obesity 48 % (of which 75 % were females), endocrine disorders 18 %, anaemia 9 %, vitamin D deficiency 9 % and head injury 4 %.
The mean LP opening pressure was 35 cm of H2O (28.5 - 56)
Treatment included acetazolamide in all, diuretics 20%, topiramate 20%, steroid 12 %, multiple LP 28 % , lumbo-peritoneal shunt 16 %, and optic nerve fenestration in 16 %
The mean time to papilledema improvement after starting treatment was 1.2 (1-3) months. The mean time to normalisation of optic disc was 3.7 (2-10) months. Papilledema was persistent in 4 cases (2 were found to have drusen in addition to papilloedema). The recurrence of papilledema occurred in 3 cases (within 6 months). In 10 children (40%) there was persistent headache without papilledema at 12 months follow up. Optic atrophy and poor vision developed in 1 child despite lumbo-peritoneal shunt.

Conclusions: Most of the cases of paediatric IIH respond well to medical therapy and have a favourable visual outcome in terms of both visual acuity and visual field. Recurrence is most likely to occur during the first 6 months after diagnosis. Higher cerebrospinal fluid opening pressure (> 40 cm H2O) and obesity were the clinical predictor at presentation for recurrence of symptoms.

Keywords:
Idiopathic intracranial hypertension, papilloedema

EPNS21-38
Miscellaneous Topics

Oral or poster

Paediatric Narcolepsy Type 1: Clinical Utility of CSF Orexin in facilitating early diagnosis in pre-adolescent children

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Objective: To demonstrate the clinical utility of CSF orexin in early diagnosis of narcolepsy in the pre-adolescent child

Methods: A retrospective case note review was conducted for the period January 2019- December 2020 of all children </=12 years, who were assessed in our hospital, and received a diagnosis of Narcolepsy Type 1 (NT1). CSF orexin testing as undertaken in all cases to confirm the clinical diagnosis. Demographic data, presenting symptoms, paediatric daytime sleepiness score (PDSS), time to diagnosis, and CSF orexin levels is summarised.

Results: 4 pre-adolescent children aged 12 or under, were diagnosed with NT1 over a 2 year period from January 2019-December 2020. Qualitative comments made by the parents/ carers and primary care practitioners in referral letters were very valuable sources of information in evaluating diagnostic symptoms, even if NT1 itself was not always considered by the initial assessing clinician. The clinical history and signs were considered sufficient to proceed to CSF examination for orexin level estimation as first line investigation for these children due to local unavailability of PSG and MSLT which would have necessitated external referral and caused further diagnostic delay. Ancillary investigations were undertaken to rule out alternate causes for these presentations. All 4 patients had extremely low/ undetectable levels of CSF orexin at <50pg/mL, which satisfied the ICSD-3 diagnostic criteria, and enabled early commencement of pharmacotherapy for symptom control.

Conclusions: Our case series demonstrates that CSF orexin estimation can be successfully used to confirm a diagnosis of NT1 at an early stage in the diagnostic pathway. With careful patient selection, it may avoid the need for more resource intensive sleep studies and diagnostic delays. A good clinical history with CSF orexin estimation should be considered by paediatric services as a standard investigation when assessing very young children presenting with EDS or cataplexy symptoms.

Keywords:
Narcolepsy, diagnosis, childhood

EPNS21-40
Miscellaneous Topics

Poster only

A near-global slowing of background activity and epileptic discharges in children with mild to moderately symptomatic COVID-19 infection: an electro-neurophysiological study

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Objective: To assess the functional involvement of the central nervous system (CNS) via quantitative electroencephalography (EEG) analysis in children with mild to moderate COVID-19 infection who were otherwise previously healthy children.

Methods: This prospective, case-control study was conducted between June and September 2020. Sleep EEG records of at least 40 min were planned for children who tested positive for COVID-19 using real-time PCR analysis and within 4-6 months post-recovery. All of the EEG analyses in this study were performed on an Ubuntu 20.04.2 LTS Operating System with the developed software using Python 3.7.6. The quantitative analysis of the epileptic discharges within the EEG records was performed using random forest after elimination of the artifacts with a model training accuracy of 98% for each sample data point. The frequency analysis was performed using the Welch method.

Results: Among the age and sex-matched groups, the global mean frequency was significantly lower among the COVID-19 patients, with a P-value of 0.004. The spike slow-wave and sharp slow-wave indices were significantly higher in the patients when compared to the controls. The mean frequency values were significantly lower in almost all of the electrodes recording the frontal, central, and occipital areas. For the temporal and parietal areas, those significantly low mean frequencies were limited to the right hemisphere.

Conclusions: A near-global involvement of background activity with decreased frequency, in addition to epileptic discharges, was recorded in mild to moderately COVID-19 infected children post-infection.

Keywords:
COVID-19, EEG, electrophysiology

EPNS21-43 Oral or poster
Miscellaneous Topics

Multi domain cognitive impairment in Children with Pseudotumor Cerebri

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Objective: Although prompt and suitable treatment of pseudo tumor cerebri syndrome (PTCS) leads to an excellent prognosis and can prevent optic nerve atrophy, adults show long-lasting neurocognitive deficits even with prompt treatment. The purpose of our study was to evaluate cognitive outcomes in pediatric patients with PTCS.

Methods: We performed a prospective study on children diagnosed with PTCS and a healthy control group. Children with pre-existing neurological conditions or psychiatric drug use were excluded. Both groups underwent a neurocognitive evaluation, using the NeuroTrax computerized battery of tests. The PTCS group were tested 3 months after the initial diagnosis.

Results: We evaluated 82 children (49 females [60%], 6.5-16 years old, mean age 13.3), including 26 diagnosed with idiopathic PTC and 56 controls. Global cognitive score ($P<0.001$), verbal memory ($P<0.001$), executive function ($P<0.001$), attention ($P<0.003$), and information processing speed ($P<0.004$) were all significantly lower in the PTCS group. No differences were found between children currently being treated and those whose symptoms had resolved and treatment was stopped.

Conclusions: Children with PTCS experience comprehensive cognitive decline that persists after the resolution of the symptoms and treatment.

Keywords:
Pseudotumor Cerebri Syndrome, Cognitive outcome, Cognitive Impairment

EPNS21-455 Oral or poster
Miscellaneous Topics

Influence of pineal gland cyst on hypothalamic - pituitary hormones in children: case series of 140 children

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Objective: The pineal gland is a small neuroendocrine organ whose function is secretion of melatonin, which may influence secretion of hypothalamic-pituitary (H-P) hormones. The aim of our study was to determine potential H-P hormone dysregulation in children with a pineal gland cyst (PC).

Methods: In this prospective study, a cohort of 140 children (57 males; 55 prepubertal; median age 11.3 years, range 4 months - 19.2 years) with a PC were evaluated in an outpatient clinic at the University Children's Hospital in Ljubljana between March 2017 and June 2021. PCs were identified using magnetic resonance imaging (MRI), which was indicated in patients for various reasons (mostly neurological). Levels of the following hormones and parameters were determined in a fasting state at a standardised morning time: thyroid stimulating hormone (TSH), thyroid hormones T3 and T4, insulin-like growth factor 1 (IGF1), IGF-binding protein 3 (IGFBP3), cortisol, adrenocorticotropic (ACTH), luteinizing (LH), follicle stimulating hormone (FSH), testosterone, oestradiol-17 beta, insulin, osmolarity of the plasma and urine. Also, the standard deviation score (SDS) of patients' height, weight and BMI were calculated.

Results: In 5 children with a PC, MRI was performed due to a previously detected endocrine dysfunction: precocious puberty (3), primary amenorrhea (1), and decreased growth velocity (1).Fifty-seven (40.7 %) children had abnormal levels of hormones. In eight (5.7 %) children, abnormal results were clinically relevant (ACTH 3/8, TSH 2/8, thyroid hormone 1/8, cortisol 1/8, testosterone 1/8). Regarding childrens' SDS, 12 had tall stature, 17 were overweight, 1 underweight, 14 were obese and 4 slim.

Conclusions: The results of our study suggest that PCs may be related to a dysfunction in secretion of H-P hormones in children, however the risk of clinically significant dysfunction was not significant in our cohort of children.

Keywords:
Pineal gland cyst, children, hypothalamic-pitutary hormones

EPNS21-47 Oral or poster
Miscellaneous Topics

Disordered eating behaviors in young individuals with idiopathic intracranial hypertension

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Objective: To assess the prevalence of disordered eating behaviors in young individuals with idiopathic intracranial hypertension (IIH), and to identify predictors of disordered eating behaviors (DEB) in this population.

Methods: Individuals with IIH aged 8-25 years and their matched controls responded to a self-rating survey comprised of the Eating Attitude Test-26 for assessing the presence of DEB, and the Depression, Anxiety and Stress Scale.

Results: Fifty-three subjects with IIH and 106 healthy controls were included. Disordered eating behaviors were significantly more prevalent in individuals with IIH ($p<0.001$). Individuals with IIH and DEB were more likely to have longer periods of treatment [odds ratio (OR) 1.07, 95% CI 1.02-1.41), $p=0.008$], and to have lost a significant amount of weight during the course of treatment [OR 9.06 (95% CI 1.30-62.9), $p=0.026$]. Depression, anxiety, and stress were more prevalent in the IIH group compared to the controls ($p=0.004$) and were associated with DEB in these individuals ($p=0.01$).

Conclusions: There is an increased prevalence of DEB among young individuals with IIH, that persists even after disease resolution, and is associated with higher reported rates of depression, anxiety, and stress. Medical caregivers should have heightened awareness to DEB in individuals with IIH with the aim of early identification and intervention.

Keywords:
Pseudotumor cerebri (PTC), headache, eating disorders, depression, children, adolescents, obesity

EPNS21-474 Poster only
Miscellaneous Topics

Evolution-based classification system for Alexander disease: a proposal from a paediatric series

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Objective: To propose a comprehensive clinical classification system for Alexander disease (AxD), considering not only age or clinical and neuroradiological features at onset, but also disease evolution over time.

Methods: Twenty-one patients with genetically confirmed paediatric-onset AxD were enrolled. Clinical data were retrospectively reviewed for age and symptoms at onset, neuromotor development and loss of motor and language skills, disease complications. Cognitive assessment was performed using standardized scales or on the basis of clinical impressions and anamnestic data. Early MRIs were re-evaluated to determine the presence of typical features of AxD. Patients were then classified according with the systems currently in use. Finally, disease evolutionary trajectories over time were assessed.

Results: Considering disease evolution over time, type I AxD patients were subdivided into four subgroups: Ia, included patients with neonatal presentation and early fatal course; Ib, patients who did not deambulate autonomously and deteriorated by 5 years of age; Ic, patients who acquired autonomous deambulation, even if delayed, and deteriorated after 6 years; Id, patients who acquired autonomous deambulation with delay but remained clinically stable beyond adolescence. Four patients at the last evaluation were too young to predict neurologic decline.

Conclusions: The study results confirmed what was previously described on the clinical features at onset. Based on the follow-up data, type I AxD patients might be further classified into Ia, Ib, Ic, and Id, according to the different evolution. Further studies and a larger cohort of patients will be required to confirm these preliminary results and to evaluate the existence of clinical and neuroradiological prognostic factors capable of predicting disease progression.

Keywords:
Alexander disease, leukodystrophy, GFAP, astrocytopathy

EPNS21-481 Poster only
Miscellaneous Topics

Neurocutaneous disorders in children and sleep

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Objective: The most common neurocutaneous disorders in childhood are neurofibromatosis (NF) including type 1, type 2 and schwannomatosis, tuberous sclerosis complex and Sturge-Weber syndrome. Children with neurodevelopmental disorders are known to have increased risk for sleep disorders, but the extent of sleep disturbances in neurocutaneous disorders is not comprehensively studied. In order to design a study of sleep in tuberous sclerosis complex, we first performed a literature review. Our aim was to explore the type of sleep disorders encountered in neurocutaneous disorders and the evaluations that were applied.

Methods: A systematic search of the literature was conducted in Pubmed and Google Scholar during autumn 2021. Data from original, peer-reviewed papers were gathered using a standardized data extraction form.

Results: The majority of data were generated from pediatric research studies in neurofibromatosis type 1 and tuberous sclerosis complex. Main sleep disorders in neurofibromatosis type 1 were abnormalities in initiating and maintaining sleep, sleep-wake transition, hyperhidrosis and parasomnias. Difficulties in initiating and maintaining sleep and sleep breathing disorders were the most common sleep disturbances among children with tuberous sclerosis complex, while epileptic seizures were not found to correlate with sleep dysfunction. The sleep disturbance scale for children (SDSC) was the main assessment tool used in these studies.

Conclusions: While the mechanisms underlying sleep dysfunction in neurocutaneous disorders remain poorly understood, screening for and identifying sleep disorders is essential, as it may not only affect the cognitive development and behavior but also the quality of life of the patient and the family. A combination of assessment tools such as accelerometer-based sleep monitoring activity, validated sleep questionnaires and polysomnography would be of value to capture the various aspects of sleep disturbances in future research.

Keywords:
'neurocutaneous disorder', 'sleep', and 'child'

EPNS21-522 Oral or poster
Miscellaneous Topics

Migraine-like Headaches starting within a COVID19 infection in Children and Adolescents.

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Objective: Our aim is to study the relationship between COVID19 infection and Migraine. We hypothesize two different mechanisms: first one as a Migraine Trigger in patients with latent Migraine and second one causing Migraine-like symptoms as a part of a wider Post-Acute COVID Syndrome (PACS).

Methods: We present five patients from a secondary level Pediatric Neurology outpatient clinics, who initiated Headaches with Migraine features in the context of a primary COVID19 infection. We contrasted our findings with publications since March 2020 about Migraine symptoms in Pediatric patients suffering from COVID19 infections.

Results: Three patients presented their headaches as a part of a wider PACS with higher impairment in daily life and with a more persistent course. In two patients, the infection was best described as a trigger of Migraine which presented in a more episodic way and with a lesser degree of impairment.

Conclusions: Our results support the existence of at least two different mechanisms for COVID19 virus to cause Migraine symptoms in Children and Adolescents. The different outcome observed in the PACS patients versus the "trigger" patients in this small case series warrants wider studies in order to support or reject these different mechanisms for COVID19 as a cause of Migraine symptoms.

Keywords:
COVID19, Migraine, Post Acute COVID, Migraine Triggers, Headache

EPNS21-574 Poster only
Miscellaneous Topics

NKX2-1-related disorders mimicking a neuromuscular disorder

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Objective: The NKX2-1 gene regulates the expression of thyroid-specific genes and genes involved in morphogenesis. Mutations in the NKX2-1 gene may manifest with variable combinations of brain, thyroid and respiratory symptoms, including benign hereditary chorea, congenital hypothyroidism, neonatal respiratory distress, and it may be associated with thyroid cancer.

Methods: Cases presentations

Results: The first patient is a six-year-old girl with congenital hypothyroidism and motor delay. Her exam was remarkable for hypotonia and prominent waddling gait. Neurophysiological studies were consistent with a myopathic process. Muscle biopsy did not show any abnormalities. Whole exome sequencing (WES) demonstrated a pathogenic mutation in the NKX2.1 gene (NM_001079668.2):c.206_207delCG. The second patient is a five-year-old girl, with treated congenital hypothyroidism and motor delay. Her neurological exam was remarkable for hypotonia, waddling gait and a partial Gower's sign. Neurophysiological studies were normal. Targeted sequencing of the NKX2.1 gene disclosed the pathogenic mutation (NM_001079668.3): p.Gln200Ter/c.598C>T.

Conclusions: We report two patients with NKX2-1-related disorder in whom the clinical presentation mimicked a neuromuscular disorder. NKX2-1-related disorders should be considered in the differential diagnosis of patients with clinical manifestations resembling congenital myopathies.

Keywords:
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EPNS21-625 Oral or poster
Miscellaneous Topics

LOSS OF CONTINUITY OF CARE IN PEDIATRIC NEUROLOGY SERVICES DURING COVID-19 LOCKDOWN: AN ADDITIONAL STRESSOR FOR PARENTS

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Objective: COVID 19-related lockdown during the so called "first wave" of the current pandemics had a deep impact on the health and the care of children with chronic neurologic disease and neurodevelopmental disorders. This work aimed to investigate its consequence on the wellbeing of children with neurological and neurodevelopmental disorders and the repercussion on parental stress.

Methods: A web-based survey was shared via mail with the parents of children affected by chronic neurologic disorders and neurodevelopmental disorders in continuity of care in two Italian tertiary centers(june-july 2020). Parental stress was measured via Perceived Stress Scale (PSS).

Results: The survey was completed by 250 parents. Sars-Cov2 infection was reported in 2 patients only. 44,2% of the sample completely interrupted school activities while 70% of parents underwent changes in their job modalities. Health care services were disrupted in 77% of patients and higher PSS scores were detected in parents who reported a significant loss of usual clinical checks.

Conclusions: The loss of continuity of care during the lockdown has to be considered as a risk factor for parents caring for children with chronic neurologic diseases and neurodevelopmental disorder in furthers phases of the current pandemics.

Keywords:
COVID 19 pandemic, caregiver, perceived stress, children

EPNS21-627 Oral or poster
Miscellaneous Topics

Neurological manifestations in children with acute COVID-19

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Objective: In the pediatric population the knowledge of the acute COVID-19 manifestations is set at small series and case reports levels, particularly when dealing with neurological symptoms. We describe the acute neurological and non-neurological manifestations of a large cohort of children with SARS-CoV-2 infection, investigating correlations between disease severity and population demographics.

Methods: Patients aged 0-18 years with a positive molecular swab between April 2020 and March 2021 were retrospectively recruited. Clinical data, imaging, and laboratory tests results upon presentation were collected through a standardized dataset. Groups were compared using Fisher's exact test.

Results: 237 patients with a mean age of 5.5 years were eligible. Thirty-two (13.5%) patients presented with neurological symptoms including headache (59.4%), altered awareness (18.8%), ageusia/anosmia (12.5%), seizures (6.3%), and vertigo (6.3%), either combined in 7 (21.9%) cases. 205 (86.5%) patients presented without neurological involvement, mainly showing respiratory (59.5%) or gastrointestinal (25.3%) symptoms. The priority access codes given to patients without neurological symptoms were white (2.8%), green (75.4%), and yellow (11.9%), while in patients with neurological symptoms triage codes were green (78.1%), yellow (18.8%), and red (3.1%). Comparison of comorbidities between subgroups resulted in a value of p=.0958. Fifty-seven (24.1%) patients required treatment, including antibiotics (12.2%), systemic steroids (4.6%), and heparin (2.9%). Only one patient developed long-term sequelae, namely post-COVID syndrome.

Conclusions: We confirm the overall benign COVID-19 course in children. Neurological manifestations, except for headache, remain a rare presenting symptom in children and disease severity stays independent from other systemic comorbidities.

Keywords:
Acute; COVID-19; children; neurological symptoms; post-COVID

EPNS21-650 Poster only
Neuro rehabilitation

Possibilities of transcranial magnetic stimulation in children with delayed psycho-speech development, including children with ASD

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Objective: In Kazakhstan autism was diagnosed in 3820 children (1 per 1000). Transcranial Magnetic Stimulation - A method of non-invasive, painless stimulation of brain structures in order to change the excitability of the cortex and affect the functional state of brain structures.

Methods: TMS was carried out from 2019 to March 2021. 782 children of various ages from 0 to 18 years old with varying severity of brain damage, different ages during TMS, most of them children from 2 to 6 years (50%).
All children had previously undergone clinical and instrumental examination and we made corrections in the diagnosis and status of the child after receiving TMS.
Follow-up observation of the examined children was carried out on the basis of Questionnaires and retrospective analysis.
In our case, we used the generally recognized DLPFC points on both sides and additionally selected Broca's zone and Wernicke's zone in the dominant hemisphere. Exposure time 4-5 minutes for each zone. Duration of treatment from 10 to 20 days without interruption. About 80% of patients underwent
repeated courses of treatment from 3 to 5 courses

Results: The positive effect was maximal at the age of 2-4 years - 430 in children and at the age of 4-6 years - 234 children. A positive response was expressed in an increase in vocabulary, a decrease in repetitive movements, stereotypes, a decrease in hyperactivity in behavior, an improvement in memory and understanding.

Conclusions: Using rTMS in pediatric practice to improve developmental neurobiology, especially in the treatment of children with delayed psycho-speech development, including children with ASD.

Keywords:
transcranial magnetic stimulation , delayed psycho-speech development

EPNS21-66 Oral or poster
Miscellaneous Topics

Incidental Findings on Paediatric Brain MRI

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Objective: Incidental findings are asymptomatic abnormalities of potential clinical relevance which are found unexpectedly and are unrelated to the original purpose of the investigation. These can pose a problem on brain MRIs in children as this area is currently under-researched. Therefore, this project aimed to perform a literature review describing the types, prevalence, and clinical implications of incidental findings in this area, and to produce a patient information resource based on this review's findings.

Methods: Ovid Medline and Embase databases were searched for relevant articles. An unpublished study was also included, resulting in a total of 32 records from which data were extracted.

Results: Prevalence data from 17 studies ranged from 6% to 50%. Using data from these studies, an overall prevalence of 22.94% was estimated. There were a wide variety of incidental findings, categorised into tumours, cysts, white matter abnormalities, vascular abnormalities, inflammatory lesions, congenital abnormalities, normal anatomical variants, ventricular abnormalities, and other findings. The majority of incidental findings were benign and only 0.43%-5% needed to be followed up. Management options are no treatment, radiological surveillance, or surgery; however, there are currently no protocols.

Conclusions: Incidental findings are common on paediatric brain MRI and can cause significant difficulties in how they should be managed. More research in this area is needed to accurately determine the prevalence of incidental findings.

Keywords:
Incidental findings; paediatric; MRI; neuroradiology

EPNS21-678
Miscellaneous Topics

Poster only

Posterior Reversible Encephalopathy Syndrome: A Paediatric Case Series

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Objective: Posterior Reversible Encephalopathy Syndrome is a clinico-radiological syndrome with myriad features including hypertension, headache, confusion, visual disturbance and seizures.

Methods: We report on clinical and neuroimaging findings of three cases diagnosed as Posterior Reversible Encephalopathy Syndrome, over an 18 month period, on the basis of clinical findings and typical magnetic resonance imaging changes including T2 hyperintensity and vasogenic oedema.

Results: Age ranged between 10-16 years. All three patients demonstrated significant hypertension during the admission. Two were diagnosed with post-streptococcal glomerulonephritis, and one with multi-organ dysfunction following an acute surgical illness. Hypomagnesia found found in this case, and has been noted in case reports in adult literature, with further research recommended to evaluate its impact on management strategies.

Significant clinical and radiological improvement was seen after management of hypertension, and all three patients made good recovery and successfully weaned from anti-convulsant therapy.

Conclusions: Posterior Reversible Encephalopathy Syndrome should be considered in the differential diagnosis of patients presenting with acute encephalopathy in the context of hypertension and underlying associated disease states.

Keywords:
PRES, hypertension, encephalopathy

EPNS21-697 Oral or poster
Miscellaneous Topics

Neurological Manifestations of Gluten Sensitivity in Children and Adolescents

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Objective: Neurological manifestations of gluten sensitivity, mainly gluten ataxia, are well-recognised in adults, with limited description in children. Further work is needed to reach a comprehensive understanding of the neurological phenotype of gluten sensitivity in children and adolescents.

Methods: A retrospective case note analysis was performed on the clinical, serological and neuroimaging profile of 9 children presenting to our specialist Ataxia referral centre with suspected gluten ataxia.

Results: All 9 patients had motor coordination difficulties and/or ataxia, with deterioration of coordination 3/9 patients. 7/9 had headaches; 5/9 had autism spectrum disorder (ASD); Neuropathic symptoms were present in 3/9, with 2/9 reporting autonomic dysfunction symptoms. 2/9 had a tic disorder. There were reports of sensory/visual processing difficulties, anxiety and depression. Serological abnormalities present: raised endomysial IgA antibody levels in 4/9, raised Transglutaminase-2 antibody levels in 5/9, raised antigliadin antibody levels in 6/7, and raised Transglutaminase-6 antibody levels in 5/6 patients. One patient had cerebellar atrophy. MR Spectroscopy of cerebellum (cerebellar vermis and hemisphere) performed showed N-acetylaspartate:Creatine ratio was reduced (<1) in 3/9 patients. Only 3/9 had coeliac disease. 7/9 went on a gluten-free diet, 1/9 received immunomodulatory treatment.

Conclusions: In this series, we present the clinical, serological and neuroimaging profile of nine children with neurological manifestations of gluten sensitivity. This may coexist with or present independently of coeliac disease
The importance of the diagnosis of gluten ataxia is under-recognised and significant, as it is a treatable cause of childhood ataxia. High index of clinical suspicion and using serological and neuroimaging protocols for diagnosis of gluten ataxia is recommended.

Keywords:
gluten ataxia transglutaminase-6 antibdies coeliac disease childhood ataxia autoimmune

EPNS21-714 Oral or poster
Miscellaneous Topics

NEUROCOGNITIVE IMPAIRMENT AND EPILEPSY IN SCHOOL-AGED CHILDREN AFTER SEVERE MALARIA IN A MALARIA ENDEMIC AREA.

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Objective: Severe malaria is a contributor to neurocognitive impairment and epilepsy in children living in sub-Saharan Africa but there is no published data on this subject in Cameroon. We thus sought to understand the possible neurological long term effects of severe malaria in school-aged children in Yaoundé.

Methods: In this retrospective cohort study of 50 eligible children who survived severe malaria in Yaoundé, demographic, clinical, neuropsychological and electroencephalographic evaluations were done using standard clinical procedures.

Results: The mean age was 9.38±3.06 years. The prevalence of neurocognitive impairment and epilepsy were 38% and 20% respectively. The risk of developing epilepsy evaluated by EEG epileptic activity was 34.4%. The incidence of neurocognitive impairment was 226 cases per 1000 person years. The incidence of epilepsy and epileptic activity on the electroencephalogram were 140 and 154 cases per 1000 person years respectively. The most affected cognitive domains were: fine motor skills, sustained attention, mental flexibility and verbal memory. There was no association between coma and neurocognitive impairment (p=0.54) but there was an association between high daily seizure frequency during malaria and subsequent epilepsy (p=0.013 respectively) and between disease duration and epileptic activity (p=0.043).

Conclusions: The prevalence and incidence rates of neurocognitive impairment and epileptic activity are significantly high in children who suffered from severe malaria in Yaoundé. High seizure frequency during severe malaria appears to be a predictor of epilepsy while coma is not a predictor of neurocognitive impairment in these children.

Keywords:
Severe malaria, Epilepsy, neurocognitive impairment, school-aged children

EPNS21-76 Poster only
Miscellaneous Topics

Late onset Group B Streptococcal meningitis: Silent attacker - spotted

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Objective: Group B streptococcal infection is a serious infection in neonatal period. Sepsis and Pneumonia are prime features of early onset illness. Meningitis is hallmark of late onset illness. GBS meningitis can have devastating neurological sequalae. Diagnosis depends on identification of GBS in Cerebrospinal Fluid culture. We present case of a baby where initial clinical picture and result was misleading. Diagnosis of GBS meningitis was obtained with 16S ribosomal DNA testing. We highlight importance of possibility of lack of obvious clinical features in late onset meningitis and the importance of considering 16S rDNA testing.

Methods: Case

4 week old baby born following concealed pregnancy to Caucasian mother and Caucasian Asian father presented with reduced feeding. Initial examination was unremarkable with normal observations. Blood tests were undertaken due to age of baby. After admission, she was noted to have slightly swollen right knee. Full sepsis screen was undertaken due to high C-Reactive Protein. CSF results prior to starting antibiotics showed protein 19, Glucose 1.1 and 850 WBC with negative gram stain and culture. MRI brain showed communicating hydrocephalous and debris in ventricles.

Results: She was commenced on antibiotics for meningitis but transferred to our hospital for suspected Tuberculous meningitis. She was started on anti TB treatment. She had extensive contact tracing and work up for Tuberculosis including right knee synovial fluid culture which did not reveal positive results. She had ventriculoperitoneal shunt insertion due to worsening hydrocephalous on imaging. 16 S rDNA of CSF showed Streptococcus agalactiae. Her anti TB medications were stopped and she completed antibiotic course.

Conclusions: Clinical signs can be subtle in late onset GBS meningitis. Low threshold for sepsis screening should be considered in neonatal age group. 16S rDNA PCR should be considered if CSF culture is negative in suspected cases even if it was obtained prior to giving antibiotics.

Keywords:
Meningitis, Neonate, 16S rDNA PCR

EPNS21-79 Poster only
Miscellaneous Topics

ARSACS: Don't Miss The Pathognomonic MRI Findings!

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Objective: Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is a rare hereditary ataxia of early childhood associated with founder mutations in the SACS gene primarily among families in Quebec. We present 2 cases of ARSACS in cousins born in the UK to consanguineous parents.

Methods: Case 1 is a female noted to have motor delay, poor balance and intention tremor. Initial baseline investigations including brain MR, metabolic studies and microarray were normal. At 6 years, she was persistently ataxic. Targeted exome sequencing identified a homozygous pathogenic variant in the SACS gene. On retrospective imaging review, bilateral thick T2 hypointense pontine transverse fibres and prominent interfolial distances in the superior cerebellum were noted, classical for ARSACS. Case 2 is a male noted to have persistent unsteady gait at age 3 years despite walking at 11 months of age. At 5 years, he could not jump or climb stairs independently and had broad-based ataxic gait. His initial MRI brain had also been reported as normal, but had similar findings as his cousin when this was reviewed. He was confirmed to have the same familial mutation.

Results: With the increased use of Whole Genome Sequencing an increasing number of novel SACS mutations will bedetected worldwide. It is crucial to consider ARSACS in children with early onset ataxia and/or cerebellar signs. This is especially important in the context of consanguinity. Previous reports of older children and adults suggest that the MR appearances are more prominent with age. However, we highlight the importance of careful neuroradiology review in children with ataxia as both our cases had classical findings even at the age of 3.

Conclusions: As an increasing number of novel mutations in the SACS gene are detected worldwide, it is crucial to consider ARSACS in the differential diagnosis of children with early onset ataxia and/or cerebellar signs. Early MRI findings may be subtle but are pathognomonic and facilitates early diagnosis.

Keywords:
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EPNS21-81 Oral or poster
Miscellaneous Topics

Clinical, demographic characteristics and prognosis of cases followed up with the diagnosis of neuroborreliosis in childhood

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Objective: It was aimed to evaluate the clinical and demographic characteristics of our patients who were followed up with the diagnosis of neuroborreliosis.

Methods: The study was conducted at Erciyes University Hospital. The data of the patients who were diagnosed with neuroborreliosis in pediatric neurology clinic in the last 10 years were evaluated retrospectively. A total 10 of patients presented with Guillain Barre Syndrome (GBS), Chronic inflammatory demyelinating polyneuropathy (CIDP), ataxia, encephalitis, facial paralysis, lyme meningoencephalitis were evaluated for epidemiologic data, clinical finding, radiologic findings, treatment and prognosis.

Results: There were 10 patients we followed and diagnosed with neuroborreliosis. Of the cases, 1 (10%) was male and 9 (90%) were female. The mean age was 8 (99 months), range 43 months- 13.5 years. Western blot test results were positive in 8 of the patients. Although Western blot was negative in 2 patients, no other factor could be detected and their serology remained positive in their follow-ups and both of them were accepted neuroborreliosis. Tick bite history, rash and arthritis were not present in any of the patients. Cases at the time of application presented with headache, neck pain, gait problems, ataxia, facial paralysis, paresthesia, encephalopathy, speech problem, muscle weakness, vomiting, seizure, fatigue, arthralgia and lethargy.

Conclusions: Lyme disease presents in a wide spectrum and one of the most frequently affected organ systems in this disease is the central nervous system. In this report we presented pediatric neuroborreliosis cases. B. burgdorferi should also be considered in a severe neurologic condition with unknown etiology even if the history of tick bite is unknown.

Keywords:
Lyme, Neuroborreliosis

EPNS21-110 Oral or poster
Movement Disorders

Case report of KCNMA1 mutation variant associated with movement disorder

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Objective: To report the phenotype of a rare KCNMA1 mutation variant associated with paroxysmal movement disorder and developmental delay.

Methods: Description of the phenotype and genetic characterisation of our patient combined with literature review of reported KCNMA1 gene mutations and treatment strategies.

Results: Our patient a 5 year old boy who presented from age of 10 months with sudden drops episodes associated with loss of his truncal tone. He also get episodes which involve looking vacant, dystonic opening of his mouth, slight dystonic posturing of one limb, opening and closing of his mouth for few seconds before coming out of the episodes. These episodes are stereotyped and unchanged over the years. He gets 35-50 episodes daily. He was born at term with no perinatal problems. He has developmental delay, currently achieved most of his milestones. He does not have autistic spectrum disorder. He was extensively investigated for possible underlying cardiac, epileptic and cataplexy associated disorders and was tried on antiepileptic medications with no benefit. Standard and Video EEGs have shown to be normal with no EEG correlates during the events. Whole exome sequence was positive for KCNMA1 DNA chain c.1595c>Tprotein chain p.Ala 532 Val inherited AD zygosity heterozygous which was classified as uncertain significance but was of highly suggestive causation to his symptoms. 37 KCNMA1 alleles have been reported to date. 3 variants reported as gain of function mutations, 14 as loss of function and 15 mutations of unknown significance. All associated with different movement disorders, epilepsy syndromes and neurodevelopmental and cognitive delay. Good responses to stimulant medications have been reported in literature in some cases.

Conclusions: Our patient has A532V variant, is a known KCNMA1 mutation of unknown effect on BK channel activity. It was found to be associated with falls, drops episodes and abnormal mouthing dystonic movements, with associated autistic spectrum disorder.

Keywords:
KCNMA1, movement, disorder, paroxysmal, dystonic

EPNS21-129 Poster only
Movement Disorders

POOLED EFFICACY ANALYSIS OF INCOBOTULINUMTOXINA IN THE MULTIPATTERN TREATMENT OF UPPER- AND LOWER-LIMB SPASTICITY IN CHILDREN AND ADOLESCENTS WITH CEREBRAL PALSY

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Objective: This pooled analysis assessed the efficacy of incobotulinumtoxinA for lower-limb (LL) and upper-limb (UL) spasticity in children and adolescents with cerebral palsy (CP) using data from the first controlled injection cycle of 2 large Phase 3 studies, TIM (NCT01893411) and XARA (NCT02002884).

Methods: Ambulant and non-ambulant pediatric patients with spasticity due to CP (2-17 years of age; uni- or bilateral CP; Ashworth Scale [AS] score >=2 in clinical patterns for treatment) were enrolled. Patients were randomized (2:1:1) to 3 incobotulinumtoxinA dose groups: 8, 6, 2 U/kg body weight (BW), maximum 200, 150, 50 U per LL clinical pattern in TIM and per UL in XARA. Additional multipattern treatment was allowed in both studies with total body doses up to 16-20 U/kg BW (<=400-500 U) depending on study and Gross Motor Function Classification System (GMFCS) levels I-V. Changes from baseline in AS score and Global Impression of Change Scale (GICS) scores at Week 4 were assessed in patients with LL treatment (TIM and XARA) and in those with UL treatment (XARA).

Results: In total, 603 patients with LL treatment from both studies (58.9% male, mean [SD] age 6.8 [4.2] years, BW 23.6 [13.5] kg, 27.2% GMFCS IV-V) and 350 patients with UL treatment from XARA (62.9% male, mean [SD] age 7.3 [4.4] years, BW 25.0 [15.0] kg, 30.9% GMFCS IV-V) were included in this analysis. Improvements in AS score for the main LL and UL clinical patterns were seen with all incobotulinumtoxinA doses at Week 4 (all P<0.0001 vs baseline except adducted thigh at 8 U/kg). Significantly greater improvement in AS score for the main UL clinical pattern was noted in the 8 U/kg versus the 2 U/kg dose group (P=0.004). Investigator's, child/adolescent's and parent/caregiver's GICS scores confirmed improvement in LL and UL spasticity at Week 4.

Conclusions: IncobotulinumtoxinA provides effective multipattern treatment of LL and UL spasticity in pediatric patients with CP (GMFCS I-V).

Keywords:
Cerebral palsy; IncobotulinumtoxinA; Lower-limb spasticity; Multipattern; Pediatric; Upper-limb spasticity

EPNS21-146 Poster only
Movement Disorders

SAFETY OF INCOBOTULINUMTOXINA IN MULTIPATTERN TREATMENT OF UPPER- AND LOWER-LIMB SPASTICITY IN CHILDREN/ADOLESCENTS WITH CEREBRAL PALSY: POOLED ANALYSIS OF 3 LARGE PHASE 3 STUDIES

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Objective: This analysis assessed the safety and tolerability of repeated incobotulinumtoxinA treatment for lower-limb (LL), upper-limb (UL), or combined LL/UL spasticity in ambulant and non-ambulant children/adolescents with cerebral palsy (CP) using pooled data from 3 large Phase 3 studies.

Methods: Pediatric patients with spasticity (2-17 years of age; uni- or bilateral CP; Gross Motor Function Classification System [GMFCS] level I-V; Ashworth Scale [AS] score >=2 in clinical patterns for treatment; clinical need for treatment) were enrolled. Patients received total body incobotulinumtoxinA doses of 16 U/kg body weight (BW, <=400 U) for LL spasticity in 2 injection cycles (ICs) in TIM (NCT01893411). In TIMO (NCT01905683), TIM completers and new recruits received 4 ICs with 16-20 U/kg (<=400-500 U) for LL or combined LL/UL treatment. In XARA (NCT02002884), patients received 4 ICs with 16-20 U/kg (<=400-500 U)
for UL or combined LL/UL treatment. Adverse events (AEs) were assessed in the pooled population.

Results: In total, 907 patients (59.6% male, mean [SD] age 6.7 [4.2] years, BW 23.3 [13.9] kg) received multipattern treatment; 753 patients (83.0%) completed the studies and received up to
6 ICs. Across all ICs, 363 (40.0%) experienced an AE; 33 (3.6%) had >=1 treatment-related AE. The most common AEs were nasopharyngitis, bronchitis, and upper-respiratory tract infection. Serious AEs (SAEs) and AEs of special interest (AESIs) were reported for 49 (5.4%) and 18 (2.0%) patients, respectively. AESIs reported in >1 patient were muscular weakness (6 patients, 0.7%), dyspnea, constipation, and dysphagia (3, 0.3% each). There was no increased incidence of AEs, SAEs, or AESIs with repeated dose. No deaths were reported in these studies.

Conclusions: IncobotulinumtoxinA was safe and well tolerated for LL, UL, or combined multipattern treatment over up to 6 ICs in a comprehensive population of ambulant and non-ambulant pediatric patients with spasticity (GMFCS levels I-V).

Keywords:
Cerebral palsy; IncobotulinumtoxinA; Multilevel; Multipattern; Pediatric; Safety

EPNS21-147 Poster only
Movement Disorders

ABSENCE OF NEUTRALIZING ANTIBODY FORMATION DURING INCOBOTULINUMTOXINA TREATMENT OF SPASTICITY IN BOTULINUM TOXIN-NAÏVE CHILDREN WITH CEREBRAL PALSY: POOLED ANALYSIS OF THREE PHASE 3 STUDIES

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Objective: Neutralizing antibodies (NAbs) have been linked to secondary non-response to botulinum neurotoxin type A (BoNT-A) injections; this still controversial issue is of special concern when treating conditions like pediatric spasticity. We investigated NAb formation in three large Phase 3 studies with incobotulinumtoxinA, a BoNT-A with no complexing proteins, in children/adolescents with cerebral palsy (CP) who received multipattern spasticity treatment.

Methods: Pediatric patients with lower-limb (LL), upper-limb (UL), or combined LL/UL spasticity (2-17 years; uni- or bilateral CP; Ashworth Scale score >=2 in clinical patterns for treatment) were enrolled. Patients received total body incobotulinumtoxinA doses of < =16-20 U/kg (max. 400-500 U) depending on the study (TIM: NCT01893411; TIMO: NCT01905683; XARA: NCT02002884) and Gross Motor Function Classification System level I-V, for up to six injection cycles (ICs). Occurrence of NAbs against BoNT-A was investigated in those >=21 kg at screening and end of study. Blood samples were analyzed using a fluorescence immunoassay (FIA) for antibodies, and positive samples were then tested for NAbs using a hemidiaphragm assay.

Results: 907 patients (59.6% male, mean [SD] age 6.7 [4.2] years and body weight 23.3 [13.9] kg) received treatment. In total, 386/403 (95.8%) and 318/422 (75.4%) patients with bodyweight >=21 kg were tested using FIA at screening and end of study, respectively, with 150/403 (37.2%) and 167/422 (39.6%) being toxin-naïve. Eleven individual patients tested positive for NAbs at screening and/or end of study, all of whom had previously been treated with other BoNT-As (onabotulinumtoxinA/abobotulinumtoxinA).
None developed a secondary non-response to incobotulinumtoxinA. No toxin-naïve patients developed NAbs after incobotulinumtoxinA treatment.

Conclusions: NAb formation was not observed in toxin-naïve children/adolescents with CP treated with up to six ICs of incobotulinumtoxinA.

Keywords:
Adolescents; Antibodies; Cerebral palsy; Children; IncobotulinumtoxinA

EPNS21-149 Poster only
Movement Disorders

SUSTAINED EFFICACY OF INCOBOTULINUMTOXINA OVER 6 INJECTION CYCLES FOR THE TREATMENT OF LOWER-LIMB SPASTICITY IN CHILDREN AND ADOLESCENTS WITH CEREBRAL PALSY

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Objective: Two Phase 3 studies assessed the efficacy and safety of incobotulinumtoxinA for the multilevel, multipattern treatment of spasticity in children and adolescents with cerebral palsy (CP). Here we report the efficacy and safety of repeated lower-limb (LL) treatment over 6 injection cycles (ICs) in patients who took part in both studies.

Methods: Ambulant and non-ambulant patients (2-17 years of age; uni- or bilateral CP; Ashworth Scale [AS] plantar flexor score >=2; clinical need for treatment) were enrolled in these studies. In TIM (NCT01893411), patients were randomized (2:1:1) to 3 incobotulinumtoxinA dose groups: 16, 12, 4 U/kg body weight (BW, maximum 400, 300, 100 U) for treatment of 2 LL clinical patterns in 2 ICs. In the open-label TIMO study (NCT01905683), TIM completers received a further 4 ICs with 16 U/kg (maximum 400 U) for LL treatment. Changes from TIM study baseline in AS scores and Global Impression of Change Scale (GICS) scores at Week 4 of all 6 ICs were assessed. The incidence of adverse events (AEs) by IC is reported.

Results: In total, 124 patients (54.8% male, mean [SD] age 6.3 [4.0], BW 21.7 [11.9] kg, 28.2% GMFCS IV-V) completed 2 ICs in TIM and entered TIMO. Of these, 107 (86.3%) patients completed TIMO and received a total of 6 ICs. AS scores for the plantar flexors, knee flexors, and thigh adductors showed sustained and cumulative improvements from study baseline across all ICs. Investigator's, child/adolescent's and parent/caregiver's GICS scores confirmed improvement in LL spasticity at Week 4 of each IC. The incidence of AEs per IC ranged from 9.2% (IC5) to 25.8% (IC2) of patients. There was no evidence of increasing incidence of AEs with increasing IC. No AEs of special interest or fatal AEs occurred.

Conclusions: IncobotulinumtoxinA showed sustained efficacy with cumulative improvements and was well tolerated over up to 6 ICs for LL spasticity treatment in patients with CP.

Keywords:
Cerebral palsy; IncobotulinumtoxinA; Lower-limb spasticity; Multipattern; Pediatric; Repeated injections

EPNS21-154 Oral or poster
Movement Disorders

EFFICACY AND SAFETY OF INCOBOTULINUMTOXINA IN THE TREATMENT OF 2-5-YEAR-OLD CHILDREN WITH CHRONIC SIALORRHEA ASSOCIATED WITH NEUROLOGICAL DISORDERS AND/OR INTELLECTUAL DISABILITY

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Objective: The SIPEXI study investigated the efficacy and safety of repeated intraglandular incobotulinumtoxinA (incoBoNT/A) injections for sialorrhea associated with neurological disorders, also in young children aged 2-5 years.

Methods: SIPEXI was a prospective, multicenter, phase III study (NCT02270736) enrolling children with chronic sialorrhea associated with neurological disorders and/or intellectual disability. The younger cohort of 2-5-year-olds (N=35) was recruited after older children had been enrolled and assessed for safety. The 2-5-year-olds received up to 4 injection cycles (ICs) of incoBoNT/A with body weight-dependent doses according to weight classes of around 2 U/kg. The follow up period was 16 weeks per IC. Efficacy outcomes included carers' global impression of change scale (GICS) ratings (scale from -3 [very much worse] to +3 [very much improved]). Adverse events (AEs) were recorded. AEs of special interest (AESIs; incl. dysphagia, aspiration, pneumonia aspiration) were questioned.

Results: We present the results for 2-5-year-old patients (mean age 4 yrs; 57% with cerebral palsy; >94% with intellectual disability). 35 patients were treated with incoBoNT/A, 33 out of 35 completed all 4 ICs. Good treatment effects were seen, although results were descriptive only (small sample size). GICS ratings showed consistent improvements at all visits, with mean ratings around +1.1. Other endpoints supported the results. A sustained effect of incoBoNT/A was seen after repeated ICs, with notable improvements over time. The AE rate varied between the ICs (1st: 14.3%; 2nd: 21.2%; 3rd: 15.2%; 4th: 33.3%). Few related AEs and serious AEs (non-related) and no AESIs occurred. Most AEs were respiratory infections. No unexpected safety concerns arose.

Conclusions: Treatment of chronic sialorrhea with body weight-dependent doses of incoBoNT/A showed clinically relevant improvements and few and minor side effects in children aged 2-5 years.

Keywords:
Botulinum neurotoxin type A, IncobotulinumtoxinA, Chronic Sialorrhea, Pediatric

EPNS21-155 Oral or poster
Movement Disorders

EFFICACY OF INCOBOTULINUMTOXINA IN THE TREATMENT OF 6-17-YEAR-OLD CHILDREN AND ADOLESCENTS WITH CHRONIC SIALORRHEA ASSOCIATED WITH NEUROLOGICAL DISORDERS AND/OR INTELLECTUAL DISABILITY

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Objective: The SIPEXI study investigated the efficacy of repeated intraglandular incobotulinumtoxinA (incoBoNT/A) injections in children/adolescents with sialorrhea associated with neurological disorders.

Methods: SIPEXI was a prospective, multicenter, phase III study (NCT02270736) with a randomized, double-blind, parallel-group, placebo-controlled main period (MP, 1 injection cycle [IC]) and an open-label extension period (OLEX, 3 ICs). Children/adolescents with chronic sialorrhea associated with neurological disorders and/or intellectual disability, and severe drooling were enrolled. Patients aged 6 17 yrs were randomized to receive a body weight-dependent dose of incoBoNT/A according to weight classes of around 2 U/kg (total dose of 75 U for patients >=30kg) or placebo in the MP. In the OLEX, all received up to 3 further incoBoNT/A ICs. The follow-up period was 16 weeks for each IC. Primary endpoints were the change in unstimulated salivary flow rate (uSFR) from baseline to MP week 4, and the carers' global impression of change scale (GICS) rating at MP week 4. Further endpoints included changes in these parameters at later visits.

Results: We present the efficacy results for 6-17-year-old patients (mean age 10 yrs; ~60% with cerebral palsy; >85% with intellectual disability). In the MP, 148 patients received incoBoNT/A and 72 received placebo. 216 patients completed the MP. Of these, 214 patients entered and 189 patients completed the OLEX. At MP week 4, significantly larger improvements were seen for incoBoNT/A compared to placebo in uSFR ($p = 0.0012$) and carers' GICS ratings ($p = 0.032$). Other endpoints consistently supported these results. During the OLEX, prolonged and sustained treatment effects were seen.

Conclusions: IncoBoNT/A is effective for the treatment of chronic sialorrhea in children and adolescents.

Keywords:
Botulinum neurotoxin type A, IncobotulinumtoxinA, Chronic Sialorrhea, Pediatric

EPNS21-156 Oral or poster
Movement Disorders

SAFETY OF INCOBOTULINUMTOXINA IN THE TREATMENT OF 6-17-YEAR-OLD CHILDREN AND ADOLESCENTS WITH CHRONIC SIALORRHEA ASSOCIATED WITH NEUROLOGICAL DISORDERS AND/OR INTELLECTUAL DISABILITY

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Objective: The SIPEXI study investigated the safety of repeated intraglandular incobotulinumtoxinA (incoBoNT/A) injections in children/adolescents with sialorrhea associated with neurological disorders.

Methods: SIPEXI was a prospective, multicenter, phase III study (NCT02270736) with a randomized, double-blind, parallel-group, placebo-controlled main period (MP, 1 injection cycle [IC]) and an open-label extension period (OLEX, 3 ICs). Children/adolescents with chronic sialorrhea were enrolled in a stepwise manner: older patients first, with safety review before recruitment of younger cohorts to give early warning of unexpected safety issues. Patients aged 6 17 yrs were randomized to receive a body weight-dependent dose of incoBoNT/A according to weight classes of around 2 U/kg (total dose of 75 U for patients >=30kg) or placebo in the MP. Injections were performed under ultrasound guidance. In the OLEX, all received up to 3 further incoBoNT/A ICs. Safety was assessed by analyzing adverse events (AEs). AEs of special interest (AESIs; incl. dysphagia, aspiration, pneumonia aspiration) were questioned. A dentist assessed dental/periodontal AEs.

Results: We present the safety results for 6-17-year-old patients (mean age 10 yrs; ~60% cerebral palsy; >85% intellectual disability). In the MP, 148 patients received incoBoNT/A and 72 placebo. 216 patients completed the MP. Of these, 214 patients entered and 189 patients completed the OLEX. AE rates during the MP were similar for incoBoNT/A (18.2%) and placebo (15.3%). Rates of serious AEs, related AEs, and AESIs were low, with only 1 AESI case (dysphagia). In the OLEX, 43.4% of patients had AEs. The rate did not increase with repeated ICs. Respiratory infections were the most common AEs; dental AEs were rare. No unexpected safety concerns arose.

Conclusions: IncoBoNT/A is safe and well-tolerated for treatment of sialorrhea in children/adolescents at body weight-dependent doses up to 75 U per IC.

Keywords:
Botulinum neurotoxin type A, IncobotulinumtoxinA, Chronic Sialorrhea, Pediatric

EPNS21-199 Oral or poster
Movement Disorders

Movement disorders in paediatric age: are they really so rare?

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Objective: The aim of our study is to examine the features of a pediatric population accessing to Neurology Outpatients for movement disorders.

Methods: This is a retrospective single-centre study. The population examined included patients evaluated for movement disorders at the outpatient pediatric neurology department at Azienda Ospedaliera Universitaria of Padova between 01/01/2015 and 01/04/2021. Patient's personal information and clinical features were reported in our database.
Data were obtained from the "Galileo" platform. Categorical variables were expressed as percentage frequencies and compared with the Chi-square test.

Results: We identified 644 patients with movement disorders, 53 (8,2%) of them had more than one disorder, for a total of 709 disorders. Our population included 392 (60,9%) males and 252 (39,1%) females. 133 (20,7%) patients were evaluated within the first year of life and 373 (57,9%) between 1 and 10 years of age. 314 (48,8%) patients had an underlying disease.
The most frequently encountered disorder was stereotypia (182 patients, 28,3%), followed by tremor (146 cases, 22.7%) and tics (145 cases, 22.5%). These three disorders and dystonia cases (78 patients, 12,1%) accounted for 77.7% of the total. Other disorders described were 39 myoclonias (6,1%) and 19 dyskinesias (2.6%).
In our population, the frequency of tics among males (25.8%) compared to females (17.5%) was higher with statistical significance (p=0.01). Dystonias and dyskinesias were more frequent in the female population (8,9% males vs 17,1% females, p=0.002; 1,5% males vs 5,2% females p=0.010 respectively).
No gender differences were observed for the remaining disorders.

Conclusions: Movement disorders represent a clinical burden of great impact on the quality of life of our patients. The most frequent conditions in our population were stereotypes, tics, tremors, dystonia and ataxia, which represented 80% of total. These data suggest the need for future research in order to define diagnostic and therapeutic algorythms.

Keywords:
movement disorders rare?

EPNS21-2051 Oral or poster
Movement Disorders

"Spazio Huntington": Tracing the Early Motor, Cognitive and Behavioral Profiles of Kids with Proven Pediatric Huntington Disease and Expanded Mutations > 80 CAG Repeats

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Objective: The "Spazio Huntington-A Place for Children" program was launched in 2019. The aim was to contact at risk kids within Huntington disease (HD) families, to provide counseling to their parents and to start a prospective follow-up of kids suspicious to manifest pediatric HD (PHD).

Methods: We met 25 at risk kids in two years, four of whom with PHD and highly expanded (HE) mutations beyond 80 CAG repeats. We rated motor, neuropsychological and behavioral changes in all PHD kids by the Unified HD Rating Scale (UHDRS)-total motor score (TMS) and additional measures of (1) cognitive level (Leiter International Performance Scale), (2) adaptive functioning (Adaptive Behavior Assessment Systems), (3) receptive language (Peabody Picture Vocabulary Test) and (4) behavioral abnormalities (Child Behavior Check List and Children's Yale-Brown Obsessive Compulsive Scale).

Results: All PHD kids showed a severe progression of neurological and psychiatric manifestations including motor, cognitive and behavioral changes. The magnetic resonance imaging contributed to confirm the suspicious clinical observation by highlighting very initial striatum abnormalities in PHD.

Conclusions: Spazio Huntington is a program to prospectively study PHD, the most atypical face of HD, and may represent the basis to recruit PHD patients in future clinical trials.

Keywords:
Huntington Disease, Pediatric Huntington Disease, HD, PHD

EPNS21-2058 Oral or poster
Movement Disorders

Lesch-Nyhan disease: extrapyramidal neurological phenotype and behavioral symptoms in a series of patients. Retrospective and cross-sectional study.

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Objective: The aim of our study is to characterize the neurological, extrapyramidal and emotional-behavioral phenotype of Lesch-Nyhan disease (LND).

Methods: We conducted a retrospective and cross-sectional study on 13 male patients ranging 6-47 years, presenting LND-classic form. Neurological characterization was performed by clinical examination, with application of the Barry-Albright Dystonia Scale (BAD) and Burke-Fahn Marsden Disability Scale (BFM-Disability). Lesch-Nyhan Behavior (LNB) was studied with 4 scales: the Behavior Problems Inventory (BPI), the Yale-Brown Obsessive-Compulsive Scale (YBOCS); the Yale Global Tic Severity Scale (YGTS) test and finally the Child/Adult Behavior Checklist (CBCL/ABCL). Data obtained were statistically analyzed and compared.

Results: Our sample presented a motor disorder with severe generalized dystonia associated with dysarthria in 100% of cases and others extrapyramidal and pyramidal signs in over 50% of patients. Self-injurious and heteroaggressive behaviors were found in 91.6% of patients, with an average of 3-5 problematic behaviors per patient. CBCL and ABCL pattern showed the prevalence of internalizing problems in 75% of cases. We did not find statistically significant correlation between dystonia intensity e LNB severity, measured by the 4 different tests.

Conclusions: We confirm that LND is neurologically characterized by a severe movement disorder with dystonia, involving especially limbs and the orofacial district. LNB is present in almost the totality of patients (92%) of our cohort. It is still debated how to appropriately describe and score the complexity of LNB: however, none of the tests applied seems able to correctly evaluate the severity of LNB. On the other hand, our data do not support the presence of a characteristic psychopathological profile: internalizing problems are predominant, while externalizing problems are rare. Future studies are needed to better characterize and measure LNB.

Keywords:
Lesch-Nyhan, extrapyramidal, behavior, phenotype

EPNS21-212 Oral or poster
Movement Disorders

Improvements in upper limb spasticity-related pain in children/adolescents with cerebral palsy after incobotulinumtoxinA injections

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Objective: This is an analysis of the effects of incobotulinumtoxinA (incoA) on upper limb (UL) spasticity-related pain (SRP) over multiple treatment cycles (ICs) in children/adolescents (C/As) with cerebral palsy (CP) using pooled data from two prospective trials in the incoA international paediatric phase 3 study program.

Methods: In the TIMO and XARA studies, C/As aged 2-17 years with CP-associated uni- or bilateral UL spasticity received incoA for up to 4 ICs that could be adjusted for individual needs. Data from all incoA doses were combined. SRP was assessed with the Questionnaire on Pain caused by Spasticity (QPS); C/A- (direct or via interviewer) and parent/caregiver (P/C)-completed modules were used. The pain population included all C/As for whom a key QPS item score was >0 at baseline (using the 10-point graphic Wong-Baker FACES scale); post-baseline scores of 0 indicated complete pain relief.

Results: Data from 155 C/As and 388 P/Cs with data for at least one item of the respective UL QPS module were included. UL general pain was reported by 69 C/As at baseline; 39.7% and 41.8% patients treated with incoA were pain-free by week 4 of IC1 and IC4, respectively ($p<0.001$ vs baseline for all ICs). C/A-reported mean UL QPS general item intensity scores improved by 1.7 and 2.2 points for patients treated with incoA at week 4 of IC1 and IC4, respectively ($p<0.001$ vs baseline for all ICs). P/Cs observed UL general pain in 277 C/As at baseline; 28.3% and 38.2% patients treated with incoA were pain-free by week 4 of IC1 and IC4, respectively ($p<0.001$ vs baseline for all ICs). C/A-reported and P/C-observed improvements were generally greater with demanding tasks than at rest and were more pronounced with increasing incoA ICs.

Conclusions: In addition to muscle tone regulation, incoA provided sustained pain relief across multiple ICs for children with CP and UL SRP, even when they were engaged in demanding tasks.

Keywords:
Botulinum toxin A, Muscle Spasticity, Movement Disorders, Paediatric, Cerebral Palsy, Pain

EPNS21-214 Oral or poster
Movement Disorders

Improvements in lower limb spasticity-related pain in children/adolescents with cerebral palsy after incobotulinumtoxinA injections

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Objective: This is an analysis of the effects of incobotulinumtoxinA (incoA) on lower limb (LL) spasticity-related pain (SRP) over multiple treatment cycles (ICs) in children/adolescents (C/As) with cerebral palsy (CP) using pooled data from three prospective trials in the incoA international paediatric phase 3 study program.

Methods: In the TIM, TIMO and XARA studies, C/As aged 2-17 years with CP-associated uni- or bilateral LL spasticity received incoA for up to 4 ICs that could be adjusted for individual needs. Data from all incoA doses were combined. SRP was assessed with the Questionnaire on Pain caused by Spasticity (QPS); C/A- (direct or via interviewer) and parent/caregiver (P/C)-completed modules were used. The pain population included all C/As for whom a key QPS item score was >0 at baseline (using the 10-point graphic Wong-Baker FACES scale); post-baseline scores of 0 indicated complete pain relief

Results: Data from 330 C/As and 839 P/Cs with data for at least one item of the respective LL QPS module were included. LL general pain was reported by 178 C/As at baseline; 35.3% and 49.4% patients treated with incoA were pain-free by week 4 of IC1 and IC4, respectively ($p<0.001$ vs baseline for all ICs). C/A-reported mean LL QPS general item intensity scores improved by 2.1 and 2.8 points for patients treated with incoA at week 4 of IC1 and IC4, respectively ($p<0.001$ vs baseline for all ICs). P/Cs observed LL general pain in 568 C/As at baseline; 25.2% and 34.1% patients treated with incoA were pain-free by week 4 of IC1 and IC4, respectively ($p<0.001$ vs baseline for all ICs). C/A-reported and P/C-observed improvements were generally greater with demanding tasks than at rest and were more pronounced with increasing incoA ICs.

Conclusions: In addition to muscle tone regulation, incoA provides sustained pain relief across multiple ICs for children with CP and LL SRP, even when they are engaged in demanding tasks.

Keywords:
Botulinum toxin A, Muscle Spasticity, Movement Disorders, Paediatric, Cerebral Palsy, Pain

EPNS21-227 Oral or poster
Movement Disorders

Dysfunctional Neuronal Signaling and Nervous System Development Link Early- and Late-Onset Ataxia with Comorbid Dystonia

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Objective: The clinically and genetically heterogeneous group of cerebellar movement disorders described as "ataxia" can have an early- and a late onset (EOA and LOA). Both EOA and LOA frequently present with comorbid features of dystonia (EOAD+, LOAD+) complicating clinical and genetic diagnostics. In EOAD+, we previously demonstrated that impairment at the cortico-basal-ganglia-pontocerebellar (CPC) network co-occurs with genes acting in pathways underlying energy failure and/or aberrant lipid metabolism, implied in dysfunctional neuronal signaling. In the present study, we aimed to investigate whether dystonia in EOAD+ and LOAD+ occurs due to shared pathogenetic mechanisms.

Methods: In this exploratory study, we used PubMed and OMIM to select all LOAD+ genes, and linked these with reported coinciding MRI findings. Subsequently, we performed gene network- and functional enrichment analyses on the LOAD+ gene group using GeneNetwork and gProfiler, and we compared the outcomes with the results of our EOAD+ study.

Results: Mutations in LOAD+ genes were associated with similar anatomical defects in the CPC network as reported earlier for EOAD+ genes. Gene network- and enrichment analyses of LOAD+ genes revealed involvement of processes implicated in nervous system development, trans-synaptic signaling and transmembrane transport. In both EOAD+ and LOAD+ groups, we observed that different pathogenetic mechanisms can lead to dysfunctional neuronal signaling, with a link to nervous system development.

Conclusions: Although EOA and LOA encompass different clinical, genetic and pathogenetic entities, our studies on ataxia with dystonic comorbidity converge on similar anatomical defects in the CPC network, in association with biological pathways involved in dysfunctional neuronal signaling and impaired nervous system development. These results may imply that EOAD+ and LOAD+ could share the same disease spectrum, suggesting a potential diagnostic benefit of genetic testing using complete ataxia-dystonia gene lists.

Keywords:
early-onset ataxia (EOA); late-onset ataxia (LOA); dystonic comorbidity; cortico-basal-ganglia-pontocerebellar network; neuronal signaling; nervous system development; gene network analysis; functional enrichment analysis.

EPNS21-241 Oral or poster
Movement Disorders

A toddler with Myoclonus Dystonia (DYT11) due to a mutation in the SGCE-gene : case description and review of the therapeutical aspects of this movement disorder.

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Objective: We present a case of a young girl diagnosed with myoclonus dystonia due to a mutation in the SGCE gene and the treatment results in this patient, comparing it to the different therapeutical options described in the literature.

Methods: Case Report an review of the literature
A 2,5 year old girl presented with a recently started limping gait. Her mother noticed already for a longer time paroxysmal shivering of the trunk.
Initially orthopaedic abnormalities were excluded. The gait abnormalities persisted and it became clear that she suffered from a dystonia. Additional investigations were negative and we started genetic elaboration. A gene panel revealed a heterozygote pathogenic variant in the SGCE-gene, confirming the diagnosis of Myoclonus-Dystonia (DYT11).
At the age of four, we started different drug trials.
We reviewed the literature on treatment options in myoclonus dystonia .

Results: In the literature a wide spectrum of treatment options is described, no single gold standard has been established. The articles on treatment focus mainly on the movement disorder and less on the psychiatric aspects.
In our patient we tried different drug regimens :
Some drugs had no effect or worsened symptoms : levodopa (no effect), zonisamide (positive effect on myoclonus but not on the dystonia and worsening of her anxiety), levetiracetam (no effect), clonazepam (tiredness as disturbing side effect)
At the age of five, our patient functions quite well under a combination of carbamazepine (excellent effect on her anxiety) and trihexyphenidyl (excellent effect on the dystonia with normalisation of her gait and reduction of the myoclonus). Clobazam had a positive effect on the myoclonus but is not needed anymore now that she takes trihexyphenidyl. She still suffers from some residual writer's cramp.

Conclusions: Our case highlights the importance of targeting the different aspects of the disorder: dystonia, myoclonus and psychiatric manifestations, each of these aspects requiring a different medical approach.

Keywords:
Myoclonus Dystonia treatment, DYT11, SGCE

EPNS21-256 Poster only
Movement Disorders

A novel familial KMT2B missense variant associated with a variable clinical manifestation comprising dystonia and non-dystonic features

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Objective: Currently, variants in lysine-specific histone methyltransferase 2B (KMT2B) are frequently found in patients with childhood-onset dystonia. Most KMT2B variants appear de novo, although parental inheritance has been reported. Notably, a non-dystonic phenotypic spectrum in carriers, including short stature and microcephaly, has been described, and incomplete penetrance has been postulated. Here, we report a novel variant in a patient with dystonia and two relatives with non-dystonic features.

Methods: We performed exome sequencing (ES) in a girl presenting with progressive dystonia, followed by segregation analysis of the family members.

Results: The 16 years old female individual reported right lower limb dystonia at the age of 8, which quickly progressed to generalized dystonia. At the time of referral, she appeared with generalized dystonia and dysarthria. Moreover, she underwent strabismus surgery and presented with short stature and microcephaly. ES revealed a novel heterozygous variant in the KMT2B gene [c.3229C>T p.(Arg1077Trp)] that affects a highly conserved arginine residue, is not found in gnomAD, and was formally classified as likely pathogenic. Her 15 years old sister and father presented with strabismus and microcephaly but without dystonia. Segregation analysis revealed that both the sister and father carry the same heterozygous variant but not the clinically healthy mother and another younger sister. We applied deep brain stimulation (DBS), which effectively improved the patient's motor symptoms, in line with publications reporting the efficacy of DBS in KTM2B-related dystonia.

Conclusions: We present a novel KMT2B variant associated with typical dystonic features in a female adolescent benefitting from DBS. We show that KMT2B variants should also be considered likely pathogenic if variant-carrying relatives exhibit specific non-dystonic features or seem to be unaffected, thus underlining the importance of early genetic diagnostics in children with dystonia.

Keywords:
KMT2B, childhood-onset dystonia

EPNS21-257 Poster only
Movement Disorders

An Unusual Cause of Frequent Neurological Symptoms

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Objective: Congenital cerebellar ataxia caused by mutation of the COQ8A gene occurs due to disturbances in CoQ10 synthesis,which has a key role in energy production.Disorders of CoQ10 biosynthesis can affect many organ systems.Some patients have cognitive difficulties,muscle weakness,cardiomyopathy and epilepsy.At the age of expected puberty,associated hypergonadotropic hypogonadism is possible.

Methods: A boy,aged 4 years and 6 months,was admitted to hospital for clumsiness,ataxia,strabismus,dysarthria and severe headaches.His problems started two years previously after he suffered from chicken pox.The parents did not have the impression that his symptoms had progressed.On physical examination,he had particular difficulty walking on stairs,and his hands shook whilst drawing and writing.

Results: His SARA(Scale for the Assessment and Rating of Ataxia)score was 15/40.His cognitive development was normal.The comprehensive workup(haematological,biochemical,metabolic and immunological) was normal,as was genetic analysis for CMT1A duplication/HNPP deletion,SCA1,2,3,6,7 and Friedreich's ataxia.Electro-physiological tests(ECG,EEG,EMNG,visual and auditory evoked potentials)MRI of the brain with tractography and the spinal cord on a high-resolution device were unremarkable.Clinical exome sequencing showed two pathogenic mutations c.1009G>A (p.Ala337Thr)and c.1028A>C(p.Gln343Pro)in the COQ8A gene.These variants,in the context of the clinical picture, indicated COQ8Ataxia, which can be treated with coenzyme Q10.At the first follow-up after six months of therapy patient showed slight improvement(SARA score 11,5/40).

Conclusions: Rare congenital ataxia,caused by mutations in the COQ8A gene, inherited by autosomal recessive trait affects many organ systems.The authors point out this rare but potentially treatable cause of ataxia, which should be considered in differential diagnosis of neuro-developmental disorders in children.Early diagnosis and treatment can prevent long-term consequences and slow down disease progression.

Keywords:
Ataxia, strabismus, dysarthria, CoQ10 synthesis

EPNS21-262 Oral or poster
Movement Disorders

Acute ataxia - etiology, clinical presentation and outcome in cohort of 76 children

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Objective: The evaluation of the etiology, clinical presentation, and predictive factors of outcome in children with acute ataxia (AA).

Methods: The retrospective study included the patients with AA treated from 2015 - 2021. The inclusion criteria were: children aged 0.5 - 18 years; evolution time of AA < 72 hours. The exclusion criteria were: anamnestic data about ataxia without confirmation by a physician; chronic/persistent or psychogenic ataxia. Clinical presentation was divided into two categories: isolated cerebellar signs (CS), and CS plus symptoms. The outcome was assessed at the end of hospitalization and was defined as complete or incomplete recovery. The predictive value of different factors (sex, age, previous infection, brain scan result, presence of additional CS plus symptoms, and structural abnormalities) in outcome was analyzed using univariate and multivariate logistic regression analyses.

Results: The study included 76 children, mean aged of 5.7 years (IQR 2.1-8.3). The most frequent causes of AA were immune-mediated/infective cerebellar ataxia in 27 (35.5%), and intoxication in 24 (31.6%), followed by vestibular ataxia, opsoclonus-myoclonus syndrome, and intracranial expansive process. The isolated CS had 41 (56%), and CS plus had 35 (46%) patients. Complete recovery experienced 62 (81,6%) patients. Univariate analysis showed that the presence of CS plus symptoms (p=0.007) and structural abnormalities (p=0.001) were related to a worse outcome. In multivariate logistic regression analysis of these factors, statistical significance remained (p=0.021 and p=0.002, respectively).

Conclusions: Immune-mediated/infective cerebellar ataxia and intoxication are the most frequent etiology of AA in children with a commonly favorable outcome. The awareness is necessary if cerebellar signs are associated with vomiting, headache, a new onset paresis, and opsoclonus since the presence of CS plus symptoms and brain structural abnormalities are related to a worse outcome.

Keywords:
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EPNS21-310 Oral or poster
Movement Disorders

The role of the unfolded protein response (UPR) in childhood genetic ataxia

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Objective: 1. To determine the diagnostic rate of genetic testing for paediatric ataxia.
Next generation sequencing (NGS) allows analysis of additional genes per patient, with a concomitant increase in variants of uncertain clinical significance (VUS). We compare diagnostic pick-up rates between single gene and NGS analysis in paediatric ataxias.
2. To determine the role of the UPR in genetic ataxia.
The UPR is an intracellular mechanism activated by dysfunction of protein production. Prolonged activation of the UPR leads to apoptosis, however therapeutic modulation of the UPR is possible. A systematic literature review to determine UPR association with rare genetic ataxia was performed.

Methods: Referrals for paediatric ataxia to Sheffield Diagnostic Genetics Service (SDGS) between 2010-2019 were analysed. Diagnostic rates for single gene and NGS panel testing were compared. All diagnostic results were subjected to systematic literature review for evidence of UPR involvement.

Results: 353 ataxia patients were referred to SDGS for genetic testing between 2010-19: 219 ataxia single gene and 134 ataxia NGS. Genetic diagnoses were identified in 16 (7%) single gene ataxia tests and 32 (24%) of ataxia NGS with a further 28 (21%) NGS tests inconclusive. Systematic review of current literature identified several paediatric ataxias with evidence for UPR involvement.

Conclusions: NGS testing can increase diagnostic rates for paediatric ataxia (7% vs 24%), with an additional 21% giving inconclusive genetic results. There is a need for further functional analysis for VUS. Paediatric genetic ataxias showing UPR involvement have been selected for further analysis.

Ethical approval has been obtained for the recruitment of paediatric patients with a genetic diagnosis of paediatric ataxias with UPR involvement. Cell based assays will be used to monitor the activation of the UPR in patient cells.

Keywords:
Genetic ataxia, next generation sequencing, unfolded protein response

EPNS21-460 Oral or poster
Movement Disorders

Mutations encoding dopamine receptors cause complex childhood-onset hyperkinetic disorders

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Objective: Dopamine receptors, especially D1 (encoded by DRD1) and D2 (DRD2) are a key component of neurological networks controlling voluntary movement. Until 2021, however, no monogenic disorders associated with their malfunction had been reported. We describe the first family affected by disease due to a DRD1 variant, and another due to DRD2.

Methods: Whole-genome sequencing was performed in a cohort of well-phenotyped patients with movement disorders believed likely to be genetic. In silico tools and structure-function modelling helped predict impact of candidate variants. For DRD1, over-expression of the variant in HEK-293T cells was used to assess production of the protein by Western blotting, cell-membrane localisation by biotinylation and immunofluorescence, and ligand binding response by luminescence-based measurement of cAMP production. For DRD2, case matching confirmed the relevance of the variant.

Results: In a child with a phenotype strongly suggestive of dopaminergic dysfunction (generalised dystonia, oculogyric crises), but with normal neurotransmitter levels, a homozygous missense variant in DRD1 was identified (c.110C>A; p.Thr37Lys). Functional investigations confirmed near-normal cellular protein levels and appropriate localisation to the cell surface membrane; however, second-messenger (cAMP) production in response to dopamine binding was significantly reduced compared with the wild-type, confirming functional deficiency of the mutant protein. A heterozygous missense variant (c.1121T>G; p.Met374Arg) in DRD2 was identified in a girl with an infant-onset choreiform disorder and neurodevelopmental delay. The same variant, predicted to cause gain of function, was identified by another team in an unrelated individual with matching clinical features.

Conclusions: Variants in DRD1 and DRD2 are associated with characteristic movement disorders. Identification of these new genetic syndromes is a first step towards developing targeted therapies.

Keywords:
dopamine; D1; DRD1; D2; DRD2; infantile dystonia-parkinsonism; chorea; dyskinesia

EPNS21-479 Oral or poster
Movement Disorders

Amyotrophic lateral sclerosis type 2: paediatric phenotype and distinctive clinical progression, as experienced in a tertiary movement disorder service

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Objective: To present the paediatric phenotype of amyotrophic lateral sclerosis type 2 (ALS2) as seen in a tertiary movement disorder clinic (MDC) and to highlight the distinctive clinical progression of the condition.

Methods: A 10 year retrospective review of MDC records (search term ALS2) identified three affected sibling pairs with homozygous mutations in ALS2 gene and 2 further children, one with homozygous mutation and one with 2 pathogenic compound heterozygous variants in ALS2 gene (8 children). Presenting features and clinical progression are described.

Results: 8 children had mean presentation to MDC at 3.7 (1.8- 6.7) years with mean follow up of 7.5 (2.4-14) years.
Development:
Normal early development in 4/8 children, 2 had mild motor delay, 2 never walked independently. First concerns raised before 2 years of age in all children, comprising gross motor difficulties and increased tone.
Clinical Features:
All children initially presented with predominantly spastic tone affecting the lower limbs. Emerging dystonia noted in the first clinical assessment at MDC. One sibling pair developed generalised muscle weakness and some cerebellar signs.
4/8 presented with early speech delay and all (8/8) showed progressive dysarthria, leading to anarthria in 2/8. These 2 patients also developed dysphagia.
3/8 developed scoliosis, 2 requiring spinal surgery.
Diagnostic features:
- MRI brain scan: normal in 3/8, non-specific immaturity of the white matter in 4/8, some cerebellar atrophy in 1/8.
- EMG/NCS: contacted in 3/8, no abnormality.
- Distinct pathogenic mutations identified in ALS2 gene on gene panel/exome or genome testing: One patient with 2 pathogenic variants, and rest with homozygous mutations- each pair of siblings sharing the same mutation

Conclusions: We report a consistent picture of mixed pyramidal and dystonic movement disorder, with bulbar involvement in 8 children, all with confirmed mutations in ALS2 gene. We suggest that ALS2 gene should be screened in patients presenting with similar phenotype.

Keywords:
ALS2, Amyotrophic lateral sclerosis 2

EPNS21-483
Movement Disorders

Oral or poster

Benefits of selective percutaneous myofasciotomy for the treatment of toe walking

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Objective: We present a prospective study with 50 patients who had been diagnosed with toe walking which required invasive treatment, following a period of failed treatment attempts using non-invasive methods. A selective percutaneous myofasciotomy was performed to treat the movement disorder. The objective of this study was to assess the benefits of this surgical method for the reduction of toe walking and the improvement in ankle mobility in patients aged 5-18.

Methods: Participants were selected from a cohort of patients receiving treatment for toe walking, with no known orthopaedic or neurological cause following an initial examination. All patients had previously been prescribed non-invasive treatment, involving pyramid insoles, night splints and botulinum toxin. These failed to treat the symptom of the toe walking gait. The severity of toe walking and the ankle mobility were recorded before and after surgery. Follow-up data was collected 1 year after surgery

Results: The surgery reduced the occurrence and severity of toe walking with lasting effect in 47 of the 50 patients. Furthermore, surgery improved the movement in the upper ankle joint by a minimum of 5 degrees. Foot deformities such as pes cavus or drop foot were reduced after one year. 10 patients developed a postoperative hematoma, which was successfully treated with lymphdranage. Toe walking reoccurred in three patients, one due to poor compliance with postoperative guidelines; in one case resulting from a growth spurt and for unknown reasons in the third case.

Conclusions: Selective percutaneous myofasciotomy is a minimally invasive treatment method for severe or persistent cases of toe walking. It improved toe walking at one year follow-up in 47 out of 50 patients. There are indications that surgery is more commonly necessary in toe walkers with mild neurological symptoms, such as speech and developmental delays.

Keywords:
Toe walking, Surgery, gait anomaly, movement disorder, neurologic symptoms of toe walking, treatment of toewalking gait, selective myofasciotomy, surgery for toe walking,

EPNS21-520 Oral or poster
Movement Disorders

Role of dopaminergic agonists in SLC18A2 associated movement disorders

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Objective: The catecholamine dopamine is integral for normal movement. Genetic variations in the monoamine transporter gene SLC18A2 result in infantile onset of parkinsonian like symptoms with pstosis and bulbar dysfunction. This is due to SLC18A2 encoding for the vesicular monoamine transporter 2 (VMAT2) which transports cytoplasmic monoamines into synaptic vesicles.

We present two siblings, born to consanguineous parents, with profound global development delay and both pyramidal and extrapyramidal movement disorders. Genetic testing revealed common SLC18A2 variants in both patients. It was, therefore, hypothesised that both patients would respond to dopaminergic agonist treatment.

Methods: The eldest sibling was initially trialed on L-Dopa with worsening of their movement disorder. They have recently been started on the dopaminergic agonist Pramipexole. High doses of Pramipexole caused worsening of the movement disorder and increased secretions. Reduction of the dose resulted in clinical improvement in the movement disorder and Trihexyphenidyl has just been commenced.

The younger sibling was started directly on Pramipexole with initial good clinical response. Unfortunately, the patient soon developed significant extrapyramidal movements. Dose alteration reduced these extrapyramidal side effects and Trihexiphenidyl has recently been commenced.

Results: Clinical deterioration was noted with L-Dopa. Treatment with dopaminergic agonists improved both patients' movement disorders but this was dose dependent and not as marked as hoped. Extrapyramidal side effects were seen in both patients with the dopaminergic agonist, Pramipexole.

Conclusions: L-Dopa was not effective in the management of these siblings with significant pyramidal and extrapyramidal movement disorders. The dopamine agonist Pramipexole did offer some symptomatic improvement but its benefit was dose dependent.

The Dopaminergic agonist Pramipexole offers dose dependent improvement in SLC18A2 variant movement disorder control.

Keywords:
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EPNS21-54
Movement Disorders

Oral or poster

CACNA1A Associated Ataxia: Improvement of Motor Skills and Speech by Acetyl-DL-Leucine

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Objective: Beneath familial hemiplegic migraine and episodic ataxia, type 2 mutations in CACNA1A are associated with a broad phenotype that also includes chronic progressive ataxia. Here we are presenting a 11-year-old severely atactic boy, whose whole exome sequencing disclosed the heterozygous mutation c.3686C>T in CACNA1A. A treatment with 4-Aminopyridin and acetazolamide failed to ameliorate his clinical symptoms. Acetyl-L-leucine (L-AL) has recently shown to improve ataxia in Niemann-Pick disease type C. The objective of this individual case of off-label use of acetyl-leucin was to explore efficacy in this patient.

Methods: We treated our patient with amino acid acetyl-DL-leucine (DL-AL) in a dosage of 0.1 g/kg/day as an "individual case of off-label use." We assessed him using the Scale for the Assessment and Rating of Ataxia (SARA) and the Spinocerebellar Ataxia Function Index (SCAFI) at baseline, with six weeks and three months.

Results: Before treatment, he was walking slowly, standing with a significant sway and could not jump. Already after six weeks of treatment, but also in the three-month follow-up he showed a dramatic improvement of his walking pattern, the time needed for the 9-hole-peg-test (9HPT-D) and the 8-meter-walk-test (8MWT), and improvement in speech (PATA test) and he could also perform bipedal jumping. (Videos to be presented).

We found a significant improvement in the Scale for the Assessment and Rating of Ataxia (SARA improved by 4.5 points) and the Spinocerebellar Ataxia Function Index (SCAFI: PATA improved by 4.5 points, 9HPT-D by 25.6 sec, 8MWT by 2 sec). AL was well tolerated and clinically significant laboratory results were detected.

Conclusions: DL-AL improved significantly gross and fine motor skills as well as speech in a twelve-year-old boy with CACNA1A-associated ataxia. These observations suggest that treatment with DL-AL or L-AL could also be a meaningful treatment option for patients with CACNA1A associated disorders.

Keywords:
ataxia, acetyl-leucin, off-label use, SARA, SCAFI

EPNS21-566 Poster only
Movement Disorders

Tetrabenazine in the treatment of movement disorders of FOXG1-related syndrome

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Objective: The FOXG1 gene plays a vital role in mammalian brain differentiation and development. Mutations in this gene are associated with severe developmental delay, absent verbal language, post-natal microcephaly, epilepsy and a spectrum of hyperkinetic movement disorder.

Methods: Case presentations

Results: The first patient is a four-year-old boy with early onset epileptic encephalopathy that required management with multiple antiepileptic drugs including levetiracetam, valproic acid and vigabatrin. His brain MRI showed a dysplastic corpus callosum. Whole exome sequencing (WES) demonstrated a pathogenic mutation in the FOXG1gene (NM_005249.4): p.Ser459fs/c.1374delC. He showed severe developmental delay, microcephaly and a severe sleep disorder. He developed generalized chorea that worsened over time. At the age of 4 years his movement disorder was interfering with trunk control and feeding. He was started on tetrabenazine (3 mg/kg/day) and showed a favorable response. After ten (10) weeks on treatment he was able to sit and eat efficiently by mouth.
The second patient is a five-year-old boy with global developmental delay, acquired microcephaly and mild chorea since infancy. His brain MRI showed corpus callosum dysgenesis. WES demonstrated a heterozygous deletion in the FOXG1gene (1490pb, chr14:29236476-29237965). His movement disorder worsened over time and by the age of 5 years it was interfering with trunk control. He was managed with tetrabenazine at 3 mg/k/d). He showed a favorable response to treatment with improvement in the amplitude and intensity of his choreic movements and his ability to sit.

Conclusions: Tetrabenazine can be efficiently used in the management of hyperkinetic movement disorders in patients with FOXG1-related syndrome.

Keywords:
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EPNS21-577 Poster only
Movement Disorders

Bradykinesia assessment in children with cerebral palsy and periventricular leukomalacia

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Objective: Prematurity and periventricular leukomalacia (PVL) is one of the most common causes of cerebral palsy (CP). Recently, we showed that in these patients spasticity often coexists with dystonia. We now hypothesize that bradykinesia is also present in this population and is connected to the presence of dystonia.
Purpose: To assess bradykinesia in children with CP and PVL.

Methods: This study involved 25 children with CP and PVL. Patients were classified according to their motor and manual functional ability. The Modified Ashworth Scale was used to measure spasticity and the Burke-Fahn-Marsden Scale to measure dystonia severity. The Unified Parkinson?s disease rating scale was used to assess bradykinesia. Patients were video-recorded following a standard protocol. Statistical analysis was performed with the python programming language. Pearson r, Mann-Whitney criteria and linear regression analysis were used for the study of correlations. $P < 0.01$ was used as the limit of the level of statistical significance.

Results: Bradykinesia was observed in 96% of children. The upper and lower extremities showed a similar degree of bradykinesia, with a slightly higher score in the upper extremities. The severity of bradykinesia, was significantly related to gross motor and manual function. There was significant correlation between the severity of bradykinesia and the severity of dystonia. None of the patients showed evidence of rigidity, resting tremor, or postural instability.

Conclusions: This study confirms the existence of bradykinesia in patients with CP and PVL which seems to be related to the presence of dystonia. Bradykinesia and dystonia appear to be an important factor influencing the level of gross and fine motor skills, as well as the activities of these children in everyday life, which in turn will affect their quality of life.

Keywords:
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EPNS21-688 Oral or poster
Movement Disorders

Increased numbers of functional tics seen in adolescents during the COVID-19 pandemic

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Objective: A global increase in numbers of functional tics in adolescents has been seen. It is important to differentiate functional tics from classic tics, as seen in Tourette's syndrome, since pathophysiology and treatment differ. Similarity between the functional tics has caused speculations whether COVID-19 and use of social media could play a role in the increased incidence. Possible triggers for development of functional tics are investigated, and the combination of the COVID-19 pandemic and social media exposure is discussed. Further, treatment and its effect will be discussed.

Methods: Journals of 28 adolescents diagnosed with functional tics, May 2020-June 2021 have been retrospectively reviewed. Analyzed with descriptive statistics.

Results: N=28 patients diagnosed with functional tics were included, 96.4% girls and 3.6% boys, mean age 14.4 years at onset. Tic phenomenology differed from classic tics among others with more complex tics. Prior to the onset of functional tics 78.6% of all patients had trauma/precipitating event and 60.7% reported psychiatric symptoms. 42.9% had a first-degree family member with psychiatric symptoms. 95.2% experienced a trigger. 40% denounced lockdown and 25% reopening of the society related to the COVID-19 pandemic as stressful events. 96.4% had social media exposure. The treatment consisted of psychoeducation and focus on psychiatric symptoms and had effect in 100% of the patients.

Conclusions: Functional tics differ from classic tics regarding e.g. sex, age of onset and phenomenology. Characteristic for the adolescents in our cohort is the vulnerability. It is possible that the consequences of the COVID-19 pandemic for already vulnerable adolescents in combination with social media exposure, could be part of the cause for the increased numbers of adolescents presenting with functional tics.

Keywords:
functional tics, adolescent, COVID-19, social media

EPNS21-707 Oral or poster
Movement Disorders

Deep brain stimulation in pediatric patients with Pantothenate Kinase-Associated Neurodegeneration (PKAN) syndrome: case series and perspectives.

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Objective: Pantothenate-Kinase-2 associated neurodegeneration is a complex genetic disorder with brain iron accumulation leading to severe and progressive generalized dystonia. No curative treatment has been proposed to date. Deep brain stimulation (DBS) of the internal globus pallidus (GPi) can bring a partial improvement of their dystonia.
In this study, we present our cohort of 6 pediatric patients suffering from the classical form of the pathology who underwent DBS in our center.

Methods: This is a prospective study to investigate the effects of bilateral GPi-DBS in 6 pediatric patients (mean age at surgery 7.8 years; Mean disease duration before surgery: 2.5 years). DBS surgery was performed under general anesthesia, with per-operative electrophysiological and imaging (CT scan) control. Target was the GPI in 6 patients. In 2 patients, additional target was the subthalamic nucleus (STN). Stimulating parameters: Frequency: 130 Hz; Pulse width: 90 - 450 µs; Intensity: 1 - 3.7 mA. Clinical evaluation was performed using the Burke-Fahn-Marsden (BFM) scale; neurobehavioral, cognitive and quality of life scales every 3 months and later every 6 months.

Results: At 6 months post op, 4 patients on 6 had a decrease in the BFM score suggesting a better clinical situation. 2 Patients worsened in the post-operative period suggesting that DBS had no effect on the course of the disease for this patients.
At 18 months FU (4 patients), all scores increased but very slowly in 2 patients. Some functional gains have endured. The benefits on pain and dystonic storm remain at 18 months follow up allowing to preserve quality of life for months or even a few years.

Conclusions: DBS seems to slow down the clinical progression of the pathology and to prevent (to some extent) motor complications related to dystonia. It remains to determine when the surgery should be performed in the course of the disease and whether an additional target in a non-degenerative structure is relevant.

Keywords:
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EPNS21-713 Oral or poster
Movement Disorders

Self Injury and Lesch Nyhan's syndrome: a fatality? Interest of DBS in this indication

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Objective: Lesch-Nyhan syndrome is an X-linked metabolic disorder affecting the purine mechanism, secondary to hypoxanthine-guanine phosphoribosyltransferase deficiency. These children have a neurological picture generally associating: a cognitive delay, a generalized dystonia, dyskinesias and compulsive self-injurious behavior (SIB) of the oro-facial sphere and the upper limbs. Permanent restraints, dental trays or edentulism are the rule to protect them from bites, as drug treatments are ineffective.
We report our experience with Deep Brain Stimulation (DBS) by bilateral electrode implantation) in the anterior and posterior parts of the Globus Pallidus Interna (GPi) in this pathology. We present the clinical outcomes in particular on SIB and compare with those of the literature.

Methods: 2 patients (13/6 years old) underwent DBS surgery in our department.All our patients had a protocolized pre and post-operative assessment including videos, dystonia and quality of life scales.

Results: Both patients had a major improvement of their SIB as early as 3 months postoperatively; there was no post DBS complications. For the first case, at 12 months FU, the reduction of SIB was more than 90%, allowing to stop the dental trays and the restraints almost permanently. In the second case, at 3 months post-op, the restraints were removed several hours a day. Dystonia improved in both patients, with improved comfort and positioning.
In the literature, 15 patients have been reported to date, with a disappearance or marked improvement in self-injury in all cases. The effect on dystonia is also constant but with a variable functional gain.

Conclusions: Multi Target DBS is a particularly interesting and effective therapeutic option for the treatment of SIB in these patients, which seriously impacts their quality of life. Early surgery may also allow an improvement in the motor abilities of these children who, without DBS are permanently restrained to protect them from SIB.

Keywords:
Lesch Nyhan, Dystonia, Self injury, DBS

EPNS21-10 Oral or poster
Neuro rehabilitation

Implementation of computer game technologies for patients with ataxia due to post-traumatic head injury: Randomized Controlled Trial

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Objective: Patients with post-traumatic brain injury often suffer motor discoordination, ataxia and dyspraxia. The formation of the correct movement patterns, improved balance are important tasks of rehabilitation for these patients. The effectiveness of rehabilitation depends on the plasticity of the nervous system stimulated by repetition of specific movements, the intensity of training and motivation. The first commercially successful computer games were developed in 1970-ies as an entertainment. Almost instantly, physicians and rehabilitologists began to use computer and video games as a part of the therapy, developed rehabilitation games. Nowadays around 60% of general population play computer games. Interesting game plot stimulates correct performance of the exercise, increases speed and amplitude of movements, develops coordination.

Methods: RCT. 206 patients (46,6% males, 43,4% females, mean age-15y2m). Control group-102 subjects, examination group-99. All of the diagnosed post-traumatic brain injury 6 to 12months after the episode. Patients of examination group were exposed to 30 min. of computer game training during 14days. We developed our own specialized computer games for patients with post-traumatic brain injuries having ataxia . Appropriate level of speed and complexity adjusted by the therapist. Stabilometry was the test to assess ellipse swing area (cm2). The Berg Balance Scale (BBS) used to measure balance.

Results: Mean ellipse area for control group was 268,4±67,4cm2 before and 265,1±64,4 after 2 weeks (p>0,05), for examination group 257,9±70,4 and 227,1±66,0cm2 (p< 0,05). BBS score improved for both groups from 38,1±2,4 to 40,4±2,7 in control group(p >0,05), 37,2±2,8 to 44,6±3,1 in examination group (p<0,05).

Conclusions: Developed computer games aimed at training of balance are an effective tool in complex rehabilitation for post-traumatic patients having ataxia. Usage of even short-term rehabilitation using these games improves balance significantly.

Keywords:
computer games, rehabilitation, brain injury, ataxia

EPNS21-383 Poster only
Neuro rehabilitation

Assessment of the burdens of caregivers of children with feeding-swallowing difficulties

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Objective: The study aimed to assess burdens of caregivers of children with brain lesions related to feeding-swallowing difficulties, compare the burdens according to phases of feeding-swallowing difficulties, and investigate its relationship with duration of feeding-swallowing difficulties.

Methods: 49 Caregivers accompanying children with brain lesions were included. Age, gender, type of feeding methods (oral vs tube feeding), and number of problems in swallowing phases (oral, pharyngeal, esophageal phases) were noted.
Parents completed the Korean version of the Feeding/Swallowing Impact Survey (FS-IS) The FS-IS has three subscales including daily activities, worry, and feeding difficulties.

Results: The median age of patients was 3.78 ± 2.22 (min = 1, max = 10) years, of which 32 were male and 17 were female. Most cases (46 patients) used the route of administration via the oral cavity.
The mean score and standard deviation (SD) of daily activities, worry, feeding difficulties, and total score from the FS-IS were 2.43±0.60, 2.81±0.84, 2.33±0.57, and 2.52±0.84, respectively. Among patients, 38 patients had only oral phase problem and 11 patients had both oral and pharyngeal phase problems.
Caregivers of children with both oral and pharyngeal phase problems showed higher scores in all subscales and total score of the FS-IS (3.00±1.37, 3.48±1.31, 2.87±1.10, and 3.14±1.13) than caregivers of children with only oral phase problem (2.24±1.00, 2.62±0.90, 2.20±0.96, and 2.34±0.88) (p-value 0.017).
Caregivers of children with tube feeding (4.20±1.05, 4.48±0.60, 3.33±1.14, and 2.32±1.25) reported higher scores in all subscales and total score of the FS-IS than caregivers of children with oral feeding (2.70±1.33, 2.27±1.18, and 2.43±1.27)

Conclusions: This study shows that caregivers of children with swallowing problems reported higher stress and more challenges with feeding and growth than caregivers of children having only oral phase problem.

Keywords:
feeding, swallowing, difficulties, FS-IS, caregivers, children

EPNS21-508 Oral or poster
Neuro rehabilitation

Changes in GMFM-88 after use of the ATLAS2030 exoskeleton in PC: a case report

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Objective: To evaluate changes in gross motor skills measured by the 88-item gross motor function measure scale (GMFM-88) in a child with cerebral palsy after receiving robotic assisted gait training.

Methods: A 4-year-old participant with a diagnosis of cerebral palsy type spastic-dystonic tetraparesis and level IV in the GMFCS received a total of 39 therapy sessions using the ATLAS2030 exoskeleton biweekly for a period of 6 months. The exoskeleton was used in automatic and active mode to walk both forward and backwards while performing ludic and rehabilitative activities. The scale was administered to the participant at the beginning, the middle, and at the end of treatment by the same trained professional. The results were exposed in a descriptive way.

Results: The GMFM-88 score improved by 20 points compared to the baseline assessment, in the A (lying and rolling) and B (sitting) dimensions. A total of 18 items improved, 56% of them in the A dimension and 28% in the B dimension. The items with the greatest improvements were those related to support, rolling, and side sitting. A 77.3% of the items remained constant in all evaluations performed due to the patient's inability to walk and stand up.

Conclusions: The results showed an improvement in the GMFM-88 scale, suggesting that gait training therapy with the ATLAS2030 exoskeleton may be effective in the improvement of gross motor function in children with cerebral palsy. Further studies are needed to confirm these findings.

Keywords:
Cerebral palsy, children, exoskeleton, gait, gross motor, neurorehabilitation

EPNS21-553 Oral or poster
Neuro rehabilitation

Brain injury cloaking Labyrinthitis Ossificans

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Objective: We report a case of subdural empyema resulting in severe hearing impairment due to labyrinthitis ossificans requiring cochlear implants.

Methods: Setting :Case report from a tertiary care Paediatric Neuroscience unit based at Cardiff, UK

Subject : A 13-year-old girl was diagnosed with subdural empyema after presenting with a febrile illness with seizures.

Intervention: She required multiple craniotomies to manage subdural empyema and raised intracranial pressure (ICP). She also had venous sinus thrombosis. Her management included intravenous antibiotics, anticoagulants and other supportive measures. Microbiology examination revealed a mixture of Streptococcus anginosa, Prevotella and mixed anaerobes.

Clinical course: She remained minimally conscious for approximately 6 weeks, with residual right hemiparesis. New communication difficulties due to receptive dysphasia became clinically evident as she emerged from the minimally conscious state.

Results:

Audiological assessment 3 months from admission revealed profound sensorineural hearing loss. Brain imaging revealed bilateral progressive labyrinthitis ossificans in addition to extensive cerebral damage. Consequently, she received bilateral cochlear implants. She improved with intensive neurorehabilitation but continues to have ongoing mobility (GMFCS level 4) and communication issues.

Labyrinthitis ossificans can be a sequela of intracranial infections, either directly due to infective labyrinthitis or mediated by neuroinflammation. Meningitis is a well-known cause where protocols are in place to check hearing (e.g., NICE guidelines, UK). However, there is no such protocol after other infections. In addition, her substantial brain injury impeded recognition of her hearing impairment.

Conclusions: Consider audiological assessment after an intracranial infection, especially if the patient is not responding well to aural input. Detection of the hearing loss will help therapy team devise patient-specific rehabilitation strategies to optimise outcomes.

Keywords:
Brain injury, Labyrinthitis ossificans, Subdural empyema

EPNS21-58 Oral or poster
Neuro rehabilitation

Rehabilitation after paediatric acquired brain injury: longitudinal change in content and relationships to domains of recovery

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Objective: To describe cross-sectional and longitudinal variation in neurorehabilitation content provided to young people recovering after severe paediatric acquired brain injury (pABI) and to relate this to observed functional recovery

Methods: Observational study in a cohort of admissions to a residential neurorehabilitation centre. Recovery was described using the Pediatric Evaluation of Disability - Computer Adaptive Testing (PEDI-CAT) instrument. Rehabilitation content was measured using the recently described Paediatric Rehabilitation Ingredients Measure (PRISM) and examined using multidimensional scaling

Results: Variation in rehabilitation content between and during admissions primarily reflects proportions of child active practice, child emotional support, and other management of body structure and function. Rehabilitation content is predicted by pre-admission recovery suggesting therapist decisions in designing rehabilitation programmes are shaped by initial expectations of recovery. However significant correlations persist between plausibly-related aspects of delivered therapy and observed post-admission recovery after adjusting for such effects.

Conclusions: The PRISM approach to the analysis of rehabilitation content shows promise in that it demonstrates significant correlations between plausibly-related aspects of delivered therapy and observed recovery that have been hard to identify with other approaches, however rigorous causal analysis will be required to truly understand the contributions of rehabilitation to recovery after pABI.

Keywords:
Neurorehabilitation, causal inference, acquired brain injury

EPNS21-611 Oral or poster
Neuro rehabilitation

Neuro-radiology correlates of Unilateral Cerebral Palsy in Children: Vascular Classification

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Objective: There is a paucity of literature describing neuro-radiology correlates of unilateral cerebral palsy in children. We aimed at studying the distribution of neuro-radiology findings in a cohort of children with unilateral cerebral palsy.

Methods: Medical resonance imaging (MRI) scans of each subject were evaluated by a pediatric neurologist and a pediatric neuro radiologist. The findings were first classified into asymmetric periventricular leukomalacia and stroke patterns. The stroke patterns were further categorized as per previously published vascular classification scheme (Kirton et al).

Results: A total of 46 children (age range: 5-18 years) with unilateral cerebral were enrolled in the study. Most common MRI pattern was that of stroke (84.8%) including first trimester, perinatal and post-natal strokes. The children with presumed perinatal ischemic stroke (PPIS) were further classified into arterial patterns [proximal M1 (PM1), distal M1 (DM1), anterior trunk AT, posterior trunk (PT), lateral lenticulo-striate (LLS)] and venous (periventricular venous infarction (PVI)] patterns. Most common PPIS radiology pattern was periventricular venous infarction (PVI) which was seen in 41.3 % children followed by proximal M1 pattern (PM1) which was seen in 15.2% children. This finding is in contrast to earlier published cohorts. This may be contributed by higher prevalence and delayed treatment of chronic maternal risk-factors like prenatal infections, bleeding, hypertension etc. owing to inadequate antenatal care in our population contributing to vascular insults early in gestation.

Conclusions: Most common radiological correlate of unilateral cerebral palsy is stroke pattern. Most common presumed peri-natal stroke pattern was found to be the periventricular venous infarction.

Keywords:
Unilateral cerebral palsy, perinatal stroke, vascular

EPNS21-635 Oral or poster
Neuro rehabilitation

Functional decline and diminished access to care: experiences of children with cerebral palsy during the COVID-19 pandemic

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Objective: For children with cerebral palsy (CP), the COVID-19 pandemic and national lockdowns caused significant disruption to rehabilitation and medical treatment and resulted in long waiting times for interventions. This study aimed to understand the experience of children with CP during the lockdown, with a focus on motor function and ability to perform activities of daily living (ADLs).

Methods: An online survey was distributed to guardians of children with CP, age less than 16 years, across the United Kingdom, with an optional survey for adolescents. Information regarding access to medical and rehabilitative care, physical activity levels, ADLs, and sleep patterns, during the pandemic, were collected.

Results: 54 parents of children with CP (child age 8.9±4.8 years), and 6 adolescents, completed the survey.
Prior to the lockdown, 92.3% of children accessed therapy and/or supervised exercise, contrasted with just 25.5% during lockdown, and this was a statistically significant change ($p<0.001$). The majority of parents (76.2%) reported difficulty in accessing medical or rehabilitative care for their child during lockdown.

A decline in motor function, and ability to perform ADLs, was prevalent across most children, and mobility tasks were the most likely to have deteriorated. Increased difficulty with walking up and down stairs (61%) and walking greater than 250m (58%) were most reported. Fine motor skills were least affected.

Conclusions: This study highlights substantial interruption of medical and rehabilitative care during lockdown, with significant physical and wellbeing consequences, for children with CP. Additional support and rehabilitation may be required for a substantial proportion of children with CP, and it is therefore imperative that innovative approaches are used to maximise therapy outcomes. Future studies should explore novel adjunct treatments, such as non-invasive brain stimulation, with the potential to boost function whilst also decreasing pressure on health services.

Keywords:
cerebral palsy; rehabilitation; COVID-19; lockdown;

EPNS21-151 Poster only
Neurodevelopmental

Application of computerized d-CPT in the diagnosis and treatment of patients with ADHD.

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Objective: d-CPT (distractor-based-Continuous Performance Test) is a standardized computerized test designed to help clinicians identify and quantify symptoms related to attention deficit / hyperactivity disorder (ADHD) in patients over 6 years of age Assessment of the usefulness of the application of a computerized d-cpt in the diagnostic and therapeutic management of patients with or suspected ADHD.

Methods: Retrospective descriptive study carried out in a neuropaediatric clinic. The diagnostic and therapeutic utility of the application of computerized d-cpt was analyzed in patients between 6 and 18 years of age with a diagnosis or suspected diagnosis of ADHD, comparing the results obtained in the test before and after the clinical intervention.

Results: 98 patients with a mean age of 9 years were reviewed. 75% were men. Carrying out a first test led to a decision on the therapeutic regimen (starting a new treatment, cessation of previous treatment or changing it) in 92 patients (93.9%).
In a second comparative test after starting a treatment, a statistically significant improvement was observed in the four parameters of interest analyzed: attention ($p < 0.000$), impulsivity ($P < 0.000$), punctuality ($P < 0.000$) and hyper-reactivity ($P < 0.001$).

Conclusions: The use of computerized d-cpt in patients with a diagnosis or suspected diagnosis of ADHD is useful for the choice of specific treatments that can lead to an improvement in the symptoms of this disorder. As it is a computerized test we find it easy and quick to perform and review. It allows obtaining relevant, more precise and objective clinical information for clinical decision making.

Keywords:
ADHD, d-cpt

EPNS21-160 Poster only
Neurodevelopmental

The Pitt-Hopkins Syndrome: Report of 5 Patients

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Objective: Pitt-Hopkins syndrome (PTHS) (MIM #610954) is characterized by developmental delay, intellectual disability and behavioral changes, distinctive facial gestalt, and breathing abnormalities. PTHS is caused by deletions or pathological variants in the TCF4 gene located at 18q21.2.
Autism spectrum disorder symptoms, sleep disturbance, stereotypic movements, seizures, constipation, and ophthalmologic impairments are other clinical findings. PTHS is phenotypically similar to several neurodevelopmental disorders and is considered to be involved in differential diagnosis with Angelman, Mowat-Wilson, and Rett syndromes. In this report, we aimed to describe the clinical and genetic findings of patients diagnosed with PTHS and compare our patients with the literature.

Methods: Patients who were followed up with severe intellectual disability and a variable association of features previously described as characteristic of the PTHS phenotype in the pediatric neurology clinic of Antalya Training and Research Hospital were screened for TCF4 mutations using next-generation sequencing (NGS)-based tests, between 2017 and 2020.

Results: A total of 67 patients with intellectual disability were screened using NGS-based tests. 13 patients had clinical features compatible with PTHS. A genetic mutation associated with PTHS was detected in five patients. Two patients had a novel heterozygous c.611-180dupT variant, and the other three patients had variants that were reported in the literature previously.

Conclusions: This study emphasis on mutational and clinical spectrum of PTHS and its significant part in the differential diagnosis of severe mental retardation.

Keywords:
Angelman syndrome; breath-holding episode; intellectual disability; Pitt-Hopkins syndrome; TCF4

EPNS21-2016 Oral or poster
Neurodevelopmental

Spectrum of co-morbidities in children with Autism Spectrum Disorder in a tertiary health care centre

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Objective: To study the prevalence of comorbidities in Indian children with Autism spectrum disorder (ASD) and whether it affects the severity of symptoms as measured by Childhood Autism Rating Scale (CARS).

Methods: Children aged 2-18 years, with ASD (DSM 5 criteria) from January 2017 to March 2021 were enrolled in the study after obtaining parental consent. These children were followed in Autism clinic at 1-3 monthly intervals. Detailed history from parents was obtained using a standard clinical proforma. Evaluation for symptom severity and behavioural co-morbidities were done by CARS, Autism Behaviour Checklist (ABC), and Childhood Behaviour Check List (CBCL) at baseline as well as on follow up visits. Children were provided applied behavioural analysis, the standard form of behavioural therapy and medications as required.

Results: A total of 1551 children with ASD (1310 boys, median age of 4.8 years with IQR 3.2-7 years) were enrolled. Proportion of children with comorbidity was 80% (1255/1551). Attention deficit hyperactivity disorder was the most common behavioural comorbidity (57.55%), followed by disruptive behaviour (4.51%) and obsessive compulsive disorder (1.42%). Other medical comorbidities were global developmental delay/intellectual disability, sleep disturbances and epilepsy which were found in 55.58%, 47.29% and 12% of the children respectively. Gastrointestinal issues including feeding disorders were found in 5.22% and 0.45% of the children were obese. Learning disability was found in 2.32 % of the children and it was higher in females in comparison to males (p-0.013). Only. Only comorbidities which were associated with higher CARS score were feeding disorder (39.08 vs 37.14, p-0.02) and disruptive behaviour (38.88 vs 37.11, p-0.008).

Conclusions: The burden of comorbidity in children with ASD is high. The comorbidities with maximum burden do not affect the severity of ASD on presentation as measures by CARS.

Keywords:
Autism Spectrum Disorders, CARS, Co-morbidities

EPNS21-2017 Oral or poster
Neurodevelopmental

The association of quantitative EEG & influence of heavy metal levels in children with Autism spectrum disorder: A cross-sectional study

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Objective: To correlate the pathogenesis of autism spectrum disorder(ASD) with mean blood levels of mercury(Hg), other heavy metal & further validation by quantitative EEG.

Methods: This is a prospective cross-sectional study, children were diagnosed as per the DSM-V guidelines, & recruited after fulfilling inclusion & exclusion criteria. 180 children aged 3-12 years diagnosed with ASD & 180 age matched controls having developmental profile(DP3) with standard score>84 were recruited. Blood samples were collected in ultrapure Metal-free, EDTA coated tubes. Nail clippings & hair samples were collected in polypropylene bags the samples were processed for quantitative analysis of the analytes on Inductively Coupled Plasma Mass Spectroscopy. EEG was recorded continuously from 128 electrodes using an Electrical Geodesics(EGI) high-density EEG system(Netstation) & digitized at a rate of 1000 Hz.

Results: ASD subjects(153 boys/27 girls, 6.5±1.6 years, Childhood Autism Rating Scale(CARS): 36.59±2.38, Developmental Quotient(DQ):59.94±5.86) had significantly higher level of following metals in blood compared to controls: mercury(Hg), chromium(Cr), manganese(Mn) ($p=0.01$ for all three); lead(Pb)($p=0.001$) & lower iron(Fe) levels($p=0.014$). The spectral power of gamma, beta, lower alpha1, theta & coherence, during eyes closed condition was significantly($p<0.0005$) lower & the spectral power of theta & coherence of lower alpha1, theta, delta, was significantly lower($p<0.0005$) during eyes open condition in ASD compared to controls. Gamma band had positive correlation with Cr, Zinc(Zn), Pb & negative correlation with Nickel(Ni). Beta band had positive correlation with Fe, selenium, Ni, Pb & negative correlation with Copper, Mn, Arsenic.

Conclusions: The findings of this study showed impaired coherence pattern in children with ASD during attention task. ASD children have different qEEG correlates, as well as, significantly higher blood Hg, Cr, Mn & Pb levels as compared controls.

Keywords:
Autism Spectrum Disorders, Heavy Metals, Quantitative EEG

EPNS21-204 Oral or poster
Neurodevelopmental

Correlation between mean age of diagnosis of ASD, specific symptoms and residence area in a cohort of patients from Romania

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Objective: Autism Spectrum disorder is a childhood developmental disorder, characterized by impaired social interaction, communication and stereotypical behavior. According to current literature, the mean age of diagnosis is 43.18 months. Our purpose was to determine the mean age of diagnosis of children in Romania and analyze the possible association between age of diagnosis, symptoms at first admission and residence area.

Methods: We evaluated 273 children diagnosed with ASD according to ICD-10 criteria, using specific ASD tests(ADOS, ADI-R). We noted the age of first admission and first symptoms leading to the diagnosis. We divided our cohort in 3 age-of-diagnosis groups(I-1 to 5 years, II-6 to 10 years, III-older than 10 years); analyzed the prevalence of symptoms in association with age of diagnosis and residence area. We used IBM SPSS22 software by applying Chi2 for association.

Results: The mean age of diagnosis of ASD was 38,80 months(12 months to 17 years). In all cases, first features noted were: hand flapping and toe walking, stereotyped play, difficult eye contact, failed social integration. Group I=227 patients, 180 from rural residence, prevalent hand flapping and toe walking(77%); group II=32 patients, 23 from rural residence, majority with difficult eye contact(87.5%) and social integration (96%); group III=14 patients, 10 from rural residence, difficult eye contact and failed social integration(100%), stereotyped play(92%). In all groups, rural area residence was prevalent(74,35%);children from urban area were diagnosed 7 months earlier ($X^2=1.75$, $p<0.05$).

Conclusions: In our study the mean age of diagnosis of ASD was 38,8months, similar with other studies. Children from urban area were diagnosed earlier. Group-age specific signs help early recognition and drastically improve outcome, along with medical access, pre and postnatal care.

Acknowledgment: The research leading to these results has received funding from the EEA RO NO Grant 2014-2021, under the project contract No 6/2019.

Keywords:
ASD, early signs, early diagnosis, urban, rural

EPNS21-2043 Oral or poster
Neurodevelopmental

Psychopathological vulnerability detected by neuropsychiatric interviews in young adults born preterm: a prospective cohort study

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Objective: Psychopathology has not yet been studied for all degrees of prematurity including late-preterm, in adults admitted to NICU at birth, particularly those who grew up with no apparent neurodevelopmental sequelae in childhood. Herein, authors present a prospective cohort study aimed at highlighting psychopathological vulnerability beyond pediatric age.

Methods: Eighty-nine young adults (40 NICU admitted with less than 37 weeks of gestation and 49 healthy peers born at term, matched by age, sex, and scholar education), without a positive medical history for other neurological or psychiatric conditions in childhood, underwent measures of cognitive and psychopathological outcome at the age of 20 +/- 1 years. Psychopathological outcome by MINI International Neuropsychiatric Interview, Beck Depression Inventory, Barratt Impulsive Scale was correlated to individual neonatal data and cognitive function.

Results: We found a significantly higher prevalence of psychopathology at MINI score (22.5% vs 4.2%; Chi-square 2 = 6.7; p=0,010) and prevalence of previous stressful life events in the preterm compared to at-term group, in the absence of abnormal IQ scores. Only delta TMT and the ROCFT Recall Index neuropsychological functions, remained statistically different between groups after correction for IQ and multiple testing (p = 0.034 and p = 0.016 respectively).

Conclusions: Young-adults born prematurely are at risk of psychopathology and lower resiliency to stressful life events, probably as the result of abnormal developmental trajectories. The MINI interview could be a useful tool to highlight psychopathology in the follow up of preterm birth, extended to adult age

Keywords:
neonate, neuropsychology, NICU, behavioural functions, resiliency ability, neurodevelopmental risk.

EPNS21-2057 Oral or poster
Neurodevelopmental

Reorganization in the motor system for the non-paretic hand in Unilateral Cerebral palsy (UCP) - insides from fMRI and DTI

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Objective: Recent data indicated presence of deficits also in the non-paretic hand of children with UCP. Possible explanation for bimanual motor deficits could be presence of bilateral lesions in UCP (found in some patients). We hypothesized that changes in the cortical function as well as microstructural changes in the white matter of the "undamaged" hemisphere could explain such deficits.

Methods: To test this hypothesis, we performed fMRI with motor task for the non-paretic hand in 39 children with UCP (mean age 15y7m), comparing the results with the dominant hand of 41 age matching TDC. Additional DTI with TBSS-analysis was performed to test for differences in FA between groups. Comparison was also made regarding the size of lesions, type of lesions (subcortical to cortical involvement) and functional capacity of the hand (better bimanual skills to worse).

Results: Results showed significant differences in the cortical activation - stronger BOLD-signal in the contralateral M1 (primary motor cortex) in TDC and higher bilateral activation in M1, as well as activation of cortical regions outside M1 in patients. Larger lesions defined an atypical pattern of motor reorganization for the non-paretic hand with activation of the ipsilateral (ipsilesional) motor cortex. Patients with subcortical lesions activated the contralateral motor cortex and basal ganglia and the ipsilateral cerebellum better than those with cortical lesions. TBSS-analysis revealed bilaterally reduced FA in patients compared to controls in the subcortical white matter, corticospinal tracts, and cerebellum.

Conclusions: Reduced functional capacity of the morphologically intact hemisphere in patients with UCP due to "crowding" or due to bilateral microstructural changes in the white matter might be considered, that leads to additional inter- and intra-hemispheric reorganization models to achieve close to normal motor function of the non-paretic limb.

Keywords:
Unilateral Cerebral Palsy, fMRI, DTI, reorganization, non-paretic hand

EPNS21-2069 Poster only
Neurodevelopmental

Transient electrocerebral silence following apnoea in a male infant with MECP2 mutation: a case report

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Objective: Rett Syndrome (RTT), a rare X-linked developmental disorder, was previously thought to be lethal in males prior to birth. Autonomic dysfunctions are common in classic RTT and include breathing irregularities, cardiac arrythmias and gastrointestinal issues. It is now known that RTT can affect males, occasionally presenting as a severe encephalopathy associated with respiratory failure.

Methods: We describe the case of a 17-month-old-boy who, despite being born at full term and appropriate for gestational age, presented transient respiratory depression and diffuse hypotonia at birth. In the first months, he was frequently hospitalized for gastroesophageal reflux, persistent cough, dysphagia, and developmental delay. Seizures presented at 13 months therefore the patient was started on valproic acid. At 16 months a severe progressive breathing disturbance led to intubation. Despite mechanical ventilation, an irregular respiratory pattern persisted, with ensuing episodes of respiratory arrest.

Results: Polygraphic recording of the episodes showed a slowing of respiratory frequency followed by complete respiratory arrest, severe oxygen desaturation (SpO2 < 10%) with no significant variation of heart rate. An abrupt and dramatic suppression of electroencephalographic (EEG) activity occurred immediately after the SpO2 nadir, lasting a few minutes with no preceding epileptic discharges. Electrocerebral silence was suddenly replaced by restoration of previous activity. Serial brain scans showed a progressive cerebral atrophy and a non-specific signal alteration in the pallidal nuclei. Whole Exome Sequencing revealed a point mutation in the MECP2 gene.

Conclusions: Autonomic disfunctions, especially breathing abnormalities, are reported in MECP2 males and they can be so severe as to compromise quality of life and threaten survival. This case stands out for the peculiar EEG picture, repeated abrupt transient EEG silence may represent an unusual response to anoxic brain insult.

Keywords:
Rett Syndrome, MECP2, autonomic dysfunctions, respiratory arrest, electrocerebral silence

EPNS21-216 Oral or poster
Neurodevelopmental

Social Robots as Tools in Special Education (the SRTSE project): preliminary results of a randomised case-control study on robot-assisted therapy for children with Autism Spectrum Disorder (ASD).

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Objective: The objective of this study, being part of the SRTSE project, was to investigate the effectiveness of a robot-assisted intervention compared to traditional therapy with regards to a wide range of ASD symptoms, based on a systematic approach and a rather long-term intervention program.

Methods: 44 children (6-13 years old) diagnosed with level 1 ASD (DSM-V) and IQ score >70 were enrolled and randomly assigned to 2 subgroups (N=22 each) that followed the same therapeutic intervention (21 sessions in total, twice weekly, by a developmental psychologist) with or without the assistance of the humanoid robot NAO. Extensive evaluation with validated scales was performed by a blinded to the intervention neuropsychologist before and after the intervention completion. Preliminary results from the statistical analysis (SPSS 23.0/Cohen's d) of the Childhood Autism Rating scale (CARS-2) evaluation are presented.

Results: No significant differences were found between the 2 subgroups (N=22 each) with regards to age, gender, IQ quotient, parental education, special therapy programs. Total CARS-2 did not differ at baseline; higher scores were found in the NAO group for the subdomains of body use,taste-smell-touch and emotional response. CARS-2 was lower after the intervention for both groups (mean d=0.67 and 0.55 for NAO and control group respectively, p=0.001). CARS-2 effect size was greater in the NAO group (dz*=1.5 vs 1.4),and especially with regards to emotional response (dz*=0.8 vs 0.7), while the fear/nervousness effect size was greater in the control group (dz*=0.71 vs 0.78).

Conclusions: The NAO-assisted intervention resulted in a significant lower end of treatment CARS-2 score, with the greater benefit being observed on the emotional responses of children with ASD. However, given the limitations of the sample, the above results will be compared to additional data of other scales from our study, and should be further confirmed in the future.

Keywords:
autism, robot-assisted therapy, special education

EPNS21-31 Oral or poster
Neurodevelopmental

Expanding the spectrum of bi-allellic TRAPPC11 variants: intelectual disability, epilepsy, movement disorders and hyperCKemia

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Objective: Transport protein particle complex (TRAPPC) is involved in endoplasmic reticulum to Golgi transportation. Bi-allelic variants in TRAPPC11 gene were initially associated with limb-girdle muscular dystrophy (LGMD) and congenital muscular dystrophy (CMD) in association with hyperkinetic movements and/or multisystemic involvement. We present 4 patients with bi-allelic TRAPPC11 variants without a LGMD or CMD phenotype.

Methods: Descriptive and retrospective study.

Results: All the patients are Roma and had elevated CK levels without muscle weakness and with normal muscle biopsy. All of them were diagnosed with the homozygous variant c.1287+5G>A in TRAPPC11 gene, resulting in a 58 amino acid in-frame deletion.

Case 1 and 2 (siblings, males, 21 and 5 year-old): Consanguineous family with history of two similarly affected individuals. Both patients presented with neurodevelopment delay since the first year and developed myoclonic jerks and chorea. The second patient suffered nocturnal focal seizures with centro-temporal spikes during sleep. CK levels were elevated (4.000U/l). Brain MRI was unremarkable.

Case 3 (female, 18 year-old): the patient was born prematurely from consanguineous parents with significant familiar history of intellectual disability. She was diagnosed with severe intellectual disability and hyperCKemia (5.000U/l). She never had seizures or abnormal movements. Brain MRI was normal.

Case 4 (female, 9 year-old): The family history was unremarkable. She presented with neurodevelopment delay, loss of speech and high CK levels (1000U/l). She developed significant stereotypic hand movements. Brain MRI showed global atrophy.

Conclusions: Bi-allelic TRAPPC11 variants should be ruled out in patients with intellectual disability and hiperCKemia, especially if consanguinity, hyperkinetic movements and epilepsy are present

Recurrent mutations in this specific population suggest a founder effect, however haplotype analysis is mandatory to confirm this hypothesis

Keywords:
hiperCKemia, intellectual disability, hyperkinetic movements, TRAPPC11

EPNS21-336 Oral or poster
Neurodevelopmental

Expanding the phenotypic spectrum of disorders of neural crest development

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Objective: Neurocristopathies encompass a group of congenital disorders caused by abnormal neural crest (NC) development. Clinical manifestations include hearing disorders, craniofacial abnormalities and multisystemic involvement. A number of neurodevelopmental disorders associated with dysmorphic features and/or congenital anomalies are reminiscent of NC maldevelopment. We hypothesize that the role of NC gene in these patients is underestimated. We aim to delineate the clinical phenotype of patients with neurodevelopmental disorders carrying CNV that include genes related to NC development.

Methods: Retrospective analysis of a cohort of 37 children with neurodevelopmental disorders and pathogenic CNVs that include NC developmental genes. Statistical analysis included Chi-squared test, Odds Ratio calculation and Kruskal-Wallis test.

Results: 19 new syndromic associations and 18 already known syndromes were detected. 125 genes were linked to NC development. All patients showed craniofacial dysmorphisms. Multisystemic findings were present in all patients (vertebral, cardiac or intestinal abnormalities in 30%, dental, endocrine, skin, or renal abnormalities in 20%). All patients had language delay, 95% motor delay, 63% autism, 84% autonomic dysfunction, 70% bulbar dysfunction, 54% microcephaly, 30% epilepsy and 27% had been diagnosed with cerebral palsy. Neuroimaging showed corpus callosum abnormalities and nonspecific white matter findings in 35%. In 97% NC genes were involved in migration and differentiation, 89% in proliferation and 70% in formation. In all patients there was involvement of the cranial NC segment, in ~ 50% the vagal or trunk segment, and in 24% the sacral segment. Statistical analysis showed that a number of clinical features could have predictive value of the disrupted gene pathway.

Conclusions: This is the first attempt to systematically assess an heterogenous group of patients carrying NC genes CNV. Analysis of a larger cohort will be needed to ascertain the validity of our results.

Keywords:
neural crest, neurocristopathies, neurodevelopmental

EPNS21-337 Poster only
Neurodevelopmental

Effectiveness of CO-OP for children with CP and brain lesions depending on the intelligence level

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Objective: The Cognitive Orientation to daily Occupational Performance approach (CO-OP) is a goal-focused approach that combines task-specific training. As CO-OP treatment was closely related to the cognitive level, it is needed to confirm whether the effect of CO-OP treatment depends on the cognitive level. This research aimed to determine whether the effect of CO-OP treatment is influenced by the cognitive level in children with brain lesions.

Methods: This retrospective study was a quasi-experimental design where 33 children with cerebral palsy (CP) or other brain lesions were recruited. We divided subjects included in the study into two groups based on 70 points by IQ score: a group with a score of 70 or more (high IQ group) and a group with a score of less than 70 (low IQ group). Subjects participated in the 24 treatment sessions.
Each session was conducted two or three times a week for 50 minutes, in a 1-1 format, and run by two Occupational Therapists trained and experienced in the use of the CO-OP. Outcome measures relating to impairment (MABC-2, motor overflow assessment), participation (COPM, Canadian Occupational Performance Measure), and performance (Performance Quality Rating Scale, PQRS) were measured at weeks 0 and 10 in the intervention group.

Results: Demographic data of participants showed no difference between the group. IQ scores of the high IQ group and low IQ group were 90 and 64 respectively. In intragroup comparisons, both groups showed a statistically significant improvement in all outcome measures after COOP intervention. The mean changes of COPM performance, COPM satisfaction, and PQRS were as follows: 3.74±2.14, 4.27±2.52, 7.95±1.61 in the high IQ group, and 2.85±2.14, 3.59±2.14, 7.82±1.99 in the low IQ group. The CO-OP effect between the two groups showed no significant difference in all outcome measures.

Conclusions: This study showed that subjects obtained significant COOP treatment effects regardless of IQ level.

Keywords:
CO-OP, CP, brain lesions, IQ

EPNS21-360 Oral or poster
Neurodevelopmental

Psychometric profile, heterogeneity, and intellectual functioning in fetal alcohol spectrum disorder

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Objective: Fetal Alcohol Spectrum Disorders (FASD) are characterized by a variety of cognitive and behavioral disorders, with intellectual, attentional, and executive impairments being the most reported. In clinical practice, the Intelligence Quotient (IQ) is rarely interpreted in this population because of a deemed too strong heterogeneity of the psychometric profile. We propose here an objective characterization of this heterogeneity and a differential analysis between global intellectual functioning and elementary reasoning, in a large retrospective monocentric sample of FASD.

Methods: Using clinical and psychometric data (WISC 4th or 5th ed.) from 107 children with FASD, with or without fetal alcohol syndrome, we characterized intra-individual heterogeneity (inter-subtest/index variance or excessive difference at 10thp cutoff), searched for profile weaknesses (average at group level, frequency of anomalies at individual level), and specified intellectual functioning in terms of IQ and elementary reasoning (GAI, best reasoning subtest), in comparison to standardization norms and/or a Monte-Carlo simulated population of normalization.

Results: Patient performance was poorer than expected on all subtests, with significant weakness in digit memory, letter-number sequencing and coding, and a trend toward better verbal performance. We found no increase in inter-subtest variance or frequency of excessive inter-index differences, but a discordance between the assessment of global efficiency (IQ 32% borderline, 21% deficient) and that of elementary reasoning (12-23% borderline, 2-16% deficient).

Conclusions: Our results, which question the notion of cognitive heterogeneity, point to attentional, executive, and procedural cognitive fragility, with strong global repercussions but most often preserving elementary reasoning in at least one modality.

Keywords:
Fetal Alcohol Syndrome; Fetal Alcohol Spectrum Disorders; Prenatal Alcohol Exposure; Psychometric Profile; Cognitive Profile; Intellectual Functioning; Intelligence; cognitive heterogeneity

EPNS21-363 Oral or poster
Neurodevelopmental

Phenotype assessment in Neurologically Impaired paediatric patients:Impact of a nutrition intervention protocol.

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Objective: Phenotypic Assessment of Neurologically Impaired Paediatric Patients(NIPP):nutritional intervention protocol following ESPGHAN guidelines:impact on phenotypic parameters.

Methods: Z-scores classification following WHO criteria for 68NIPP(1m-17 years). Gross Motor Function Classification System(GMFCS),Manual Ability Classification System(MACS),Dysphagia Disorder Survey(DDS),Saliva Severity Score(SSS),gastrointestinal complications(GC),energy and nutrient intake assessment at zero point,after 6(point1)and 12(point2)months. Customized nutrition plans were given(point0). Primary outcomes:anthropometric parameters(Waz),as indicators of nutritional status.GMFCS,MACS,DDS,SSS,FA(Feeding Ability)as possible predictors of this outcome. Secondary outcomes:impact of intervention on phenotypic parameters.

Results: Based on weight for age z-score(Waz<-2)17 NIPP(32.1%)were undernourished,5/68(10,4%)with triceps skinfold thickness z-score(TSTz)<-2 and 3/68(7%)with mid upper arm circumference z-score(MUACz)<-2. Waz(p1=0,036)(p2=0,003),body mass index(BMIz)(p2=0,000),MUACz(p1=0,029)and TSTz(p1=0,021)(p3=0,044)significantly improved.NIPP had lower Haz on higher levels of GMFCS(p1=0,040),MACS(p1=0,028),DDS(p1=0,001)and SSS(p1=0,005). Patients had lower TSTz on higher levels of SSS(p1=0,002). Energy(p3=0,028),protein(p1=0,026,p3=0,003),fat intake(p3=0,012)were higher at follow-up. Intake of energy(p1=0,026)(p2=0,046)(p3=0,048)carbs(p1=0,014)(p2=0,042),protein I/R(p1=0,032)(p3=0,013),fat(p2=0,033)(p3=0,037)were lower in higher GMFCS levels. GC correlated with Waz(r=-,285 p1=0,011). FA was the only strong predictor for Waz at baseline evaluation(p=0,012)when multiple regression was run along with DDS.

Conclusions: 1/3 of NIPP was underweight, 69% with some degree of dysphagia,58.8% with GC. Haz was the most sensitive parameter to the ranking changes on motor and functional feeding scores. The intervention protocol improved nutritional status of NIPP. Patients' feeding ability is of importance for predicting Waz.

Keywords:
neurological impairment, functional feeding disorders, nutrition, DDS, MACS, GMFCS

EPNS21-367 Oral or poster
Neurodevelopmental

New MRI sulcal-based connectivity-driven segmentation of the medial corpus callosum: interest for the study of inter-individual size variations and callosal dysgenesis

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Objective: The corpus callosum (CC) is a major white matter bundle that can be studied through its midsagittal section (MSSCC). Yet conventional segmentations of this sagittal section may not consistently fit interindividual or pathological variations. Here we propose and explore a new way to parcellate the MSSCC, from T1 and diffusion-weighted MRI, into 7 anterior-posterior parcels, through the fiber-based projections of 6 sulcal meridians defined in a geodesic representation of the cortex. Our individually-set, sulcal and connectivity-based, hemispherotopic parcellation may overcome these limitations, revealing interesting cortical-callosal correlates.

Methods: From a 39 healthy subjects data-set, we obtained an individually-set cortical segmentation into 7 parcels separated by 6 sulcal meridians. We then generated a whole CC tractography and labelized each fiber according to its homologous bilateral connectivity to the cortical parcels. Eventually, we parcellated the one-voxel-thin mask of the MSSCC according to the labelized fiber density map. To improve the original cortical parametrization, we tested the adjunction of the posterior perpendicular ramus of the cingular sulcus (pPRCS) to the 2nd meridian of the model.

Results: The process always resulted in one-piece parcels comparable in size, not similar but consistent with more classical geometric segmentations of the MSSCC, highlighting the large representation of frontal and pericentral projections and the interest of sulcal landmaks. We showed that, beyond the absence of correlation between MSSCC and total cortical surface areas, a significant part of the variance in some callosal parcels area could be explained by the corresponding cortical variance. Adding the pPRCS reduced the variance for the prefrontal parcels without the loss of these interesting correlates.

Conclusions: Successfully applied to 5 cases of fetal alcohol-related partial agenesis of the CC, this new parcellation could be of interest in the study of developmental CC anomalies.

Keywords:
corpus callosum, connectivity, parcellation, sulcus, hemispherotopy

EPNS21-387 Poster only
Neurodevelopmental

SLEEP DISORDERS AND PERINATAL RISK FACTORS: A PROSPECTIVE COHORT STUDY

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Objective: To study prevalence and severity of sleep disorders in children at risk of abnormal neurodevelopmental outcome because of NICU admission and to compare with healthy children. To correlate the presence and severity of sleep disorders with risk factors reported in literature.

Methods: Children participating to the post-discharge from NICU follow-up and healthy children from a cohort of volunteers matched for the age were recruited. Questionnaires were face-to-face administered to parents via structured interviews. Two questionnaires were developed based upon previous validated sleep instruments adapted for two range of age (0-12 months and 13-30 months). Perinatal, family and environmental risk factors were compared between subgroups with and without sleep disorder, with mild and severe sleep disorder. Parents' subjective perception was examined.

Results: The cohort included 215 subjects. An overall high prevalence of sleep disturbance emerged (93%), significantly higher in the control group (p=0,0042). The control group used more electronic devices (p=0,001) and had them in their bedroom (p=0,006). Prematurity and low birth weight were the only perinatal risk factors correlated with sleep disorders. The 51,2% of the whole sample had a severe sleep disorder, but no predictors for severity were identified. Subjective perception of sleep disorders reported by parents was inadequate, especially that of mild-moderate disorders (p=0,001).

Conclusions: The present study confirms the high prevalence of sleep disorders in children at risk of abnormal neurodevelopmental outcome requiring admission to NICU. Unexpectedly, a greater prevalence of them was found in healthy infants. The multifactorial nature of sleep disorders must be kept in mind, including social, psychological and environmental factors, many of them modifiable. Sleep education should be promoted in all infants, considering that parents may not be aware of less severe disorders.

Keywords:
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EPNS21-389 Poster only
Neurodevelopmental

The visibility of transient fetal compartments on brain MRI and neurodevelopmental outcome in preterm infants

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Objective: The neonatal brain MRI is an essential clinical tool for predicting the long-term outcome of brain injury in preterm neonates. The level of cerebral maturity in preterm is estimated by assessing the MRI characteristics of transient fetal compartments (periventricular crossroads areas, subplate, and von Monakow segments) that persist at term-equivalent age.

Methods: The study enrolled 64 preterm infants born between 2012 and 2016. Brain MRI was performed at the exact term-equivalent age. The signal-intensity characteristics of the frontal and parietal periventricular crossroads were evaluated and classified into four grades. The neurological outcome was assessed at the age of three years.

Results: MRI abnormalities were mostly found in neonates with non-favorable outcomes. Visible frontal and parietal periventricular crossroads were associated with a normal neurologic outcome (p 0.0004; P.0009). Not-visible or slightly visible periventricular crossroads were associated with non-favorable outcomes in the case of frontal crossroads (p 0.036) and not-visible periventricular crossroads in the case of both frontal and parietal crossroads (p 0.001, p 0.015).

Conclusions: Neonatal visibility of the periventricular crossroads of pathways could have a predictive value for the neurological outcome as biomarkers of brain injury.

Keywords:
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EPNS21-392 Poster only
Neurodevelopmental

Motor performance and loneliness in children born very preterm at 11 years of age.

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Objective: Children born very preterm have an increased risk for cerebral palsy (CP) and developmental coordination disorder (DCD) compared to children born full term. Our aim was to study if motor performance was associated with perceived loneliness in children born very preterm at 11 years of age. We hypothesized that motor problems would correlate with loneliness.

Methods: This study is part of the Finnish prospective follow-up study PIPARI (The Development and Functioning of Very Low Birth Weight Infants from Infancy to School Age). Children born very preterm (birth weight ≤1500g and/or gestational age <32 weeks) in Turku University Hospital from 2001 to 2006 were included. At 11 years of age, motor outcome was evaluated using the Movement Assessment Battery for Children - Second edition (Movement ABC-2) and Touwen examination was used to exclude other neurological conditions. Loneliness was self-assessed by using the Finnish version of the Peer Network and Dyalic Loneliness Scale (PNDLS).

Results: A total of 165 children born very preterm were included: 141 (85%) children had typical motor development, 6 (4%) had CP and 18 (11%) had DCD (Movement ABC-2 ≤5th percentiles). Better motor performance correlated negatively with perceived social loneliness (Pearson's rho=-0.2, p=0.05).

Conclusions: Motor problems correlated with perceived social loneliness in children born very preterm at 11 years of age. It would be important to recognize motor problems early to provide proper interventions and support services, and to prevent loneliness in children born very preterm.

Keywords:
CP, DCD, long-term follow-up, Movement ABC-2, PNDLS

EPNS21-417 Oral or poster
Neurodevelopmental

Role of Methylation Pathway biomarkers in Autism Spectrum Disorders: A case-control study

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Objective: Autism spectrum disorders(ASD), a group of common neurodevelopmental disorders is incriminated by various genetic, metabolic and environmental factors in the etiopathogenesis, but the exact mechanisms remain to be elucidated. We compared the levels of methylation pathway biomarkers(blood methionine, cysteine, homocysteine and MTHFR C677T polymorphism) between children with ASD and age-gender matched typically developing children. We also compared the blood levels of advanced glycation end-products(AGEs)[N-Carboxymethyl-Lysine(CML)/N-Carboxymethyl-Arginine(CMA)/dityrosine], urine uric-acid:creatinine ratio, arterial lactate, blood vitamin-E, B12 and folate levels and correlated their levels with severity of autism(CARS score), sensory issues(SP2 score), comorbidities(CBCL score) and DQ/IQ(MISIC/VSMS/BKT)

Methods: Children with ASD(2-18 years) fulfilling DSM-5 criteria and age-sex matched typically developing children, were enrolled, and their blood samples were taken. Subjects with chronic illness/antioxidant therapy/multivitamins/anti-seizure medications were excluded.

Results: 100 cases(82 males) and 50 controls(41 males) were enrolled. The frequency of CC, CT and TT genotypes was similar between the two groups[(ASD:84%, 14%, 2%);(Controls:86%, 12%, 2%)]. Thus, C677T polymorphism was not associated with increased ASD risk. The serum homocysteine levels(µmol/L) in ASD group was significantly higher.[ASD-9(95%CI:7-16); Controls-7(95%CI:4-11)(p=0.01). The prevalence of hyperhomocystinemia(>15µmol/L) was higher in ASD group(13.4% vs 3.8% in controls)(p=0.04). No significant difference was observed between the plasma cysteine/methionine, urine uric acid:creatinine ratio, arterial lactate, serum vitamin E, B12 and folate levels between the two groups.

Conclusions: The prevalence of hyperhomocysteinemia is significantly higher in ASD compared to controls and is independent of MTHFR polymorphism or vitamin-B12 or folate levels. MTHFR C677T polymorphism is neither a risk nor a protective factor for autism.

Keywords:
Autism Spectrum Disorders, Homocysteine, Methylation pathway, MTHFR

EPNS21-431 Oral or poster
Neurodevelopmental

Corpus callosum and vermis abnormalities in Fetal Alcohol Spectrum Disorder: toward a diagnostic combination of neuroradiological markers.

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Objective: Without the specific pattern of Fetal Alcohol Syndrome (FAS), the diagnosis of Non-Syndromic Fetal Alcohol Spectrum Disorder (NS-FASD) remains probabilistic, insufficiently made despite high prevalence. Apart from microcephaly, neuroanatomical impairments to be considered in the diagnosis remains underspecified. Our objective is to characterize recurrent anomalies on brain MRI whose combination could be useful for diagnosis.

Methods: On retrospective (2014-2020) monocentric 3DT1 MRI data from 89 FASD patients (52 FAS, 37 FASD-NS, 6-20 years old) and 94 typically developing controls, we measured a reference brain area, length and 4 thicknesses of the corpus callosum, height of the vermis, proposed and ranked a Likert scale of foliation of the suprahorizontal vermis (5 ranks).

Results: Reference brain area, corpus callosum length, isthmus and splenium thickness and height of the vermis were significantly smaller in the FASD population. The interobserver agreement (x3) for ranks 4 and 5 (abnormal) of the vermis Likert scale were strong (Kappa=0.65), 16 FASD patients showing pathological foliation (18% vs. 0 control). Beyond age charts, based on normative curves for brain size established in controls, FAS patients showed a significant excess of abnormal (<10ep) isthmus thickness (p=0.0027) and height of the vermis (p<0.0001). 48 FAS and 27 NS-FASD had reduced brain size, 16 FAS and 6 NS-FASD had abnormal corpus callosum (partial agenesis or isthmus<10ep), 25 FAS and 10 NS-FASD had abnormal vermis (pathological foliation and/or height of the vermis<10ep). Finally, 20 FAS and 10 NS-FASD had 2 of the 3 anomalies (38% and 27% vs. 2% of controls) and 10 FAS had all 3 (19% vs. 0 control).

Conclusions: We found recurrent anomalies of the callosal isthmus and the cerebellar vermis in FAS. We showed that a rather specific combination of these markers with brain size deficit could be extended to NS-FASD and contribute to the diagnosis, especially of these non-syndromic forms.

Keywords:
Fetal Alcohol Spectrum Disorder, Fetal Alcohol Syndrome, Magnetic Resonance Imaging, Corpus Callosum, Cerebellum, Vermis, Neuroanatomical markers,Diagnostic Criteria

EPNS21-45
Neurodevelopmental

Oral or poster

School Reports as Real World Evidence for the Study of Batten Disease

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Objective: The use of qualitative and real world data (RWD) are important complementary methods for disease and treatment outcomes research. However, neuronal ceroid lipofuscinosis (CLN2) research has been restricted to clinical study due to practical and ethical concerns regarding the affected children. To our knowledge, this is the first study undertaken to explore the utility of non-clinical RWD (i.e. school reports) for the qualitative study of CLN2 experiences and enzyme replacement therapy.

Methods: Annual school reports and surveys were collected from a purposive sampling of 9 children with CLN2. A retrospective, reflexive thematic analysis was conducted to explore how these reports represent children and CLN2, and how this compares to guardians' perceptions of their child's life out with school.

Results: Findings revealed that each examined site has used statutory reporting frameworks in inconsistent ways to report on curricular attainment and future-focused targets. School reports represented children with CLN2 through: 1) subjective observations of their behaviours and (inter)personal, physical, and intellectual development; and 2) the interests of educators and guardians. Sparse reporting was found regarding the atypical development or regression experienced by children. Dissonance was also found between report content and guardians' perceptions and experiences.

Conclusions: For the purposes of disease and treatment outcomes research, school reports offer inconsistent RWD unable to clearly represent atypical development or regression. Their utilisation would therefore require the support of education systems to develop more relevant and consistent reporting methods. However, school reports do offer an unobtrusive method of data collection that can help describe positive treatment outcomes for children living with paediatric neurodegenerative diseases in support of their right to the highest attainable standard of health.

Keywords:
Batten disease, CLN2, paediatric neurodegenerative disease, real world data, school reports

EPNS21-482 Oral or poster
Neurodevelopmental

Intense Imagery Movements: a professionally under-recognized subgroup of severe complex motor stereotypies

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Objective: Intense Imagery Movements (IIM) concern a recently described subgroup of complex motor stereotypies (CMS) characterised by simultaneous execution of CMS and imagination of specific virtual scenes. Primary CMS reveal relatively intact psychosocial profiles, but the information on IIM is incomplete. We aimed to explore the psycho-societal profile, diagnostic recognition and motor features of patients engaging in IIM.

Methods: We applied two on-line inventories, addressing: 1. patients/parents from an international IIM forum to evaluate the psycho-societal profile and phenotype of IIM-performances, 2. health care professionals (paediatric neurologists and (neuro)psychologists) to evaluate the awareness of the diagnosis IIM.

Results: We received 31 international patient responses concerning the psycho-societal impact of IIM. Patients were in the age-range from 3-58 years; mean age 17 years; mean duration of IIM-engagement 15 years. IIM-severity was significantly associated with psychological comorbidities, impaired social functioning and quality of life (all $p<0.02$). Of the responding health care professionals, 23/97 (24%) indicated to be familiar with the diagnosis IIM (18/28 (64%) paediatric neurologists and 5/69 (neuro)psychologists (7%)). 68% of the parents/patients from the IIM forum stated that the diagnosis was not recognized by health care professionals. In these patients, phenotypic assessment revealed episodic IIM with dystonic, choreatic and tic-like features.

Conclusions: In contrast with primary CMS, engagement in IIM is associated with a relatively unfavourable psycho-social profile. In perspective of incomplete diagnostic recognition and a tendency of long duration, we suggest that increased professional awareness may help to address the comorbidities and provide anticipatory care.

Keywords:
Complex Motor Stereotypies, Intense Imagery Movements, Stereotypy Severity Scale, Quality of Life Scale, Motor Phenotype; Comorbidity

EPNS21-490 Oral or poster
Neurodevelopmental

Elementary visuo-spatial perception deficit in CP child

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Objective: Visuo-spatial function is often impaired in child with Cerebral Palsy (CP child). However, detect this disorder is not easy due to the motor disorder. Moreover, early detection of visuo-spatial deficit is necessary to prevent learning disabilities and to guide specific therapeutic and educational intervention.
The aim of our study was to assess the prevalence of elementary visuo-spatial perception (EVSP) deficit in CP child.

Methods: We designed and validated a simple and rapid screening test measuring elementary visuo-spatial perception (EVSP) without involving any complex language, motor, and gnosic function, (Pisella et al. 2013, 2019).
The EVSP test was administered to 50 children with CP, aged between 5 an 10 years. Our population consisted of hemiplegic children (13 with left hemispheric lesion (LHL) and 12 with right hemispheric lesion (RHL)) and 25 pre-term diplegic spastic children with periventricular leukomalacia. IQ level was controlled and none of them presented an intellectual disability. All the participants were seizure-free.

Results: Score obtained on EVSP test below interquartile range of typically developping children was observed in all subjects. 17% of LHL were severely impaired, with score as outliers, 19% for RHL and 21% for spastic diplegia. These results could be explained by the « crowding effect » for the LHL; the direct impact of the right hemispheric lesion on visuospatial function for the RHL and a specific involvement of the dorsal stream or the occipto-parietal pathway for spastic diplegia.

Conclusions: These results confirm the importance of assessing as soon as possible EVSP in the clinical evaluation of CP children to prevent repercussions of EVSP deficit on global cognitive development and leaurning abilitiies and to adapt therapeutic and educational intervention.

Keywords:
Child, cerebral palsy, elementary visuo-spatial perception test

EPNS21-503 Oral or poster
Neurodevelopmental

Neuropathic pain in severe cerebral palsy: an explorative study in verbal and non-verbal children

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Objective: Children with cerebral palsy (CP) may sometimes respond to normally non-painful stimuli like touch (allodynia) suggesting the presence of neuropathic pain. We wanted to explore if allodynia is present in children with severe cerebral palsy (CP), where almost half of children are non-verbal. No diagnostic tools were suitable in non-verbal children or adults. Therefore, we used r-FLACC (revised Face, Leg, Activity, Cry, Consolability) score to evaluate pain during sensory testing of children with severe cerebral palsy.

Methods: We recruited 16 children with severe CP, Gross Motor Function Classification System levels III-V. Parents and children with communicative abilities were interviewed about the child's pain and sensory disturbances using descriptors from r-FLACC. A standardized sensory test was performed using normally non-painful stimuli (touch, pressure, warmth, and cold). Afterwards, a short painful pinprick was applied on hands. Children with communicative abilities reported on painful stimuli themselves. Furthermore, a parent evaluated the child's non-verbal reactions using r-FLACC with a total score of 0 to 10.

Results: Of the 16 children, 50% were able to communicate. None of these children had any negative (i.e. loss of sensory modalities) or positive (e.g. allodynia) sensory signs. Furthermore, they had no pain descriptions suggestive of neuropathic pain. Of the eight non-verbal children, six had spastic CP and two had dyskinetic CP. The two children with dyskinetic CP both had pain-reactions to normally non-painful stimuli during the sensory test. The maximal pain intensity was two, corresponding to a mild discomfort. No pain or discomfort were observed in the six non-verbal children with spastic CP.

Conclusions: These preliminary data suggest that allodynia is more common in children with dyskinetic CP type compared to children with spastic CP. Parental observations need to be confirmed by health professionals reviewing video-records using r-FLACC.

Keywords:
cerebral palsy, neuropathic pain, allodynia, non-verbal children

EPNS21-516 Oral or poster
Neurodevelopmental

Comparison of sleep problems between ADHD and Typically Developing Children and Adolescents: Analytical Cross-sectional Study

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Objective: To compare sleep problems as per Children sleep Habit Questionnaire (CSHQ) and Polysomnography variables in 6-18-year-old children and adolescents with ADHD and age and gender-matched typically developing children and adolescents.

Methods: 30 ADHD subjects diagnosed as per DSM V criteria and, 30 matched controls were enrolled from the pediatric OPD of a tertiary care center. The sleep abnormalities were assessed as per Children Sleep Habits Questionnaire (CSHQ) in all participants (ADHD n-30, Control n-30) and an overnight Polysomnography (PSG) study (ADHD n-30, Control -12) was done, in 1 ADHD subject the PSG data was not analyzable. The PSG data were analyzed as per American Academy of Sleep Medicine (AASM) guidelines.

Results: On CSHQ (ADHD n-30, Control n-30) the prevalence of poor sleepers in ADHD and typically developing children were 63.3% and 6.7% respectively and the difference was statistically significant. ADHD subjects in comparison to controls had statistically significantly increased bedtime resistance, delayed sleep onset, increased daytime sleepiness, increased sleep anxiety with frequent night time awakenings, parasomnias, and sleep-disordered breathing episodes. PSG study (ADHD n-29, Control -12) showed that ADHD subjects had lesser sleep efficiency as compared to controls (77.6% vs 91.2%), with increased sleep latency (22.7 minutes vs 10.3minutes p-value 0.02). ADHD subjects had statistically significantly decreased NREM 2 and 3 latency as compared to controls.

Conclusions: Sleep disturbances are commonly seen in children with ADHD and can worsen the Quality of life of ADHD patients and their family. It is important to actively evaluate and manage sleep problems in ADHD patients.

Keywords:
ADHD, Sleep problems, Children Sleep Habits Questionnaire (CSHQ), Polysomnography

EPNS21-517 Poster only
Neurodevelopmental

Association between pelvic obliquity and scoliosis and risk factors for scoliosis progression

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Objective: This study aims to investigate the effect of pelvic obliquity on the direction of scoliosis and the factors that predict the progression of scoliosis, including pelvic obliquity in children with neurodisabilities.

Methods: Children or adolescents with neuromuscular disabilities under age twenty who had taken whole spine anteroposterior and lateral radiographs more than three times between 2005 and 2020 were recruited. A retrospective review of medical records of radiographs, GMFCS level, sex, seizure history was performed.A Chi-squared test was performed to evaluate the association between the direction of scoliosis and pelvic obliquity. To assess the pattern of the annual changes in scoliosis with age, we used linear-mixed effect model (LMM) and conducted likelihood ratio test associated with it for slope and intercept difference.

Results: Overall, 115 subjects with 384 radiographs were analyzed. There was a significant difference in the proportion of the direction of scoliosis according to the direction of the pelvic obliquity ($p<0.001$). The proportions of patients with apex side of scoliosis opposite the high side of pelvic obliquity were 71.3% (57/80) in groups with a reference of 3°, and 78.9% (48/61) in groups with a reference of 5°. Significant risk factors for progression of scoliosis were pelvic obliquity greater than 2°, poor development of lumbar lordosis, GMFCS level V and a seizure disorder ($p<0.001$).

Conclusions: Our results indicated that pelvic obliquity, poor development of lumbar lordosis, GMFCS level and seizure history were important factors affecting the progression of scoliosis. Also, there was a significant association with pelvic obliquity and scoliosis curve direction. The factors identified in our study can be used for further studies on the predictive model of scoliosis progression in children with neurodisability.

Keywords:
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EPNS21-591 Oral or poster
Neurodevelopmental

CLINICAL-GENETIC CHARACTERIZATION OF PATIENTS WITH GNB1-ENCEPHALOPATHY: A DEVELOPMENTAL ENCEPHALOPATHY ASSOCIATED WITH INTRACELLULAR SIGNALING

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Objective: The description of complex developmental encephalopathies associated with different intracellular signaling pathways have increased in the recent years. A total of 58 cases of GNB1-encephalopathy were reported.
We aim to characterize the spectrum of clinical, biochemical and genetic findings in GNB1-encephalopathy (GNB1-E).

Methods: Assessment of 7 individuals carrying pathogenic variants in GNB1. A standardized questionnaire and a predefined list were used to obtained the data. CSF was analyzed in 7 patients. Photos and video-recording were obtained to assess the phenotype and the motor pattern of each subject.

Results: The perinatal history was normal in 3/7 cases. The other cases presented important issues to adress (oligoamnios, prematurity, and neonatal depression). All the cases presented an early neurodevelopmental delay with hypotonia. Gait with support was achieved by 4/7. The main features found were: spastic-dystonic quadriparesis (4/7), epilepsy (4/7) (onset: range: 1-4 years), gastrointestinal disorders (3/7), relative macrocephaly (2/7), mastocytosis (2/7), cleft palate (1/7) and central hyperthermia (1/7). Neuroimaging was normal (5/7), and in the other cases a nonspecific enlargement of the extra-axial space was described. CSF neurotransmitter's study showed in 3/7, a decrease 5-hydroxyindoleacetic acid level with high homovanilic acid/5-hydroxyindoleacetic acid ratio.

Conclusions: The deep phenotyping showed a wide clinical spectrum and the extraneurological features has been a key factor for the diagnosis. The finding of low biomarkers in the serotonergic pathway is probably associated with the genetic defect and may have therapeutic consequences, this will require confirmation with further studies.

Keywords:
GNB1 - Encephalopaty - Movement Disorders - Epileptic encephalopathy

EPNS21-617 Poster only
Neurodevelopmental

PeriNAA - peripheral N-acetylaspartate metabolism and Canavan disease patient registry

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Objective: Canavan disease (CD) is a rare, metabolic, neurodegenerative leukodystrophy. Aspartoacylase (ASPA) deficiency prohibits N-acetylaspartate (NAA) breakdown and damages of brain white matter. Patients exhibit macrocephaly and severe psychomotor impairment during the course of disease. Treatment options are symptomatic. Natural disease history and the role of NAA is insufficiently understood. NAA is found elevated in CD and in peripheral tissues, e.g. in cancer cells. The goal of this project is an in-depth disease course characterization and a more comprehensive description of central and peripheral NAA metabolism.

Methods: CD patients are enrolled in a registry. Data of disease course and peripheral manifestations is evaluated pro- and retrospectively. Patients' tissue samples are analyzed biochemically. Patients' and biochemical data are integrated and analyzed using computational modelling.

Results: The registry currently includes 36 datasets of CD patients. Partially, bio samples are available. Early disease signs could be determined. Macrocephalus is found in 22/28 patients within the first year of life with a mean onset at the age of 6.4 months. Head control is achieved in 8/32 and lost in 2/8. Rolling over is achieved in 12/33 and lost in 6/12 patients within the first year of life. Gastrointestinal findings are common including vomiting, constipation, reflux, and tube feeding.

Conclusions: The goal is to develop a predictive, statistical model of NAA metabolism. A better understanding of the natural disease course and the function of NAA may foster treatment development for CD. Due to the rarity of the disease referral of CD patients from various centers is essential for the project.

Keywords:
Canavan disease leukodystrophy

EPNS21-620 Oral or poster
Neurodevelopmental

Prognostic value of various diagnostic methods for long-term outcome of newborns after hypoxic-ischemic encephalopathy treated with hypothermia

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Objective: Outcome prediction in infants with hypoxic-ischemic encephalopathy (HIE) has changed in the era of hypothermia treatment (HT). Our aim was to assess the predictive value of various diagnostic methods, used in the neonatal period, for short (STNO) and long-term neurological outcome (LTNO) of newborns with HT after HIE.

Methods: In this longitudinal study 50 term newborns who underwent HT after HIE between July 2006 and August 2015 and met the eligibility criteria were included and were followed-up until preschool age. Sensitivity and specificity for unfavourable STNO and LTNO were estimated for Amiel-Tison Neurological Assessment (ATNA), electroencephalography (EEG) and magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) performed in the neonatal period.

Results: The predictive accuracy of all neonatal methods tested increased over time, as LTNO exceeded predictive accuracy of STNO. Sensitivities and specificities in predicting unfavourable LTNO were: ATNA (sensitivity 0.94 [95%CI 0.71 - 1.0]; specificity 0.91 [95%CI 0.76 - 0.98]) EEG (sensitivity 0.94 [95%CI 0.71 - 1.0]; specificity 1.0 [95%CI 0.89 - 1.0]) and MRI (sensitivity 1.0 [95%CI 0.96 - 1.0]; specificity 0.91 [95%CI 0.86 - 1.0]).

Conclusions: Standard T1/T2 weighted MRI combined with DWI is a powerful predictive tool for LTNO, when performed in the first week after HIE in HT treated children, as are EEG and ATNA performed in the second or third week of life.

Keywords:
Hypoxic-ischemic encephalopathy, perinatal asphyxia, hypothermia treatment, long-term neurodevelopmental outcome, prognostic value

EPNS21-63 Oral or poster
Neurodevelopmental

Evaluation of neurological development of infants with prenatal exposure to COVID-19

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Objective: The effects of COVID-19 infection during pregnancy on the fetus are unknown. We aimed to investigate neurological development of infants with the history of prenatal exposure to COVID-19.

Methods: Neurological examinations and Denver developmental screening tests were performed on 42 infants aged between 2-12 months to evaluate the neurological effects of prenatal exposure to COVID-19 on the infant.

Results: Neurological examinations and neuromotor developments of 40 infants (96%) were normal consistent with their age.

Conclusions: In this study, it was thought that prenatal exposure did not have negative neurological effects on the infant. Large-scale long-term prospective studies are needed to evaluate the neurological effects of prenatal exposure more comprehensively.

Keywords:
COVID-19, infant, Denver II developmental screening test

EPNS21-651 Oral or poster
Neurodevelopmental

Pain and Sensory Disturbances in Children and Youth with Cerebral Palsy

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Objective: Cerebral Palsy (CP) is an impairment of motor function due to injury of the immature brain. Pain is common in children with CP with a prevalence of 27-77%. The causes of pain are many and treatment depends on the type of pain. Muscle spasms, contractures and stretching during physiotherapy are common causes of nociceptive pain and are well described in literature. In contrast, central neuropathic pain has not been studied despite its presence in adults with acquired brain injury.
Neuropathic pain is often described as burning pain, electric shocks, shooting pain, or pins and needles. When diagnosing neuropathic pain the presence of sensory disturbances are essential e.g. pain evoked by light touching or cold, and loss to one or several sensory modalities.
The primary aim was to examine whether central neuropathic pain is common in patients with CP.

Methods: Ambulant patients with CP aged 7-22 years were recruited from Danish pediatric departments. Pain and sensory disturbances were documented during an interview and the somatosensory function was examined using quantitative sensory testing i.e. a standardized test battery examining sensations such as touch, vibration, pressure, pinprick, warmth, and cold.

Results: Among 39 patients with CP, 77% had chronic or recurrent pain consistent with musculoskeletal pain predominantly of the motor-affected extremities. None had pain descriptions suggestive of neuropathic pain. Furthermore, 36% had chronic headaches.
Sensory disturbances were reported by 49% of the patients during the interview, while 79% of the patients had sensory abnormalities when assessed using quantitative sensory testing. The most common sensory abnormalities were mechanical hypoesthesia and mechanical hyperalgesia.

Conclusions: Chronic musculoskeletal pain is common in children and youth with CP. Despite an underlying brain lesion and the presence of sensory disturbances, none of the ambulant patients with CP had probable neuropathic pain.

Keywords:
cerebral palsy, cp, pain, neuropathic pain, sensory function, quantitative sensory testing

EPNS21-683
Neurodevelopmental

Oral or poster

Rett Syndrome and epilepsy/status epilepticus: our experience

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Objective: Rett Syndrome (RS) is a rare genetic disease of neurodevelopment, one of the most frequent causes of intellectual disability in girls. Epilepsy was found in 60-80% of cases.
The present retrospective study aimed to establish a possible association between the age of onset of the first seizure and the severity of epilepsy in RS, as well as confirming the different susceptibility to seizures conferred by the different genotypes.

Methods: The sample studied was made up of 33 female patients affected by RS (32 with MECP2 gene mutations, 1 with CDKL5 mutations). The presence or absence of epilepsy/status epilepticus, the age of onset and the type of seizures, medications taken and genotype were considered. Prevalence measures, weighted average, were used for the statistical analysis and OR.

Results: Epilepsy was found in 82% of patients (27/33); only 2 (7.4%) presented at least one episode of status epilepticus in their life, including the CDKL5 patient. The average age of onset of epilepsy is 4.7 years with a range from 1 month to 12 years. 27.3% of patients with epilepsy have the R306C mutation, while 18.2% have the R255X mutation. Among patients with early onset of seizures, 33.3% have the mutation R255X.
One of the most significant risk factors is the age of onset: the earlier the age of onset, the more epilepsy is likely to be drug-resistant (OR: 2.22). In our sample, there was only one RS with the CDKL5 gene variants with early-onset and searchable seizures and none with FOXG1 gene variants.
Mutations in MECP2 appear to confer a different susceptibility to seizures. A higher incidence of epilepsy has been reported in patients with R306C and R255X variants; moreover, the latter would be associated with early onset of crises (<3 years).

Conclusions: Epilepsy is a prominent condition in RS and contributes significantly to the clinical course of the disease. The knowledge of the different risk factors, including the genotype, could be useful to improve the clinical management of these patients.

Keywords:
Rett Syndrome - epilepsy - status epilepticus - MECP2 - CDKL5

EPNS21-73 Poster only
Neurodevelopmental

A case of a ADPRHL2 Mutation; Neurodegeneration with Developmental Delay, Ataxia, and Axonal Neuropathy

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Objective: ADPRHL2 is thought to function in the pathway of ADP ribosylation, which is a reversible posttranslational modification used to regulate key cellular processes such as transcription, DNA repair, translation, and apoptosis. Loss-of-function mutations in the ADPRHL2 gene result Neurodegeneration with Developmental Delay, Ataxia, and Axonal Neuropathy. Here we report of an individual diagnosed Neurodegeneration with Developmental Delay, Ataxia, and Axonal Neuropathy.

Methods: 14-year-old girl was consulted from the orthopedics clinic to pediatric neurology clinic due to scoliosis. Her prenatal and natal history was unremarkable and was born to healthy
consanguineous parents. Her early development was normal. She was diagnosed epilepsy and seizures were controlled with valproate therapy. She had moderate mental retardation. Her neurological exam revealed distal weakness in upper and lower extremities, pes cavus and hammer toes were noted. EMG was found to be consistent with axonal polyneuropathy.

Results: Whole exome sequencing (WES) study was done and a mutation in the ADPRHL2 c.235A>C gene was detected.

Conclusions: The present study underscores the usefulness of WES in finding the genetic basis of neurological disease.

Keywords:
ADPRHL2, Developmental Delay, Scoliosis

EPNS21-115 Poster only
Neuromuscular

RARE CAUSE OF PERIPHERAL NEUROPATHY: ANDERMANN SYNDROME

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Objective: Andermann syndrome (AS), also known as agenesis of corpus callosum with peripheral neuropathy is an autosomal recessive disorder caused by mutations in SLC12A6 gene. The disorder appears early in life with delayed developmental milestones. Patients have an axonal type severe motor-sensory polyneuropathy with areflexia. A total or partial ACC is detected by cerebral MRI. Patients typically begin walking between 3-4 years of age and become wheelchair dependent in the second decade of their life. Here we report 2-year-old and two siblings 6 and 12 years old Turkish patients, born to consanguineous parents with agenesis of the corpus callosum and peripheral neuropathy due to a mutation in SLC12A6 gene.

Methods: Molecular genetic study (NGS) demonstrated homozygous mutation in SLC12A6 gene.

Results: Cranial magnetic resonance imaging (MRI) showed total agenesis of the corpus callosum (ACC) in all patients. Electrodiagnostic studies performed in all patients. EMG showed slowness of motor nerve conduction velocities in median and peroneal nerves, low compound motor nerve action potentials and prolonged distal latencies in both nerves.

Conclusions: Andermann syndrome is a very rare autosomal recessive disorder associated to mutations in the SLC12A6 gene, also known as KCC3, a co-transporter of potassium and chloride ions. SLC12A6 directly interacts CK-B and has a significant role in the energy regulation of neurons. ACC is the most common structural brain abnormality in Andermann syndrome. Andermann syndrome should be suspected in pediatric cases of delayed developmental milestones, peripheral neuropathy and agenesis of corpus callosum. It is not always clinically possible to differentiate from other diseases. Genetic diagnosis methods are beneffical and necessary after no other spesific metabolic abnormality has been linked with it.

Keywords:
Andermann syndrome; Chloride homeostasis

EPNS21-153 Oral or poster
Neuromuscular

Effects of the Covid-19 Pandemic on Education and Participation in Children and Adolescents with Duchenne Muscular Dystrophy in Switzerland

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Objective: Duchenne Muscular Dystrophy (DMD) is a genetic disorder characterized by progressive muscle weakness. Two thirds of patients with DMD have cognitive and neuropsychiatric problems. For the quality of life of patients with DMD, negative factors are the lack of qualifying education and the lack of opportunities for participation in sporting and leisure activities. Adapted assistance in education and support to pursue academic goals and facilitate participation in social life are immensely important. During the Covid-19 pandemic, the pediatric population has shown to be less severely impacted by the disease itself, but by the restrictions associated.
The aim of this study is to evaluate the impact of the Covid-19 pandemic on education and participation in young patients with DMD in Switzerland.

Methods: We conducted a survey study from May to August 2021 assessing the impact of the Covid-19 pandemic on education and participation in 8 to 18 years old patients with DMD in Switzerland.

Results: Of a total of 60 sent surveys, 42 were returned (70%) and 40 were included. Mean age of participants was 13.51 years (+/- 3.099 SD). 55% of the participants were wheelchair-bound. Of the 40 boys and adolescents included, 21 (53%) attended a special school and 19 a regular school. Of the 22 (55%) participants receiving assistance at school, 7 (18%) reported a change caused by the pandemic: In 5 the assistance was paused or stopped. Of the 12 (30%) boys and adolescents attending sporting activities, in 10 (25%) of 12 these activities were paused. 9 (23%) attended leisure activities like scouting, club membership or music bands, in 3 (8%) of them the activity was paused.

Conclusions: The Covid-19 pandemic had direct effects on school assistance and sporting and leisure activities in young patients with DMD in Switzerland.

Keywords:
Duchenne Muscular Dystrophy, Participation, Covid-19 pandemic

EPNS21-194 Poster only
Neuromuscular

SUNFISH: Efficacy and safety of risdiplam in Types 2 and 3 SMA

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Objective: Risdiplam (EVRYSDI®) is a centrally and peripherally distributed, oral survival of motor neuron 2 (*SMN2*) pre-mRNA splicing modifier that has been approved by the European Commission for the treatment of patients aged ≥ 2 months, with a clinical diagnosis of Type 1, 2 or 3 SMA or with 1-4 *SMN2* copies. The objective of these analyses is to determine longer-term efficacy and safety of risdiplam in patients with Types 2 and 3 spinal muscular atrophy (SMA).

Methods: SUNFISH (NCT02908685) is a multicentre, two-part, randomised (2:1, risdiplam: placebo), placebo-controlled, double-blind study in a broad population of patients with Types 2 and 3 SMA (inclusion criteria 2-25 years at enrolment). Part 1 (N=51) assessed the safety, tolerability and pharmacokinetics/pharmacodynamics of different risdiplam dose levels in Types 2 and 3 SMA (ambulant and non-ambulant). Part 2 (N=180) assessed the efficacy and safety of the Part 1-selected dose of risdiplam versus placebo in Type 2 and non-ambulant Type 3 SMA. In Part 2, participants were treated with risdiplam or placebo for 12 months; all participants then received risdiplam until Month 24, when patients were offered the opportunity to enter the open-label extension.

Results: The primary outcome of Part 2 was met, showing a statistically significant difference in the change from baseline in 32-item Motor Function Measure total score at Month 12 in patients treated with risdiplam (n=120) versus placebo (n=60) (data cut-off: 6 September 2019). The gains observed with risdiplam treatment at Month 12 were maintained or improved upon at Month 24 (data cut-off: 30 September 2020). At Month 24, there were no treatment-related safety findings leading to withdrawal. Here, we present longer-term efficacy and safety data from patients who have received risdiplam for ≥ 3 years.

Conclusions: SUNFISH is ongoing and is providing long-term efficacy and safety data of risdiplam in a broad population of children, teenagers and adults with SMA.

Keywords:
Spinal muscular atrophy, risdiplam, clinical trial

EPNS21-2027 Poster only
Neuromuscular

Neuropsychological assessment of patients with early onset Friedreich's ataxia

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Objective: Friedreich's ataxia (FRDA) is an inherited autosomal recessive disorder. The disease usually manifests in adolescence with gait problems and poor movement coordination. Other symptoms include scoliosis, cardiomyopathy, impaired speech, diabetes mellitus, etc. The disease can sometimes be associated with cognitive affective cerebellar syndrome. A progression is measured by using tests (Scale for Assessment and Rating of Ataxia; Inventory of Non-Ataxia Signs; Speech Test; Timed 25-Foot Walk Test; 9-Hole Peg Test).
The aim of the study was to advance understanding of the cognitive profile in patients with FRDA.

Methods: We evaluated 7 patients aged 7 to 21 years with FRDA, which was genetically confirmed and clinically diagnosed in accordance with recent WHO, ERN-RND and expert recommendations, and 7 healthy controls matched for age and gender.
The data of complete history, clinical, developmental and neurological examination, including some scales and assessments based on the EFACTS consortium's protocol (SARA - Scale for Assessment and Rating of Ataxia; ADL - Activities of Daily Living) and the results of comprehensive neuropsychological evaluation using Neuropsychological Test Battery for Children were compared via t-tests, we computed also the Pearson's correlations.

Results: Patients with FRDA performed significantly lower compared to controls in 4 of 7 tested cognitive domains - motor functions (graphomotor and motor coordination), visual spatial processing, auditory attention and attention. We did not find in children with FRDA intellectual impairment, language impairment (naming, verbal fluency or comprehension was not impaired) or alteration of social cognition (affect recognition, theory of mind).

Conclusions: Pediatric FRDA patients have only specific cognitive deficits, which are not crucial for overall functioning. Even it was a pilot study with a small number of pediatric FRDA patients, it is still one of the largest groups with comprehensive neuropsychological examination.

Keywords:
Friedreich's ataxia in children, neuropsychology, cognitive profile

EPNS21-2030 Oral or poster
Neuromuscular

The outcome of two SMA cases treated with nusinersen at seven hours and at three days of life: the earliest ever

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Objective: Starting by the end of 2016 initially two alternative therapies for spinal muscular atrophy (SMA) appeared: nusinersen, an intrathecally administered antisense oligonucleotide molecule to promote the transcript from the homologous gene SMN2, and a AAV9 virus based SMN1 gene therapy. Here we present two babies whom we were able to treat at seven hours and three days of life. To our knowledge our babies were the earliest ever treated SMA cases.

Methods: Case 1: This boy was the third baby born to first cousin parents at term after an uneventful pregnancy. Their first and second child had deceased at the age of 2 months and 6 months, respectively, due to SMA type 1. The diagnosis of SMA was made prenatally with homozygous deletion of SMN1 gene and 2 copies of SMN2 gene. Treatment with nusinersen was initiated at seven hours postnatally. Case 2: This baby girl was diagnosed in utero based on the family history. Her 6-year-old sister had SMA 2 (sitter). They both had deletion of exons 7 and 8 of the SMN1 gene with 3 copies of SMN2 gene. She received her first dose at 3 days of life.

Results: Case 1: On the last visit at 11 months of age, his neurological examination was completely normal with the presence of deep tendon reflexes (DTR) and with normal tonus. He was never hospitalized due to respiratory infections, and he never had feeding difficulties. He follows a normal growth curve. Case 2: When examined at 700 days she had already reached the maximum score of 64 on the CHOP-Intend test. There after she demonstrated normal physical and neurological examinations with preserved DTR's.

Conclusions: Race against time is essential and an established basis in SMA. No delays are allowed. We will continue to observe the outcome and evolution of our babies.

Keywords:
SMA, nusinersen,

EPNS21-2048
Neuromuscular

Poster only

Early-onset MYH7 related myopathy 2 case reports

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Objective: Early-onset distal myopathies are rare diseases and there is currently no consensus around clinical criteria, or practice guidelines. Clinical features such as tiptoe walking, foot drop, distal and proximal muscle weakness mimic other neuromuscular disorders. Initially, imaging, electrophysiology and blood tests may be normal or non-specific, making the diagnosis challenging. We report 2 cases of Laing distal myopathy (LDM) in 5 and 8 years-old boys who presented with tiptoeing and later distal>proximal muscle weakness altering their balance.

Methods: Initial nerve conduction studies and electromyography (EMG) were normal or showed non-specific anomalies. As the disease progressed, neurogenic changes appeared on the EMG, corresponding to clinical deterioration with distal and proximal weakness, foot drops. The muscle MRIs showed fatty atrophy of the lower limb anterior muscles but no other signal anomalies. Blood tests including CK and genetic tests for HMSN were normal. Whole genome sequencing showed that both children had MYH7 (Myosin Heavy Chain 7) mutations. One had an MYH7 variant not previously reported in the literature (c.5000T>C p.(Leu1667Pro)), and the other was found to have a known MYH7 pathogenic variant (c.4850_4852del p.(Lys1617del)) alongside with a previously unreported TTN (Titin) mutation (c.104582G>A p.(Arg34861His)). Muscle biopsy was avoided in view of the genetic results.

Results: Initially, serial casting and splints helped improving their gait. Orthopaedic surgery was required and successful for one child in improving function and maintaining his walking, the other is awaiting surgery.

Conclusions: LDM should be considered as a differential diagnosis in cases of severe tip toe walking and distal weakness when genetics for HSMN is negative. Muscle MRI may show diagnostic clues as the disease progresses. Whole genome sequencing will help aid early diagnosis, avoid invasive muscle biopsy and guide specific management options to improve the outcome for this group of patients.

Keywords:
myopathy, early-onset myopathy, distal myopathy, Laing distal myopathy, MHY7 gene, MPD1, TTN gene

EPNS21-2063 Poster only
Neuromuscular

Eteplirsen therapy in DMD. Kazakhstan experience

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Objective: Description of Eteplirsen therapy in terms of the small group patients with DMD in Kazakhstan.

Methods: Patients received once-weekly intravenous doses of Eteplirsen 30 mg/kg on an outpatient center at a children's hospital in Almaty from June 2021 to present day.Single-use vials of Eteplirsen were diluted in 150 ml normal saline and infused over 60 min. 3 boys aged 7,10,12 years with confirmed out-of-frame DMD deletions potentially correctable by skipping exon 51 and the ability to walk 180 to 440 m on the 6MWT. Patients have been on stable glucocorticoids (deflazacort) for more 24 weeks in dose: 18,21,24 mg/day. Cardiac and pulmonary functions were stable. The 6MWT and other functional motor tests were performed at baseline and week 24.

Results: After 24 weeks of treatment with Eteplirsen was well tolerated, with no treatment-related adverse events. No changes were observed in vital signs or physical examination, including injection site reactions. Cardiology and pulmonary functional tests were remained stable, and no changes were observed in chemistries, hematology, coagulation, or renal or liver function.
1 patient A., 7 yo., del 48-50 ex. Functional evaluation: Scott scale 29/33 points, Vignos scale I/I class, climbing 4 steps 4.3/5 sec; supine to stand 7/3.5 sec; 6MWT 452/461 m.
2 patient K., 10 yo., del 49-50 ex. Functional evaluation: Scott scale 21/23 points, Vignos scale III/III class, climbing 4 steps 19/28 sec; supine to stand 30/30 sec; 6MWT 208/198 m.
3 patient R., 12 yo., del 48-50 ex. Functional evaluation: Scott scale 23/25 points, Vignos scale II/II class, climbing 4 steps 8,5/7 sec; supine to stand 10.4/8.5 sec; 6MWT 270/270 m.

Conclusions: The first Kazakhstan experience of DMD therapy with Eteplirsen is presented. There is a good safety profile: no adverse reactions were reported.Intermediate results showed positive dynamics on all scales in the youngest patient. In perspective is to determine the safety and efficacy profile of Eteplirsen therapy in a large cohort of patients.

Keywords:
DMD, eteplirsen, safety profile, 6MWT, functional tests

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Neuromuscular

Nonsense mutation in Kazakh population of DMD patients

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Objective: The study provided a group of Kazakh patients with a nonsense mutation in the dystrophin gene.

Methods: This was data of a retrospective/prospective analysis, clinical and genetic examination of 20 DMD patients with a nonsense mutation aged between 2 to 16 years from 6 southern regions of Kazakhstan

Results: Between Aug.2018 and Dec.2021, we examined 137 patients with suspecting of DMD by MLPA and sequencing. Nonsense mutations were found in 20 boys who made up the study group. The average age of patients was 8.8 y. Family history in 11 cases (55%) was positive. The onset of independent walking was at 20.9 mo. Currently, 10 out of 20 patients have ability to walk, 10 are non-ambulatory. Disease onset was at 3.9 y; clinical diagnosis definition was at 6.4 y; the genetic diagnosis was at 9.1 y. The age of loss of ambulatory ability was observed in the period from 8 to 13 y (10.2 y). Nonsense mutations accounted for 14.6% of total detected mutations and 36.4% among small and point mutations. Types of formed premature stop codons: UGA (15),UAA (3),UAG (2).
10 patients are receiving combination therapy: Ataluren and glucocorticoids. Specific pathogenetic therapy started in the first patients in October 2020. Currently, the duration of therapy has ranged from 4 to 17 months in different patients.

Conclusions: The frequency of occurrence of nonsense mutations in the Kazakh population of DMD patients corresponds to the literature data (14.6%). An analysis of a small group of children with a nonsense mutation showed a high family burden (55%), a history of delayed onset of independent walking (20.9 months), a 100% predominance of the DMD phenotype with the development of the non-ambulatory stage in half of the patients at an average age of 10.2 years. Patients are being followed up prospectively. Comprehensive work is being carried out to reduce the time for making a final diagnosis. The evaluation of the safety profile and efficacy of Ataluren is planned to be carried out on a large group of patients.

Keywords:
DMD, ataluren, nonsence-mutation, stop-codon, Kazakh

EPNS21-207 Poster only
Neuromuscular

Pulmonary function decline analysis in non-ambulatory patients with DMD: ataluren Study 019 compared with the CINRG Duchenne Natural History Study

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Objective: We investigated whether non-ambulatory nonsense mutation Duchenne muscular dystrophy (nmDMD) patients receiving ataluren+standard of care (SoC) in the Study PTC124-GD-019-DMD (019; NCT01557400) experienced a slower decline in pulmonary function vs DMD patients receiving SoC only in the CINRG Duchenne Natural History Study (DNHS; NCT00468832).

Methods: Study 019 was a phase 3, long-term, multicenter, open-label study assessing ataluren safety in nmDMD patients who had received ataluren in prior studies. Propensity score matching (PSM) identified Study 019 and CINRG DNHS patients (N=45) comparable in established predictors of disease progression: age at first symptoms; age at corticosteroid initiation; deflazacort use duration; and other corticosteroid use duration. CINRG DNHS patients who had received investigational drugs for DMD were excluded. In Study 019, age at first symptoms was not recorded; therefore, age at diagnosis was used as a conservative proxy for PSM. Annual percent-predicted forced vital capacity (%pFVC) decline rates were compared between Study 019 (ataluren+SoC) and CINRG DNHS (SoC) cohorts using a mixed-model for repeated measures analysis. The slope of %pFVC vs patient age for each treatment group was the annual rate of %pFVC decline for each cohort.

Results: Annual %pFVC decline rates for Study 019 (n=33) vs CINRG DNHS (n=25) were 4.29% and 5.62%, respectively (p =0.0133). The lower annual %pFVC decline rate for Study 019 patients, indicated by the shallower slope, demonstrates slower pulmonary decline in nmDMD non-ambulatory patients receiving ataluren+SoC vs DMD CINRG DNHS patients receiving SoC only.

Conclusions: These data demonstrate that long-term ataluren treatment (+SoC) may delay disease progression in non-ambulatory nmDMD patients.

Keywords:
ataluren, nonsense mutation Duchenne muscular dystrophy, pulmonary, forced vital capacity

EPNS21-2074 Oral or poster
Neuromuscular

Tymectomy experience in Juvenile Myasthenia Gravis

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Objective: Juvenile Myasthenia Gravis(JMG)is an autoimmune disease presenting with fluctuating muscle weakness and fatigue under 18 years of age. Tymectomy is usually preferred for patients refractory to treatment. Timing and outcomes are still controversial.
Tymectomy outcomes of five patients diagnosed with JMG are presented.

Methods: Follow up data of patients who underwent tymectomy within years 2020 and 2021 in our clinic were retrospectively reviewed. Clinical characteristics, indications and surgical outcomes were noted.

Results: All patients were positive for acetylcholine esterase antibody.
Patient one presented at 9 years of age with articulation and swallowing difficulty. Tymectomy was performed after 17 months due to corticosteroid complications (cataract and weight gain). After tymectomy, she was symptom free for 3 months when her symptoms recurred and corticosteroids were restarted.
Patient two presented with acute respiratory failure at 14 years of age. Tymoma was detected and tymectomy was performed 6 months after diagnoses. The patient remained symptom free since then(14 months)
Patient three presented with fluctuating weakness at 12 years of age. Tymectomy was performed 7 months later because pelvic fracture occured as a complication. She was symptom free since then(15 months).
Patient four presented with swallowing and articulation dysfunction which started short after starting ethosuximide at 10 years of age. Tymectomy was performed after 8 months as her symptoms did not regress with sole medical treatment. She remained symptom free since then (6 months).
Patient five presented with generalised weakness and difficulty in swallowing at 13 years of age. Tymectomy was performed after 17 months due to steroid dependance. He is symptom free with low dose corticosteroids since then.
Thoracoscopic tymectomy was the applied surgical procedure without any complications.

Conclusions: Tymectomy is a safe treatment option and should be considered earlier in JMG.

Keywords:
tymectomy, juvenile myasthenia gravis

EPNS21-209
Neuromuscular

Oral or poster

Leading causes of death in children and adolescents with Duchenne muscular dystrophy

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Objective: Duchenne muscular dystrophy (DMD) is a progressive neuromuscular disease resulting in premature death, most commonly from respiratory or cardiac failure. The aim of this nation-wide, population-based study was to explore the life expectancy and leading causes of death in patients with DMD in Sweden and identify age-related differences in causes of death.

Methods: Patients with DMD were identified via the National Quality Registry for Neuromuscular Diseases, the Swedish National Registry for Respiratory Failure, pathology laboratories, medical clinics, as well as the Swedish network for neuromuscular diseases. Information regarding the age and cause of death were retrieved from the Cause of Death Registry and were cross-checked with the medical records.

Results: In total, 129 patients with DMD who were born between 1970 and 2019, had deceased during the study period. 25 patients died during childhood and adolescence, at a median age of 16.25 years old (min, max: 6, 18). The leading cause of death in the pediatric population was non-cardiopulmonary in 44% of patients, followed by respiratory failure in 36%, while heart failure accounted for 20% of causes of death. In contrast, heart-related complications were the leading cause of death among adult patients accounting for 47% of causes of death. Age at loss of ambulation was similar between the pediatric and adult population (10.5 and 10 years respectively) and did not have an impact on life expectancy.

Conclusions: Non-cardiopulmonary causes of death are common among young patients with DMD urging prompt attention and further investigation by health-care providers.

Keywords:
muscular dystrophy, neuromuscular, Duchenne

EPNS21-213 Poster only
Neuromuscular

MANATEE: A study of RO7204239 in combination with risdiplam treatment in paediatric patients with SMA

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Objective: Risdiplam is a centrally and peripherally distributed, oral survival of motor neuron 2 (*SMN2*) pre-mRNA splicing modifier that has been approved by the European Commission for the treatment of patients aged ≥ 2 months, with a clinical diagnosis of Type 1, 2 or 3 SMA or with 1-4 *SMN2* copies. RO7204239 is an investigational molecule that negatively regulates skeletal muscle growth.
The objective of this study is to assess the safety, tolerability and pharmacokinetics/pharmacodynamics of RO7204239, a recycling and antigen-sweeping monoclonal antibody, in combination with risdiplam (EVRYSDI®) in patients with spinal muscular atrophy (SMA).

Methods: MANATEE (BN42644) is a multicentre, two-part, randomised, placebo-controlled, double-blind study that will investigate the effect of RO7204239 in combination with risdiplam in treatment-naïve and non-treatment-naïve ambulant patients, aged 2-10 years at screening. Part 1 (target enrolment N~36) will assess safety, tolerability and pharmacokinetics/pharmacodynamics of different RO7204239 doses in combination with risdiplam. Part 2 (target enrolment N~144) will assess efficacy and safety of the Part 1-selected dose of RO7204239 in combination with risdiplam.

Results: Risdiplam has demonstrated clinically meaningful benefit in patients with SMA and there have been no treatment-related safety findings leading to treatment withdrawal in the risdiplam studies to date. The combination of RO7204239 and an SMN2 splicing modifier was found to further improve muscle size and strength in an SMA disease mouse model compared with SMN2 splicing modifier treatment alone. This approach may lead to a complementary effect on improvement of skeletal muscle atrophy/weakness. Here, we present the study design of the MANATEE study.

Conclusions: This study will provide valuable information about efficacy and safety of RO7204239 in combination with risdiplam treatment in ambulant paediatric patients with SMA.

Keywords:
Spinal muscular atrophy, risdiplam, RO7204239, clinical trial

EPNS21-233
Neuromuscular

Oral or poster

Mind the Gap: Acetazolamide Prolonged Periods without Paralysis in a Girl with Andersen-Tawil Syndrome

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Objective: Andersen-Tawil Syndrome (ATS) is a rare potassium channelopathy. It is characterized by a triad of periodic paralysis and muscle weakness, ventricular arrhythmias, and dysmorphic features. The presented case is a 13-year-old girl with an atypical presentation of ATS, who experienced muscle paralysis on a daily basis. Although it is not a standard therapy for children with ATS, and despite reports of adverse effects in patients with ATS, acetazolamide was introduced into our patient's treatment in a controlled environment.

Methods: The data was obtained by interviewing the patient and her relatives as well as reviewing her medical reports since birth up until adolescence. As acetazolamide was introduced into her treatment, we scheduled trimonthly appointments and followed her medical state and laboratory tests. The discussion of our case was based on available literature on ATS and anecdotal reports on effects of acetazolamide.

Results: One month after the introduction of 750 mg of acetazolamide per day, without additional potassium supplements, our patient reported a significant reduction in the frequency and severity of muscle paralysis episodes. Although the muscle weakness still occurred daily it was more manageable and did not require assistance or wheelchair use. In the last 9 months of treatment with acetazolamide, she only had 2 severe episodes of paralysis that required the use of a wheelchair. She has also improved socially, as she can now play outside with her friends, cook, and is almost independent in personal care. She did not experience any side effects.

Conclusions: Multidisciplinary management is important in patients with ATS. Successful cardiac treatment allows survival, while treatment of periodic muscle paralysis contributes to improved daily function, greater independence, and better quality of life in these patients. Based on our experience, we recommend a supervised trial of acetazolamide in patients with genetically confirmed ATS.

Keywords:
Andersen-Tawil Syndrome, acetazolamide, periodic paralysis

EPNS21-250
Neuromuscular

Oral or poster

Safety, Tolerability, and Pharmacokinetics of Eteplirsen in Patients 6-48 Months Old With Duchenne Muscular Dystrophy Amenable to Exon 51 Skipping

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Objective: Eteplirsen is indicated for treatment of exon 51 skip-amenable patients with Duchenne muscular dystrophy (DMD). Previous studies in patients >4 years of age indicate eteplirsen is well tolerated and attenuates pulmonary and ambulatory declines compared with matched natural history cohorts. Our objective was to evaluate the safety, tolerability, and pharmacokinetics of eteplirsen in patients aged 6-48 months, the youngest population of patients with DMD in a clinical trial to date, in Study 4658-102 (NCT03218995).

Methods: In this open-label, multicenter, dose-escalation study, patients who have a confirmed mutation of the *DMD* gene amenable to exon 51 skipping (Cohort 1: aged 24-48 months, n=9; Cohort 2: aged 6 to <24 months, n=6) received ascending doses (2, 4, 10, 20, 30 mg/kg) of once-weekly eteplirsen intravenously over 10 weeks, continuing at 30 mg/kg up to 96 weeks. Endpoints included incidence of adverse events and clinically significant laboratory abnormalities (primary) and pharmacokinetics (secondary).

Results: All patients completed the study (N=15). Average time since diagnosis was 10.5 months, and most (13/15, 86.7%) were not taking corticosteroids. Eteplirsen was well tolerated with no treatment-related discontinuations, deaths, or evidence of kidney toxicity. Most treatment-emergent adverse events were mild, and the most common were consistent with those commonly seen in pediatric populations (pyrexia, nasopharyngitis, vomiting, cough, diarrhea). Eteplirsen pharmacokinetics were consistent between both cohorts and aligned with expectations based on previous clinical experience in boys with DMD older than 4 years of age.

Conclusions: These safety and pharmacokinetic results contribute to the body of evidence supporting the early use of eteplirsen in boys with DMD.

Keywords:
dmd, exon 51 skipping, pmo, young patients, iv infusion

EPNS21-284 Poster only
Neuromuscular

A novel splice site variant in a patient with spinal muscular atrophy and hypoplastic left heart syndrome

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Objective: Spinal muscular atrophy (SMA) is an autosomal recessive disorder causing degeneration of motor neurones in the anterior horn of the spinal cord. SMA is caused by homozygous in activation of the *SMN1* gene but a highly homologous copy (*SMN2*), which also produces a small amount of functional SMN protein, can mitigate disease severity. We present a patient with a severe SMA phenotype with hypoplastic left heart syndrome (HLHS) , characterise a novel spice-site variant in the *SMN1* gene and describe the unusual pathological features in muscle biopsy.

Methods: The patient was born to consanguineous parents in a national heart center due to antenatal diagnosis of HLHS. Postnatal examination (day 4) revealed decreased tone, a lack of anti-gravity movements, absent deep tendon reflexes but no respiratory distress or feeding problems. Due to the combination of suspected muscle disease and HLHS, together with the results below, treatment was discontinued and the patient died on day 10 of life.

Results: Whole genome sequencing (WGS) revealed an apparently homozygous variant in *SMN1* located in the donor splice-site between exon 7 and intron 7, c.*3+1G>T (NM_000344.3). MLPA identified one copy of *SMN1* and *SMN2*. Analysis of RNA showed a transcript lacking exon 7 and western blotting of SMN protein from muscle showed reduced levels comparable to other SMA1 patients.
Muscle biopsy and subsequent immunohistochemical and immunofluorescence showed unusual expression of embryonic myosin heavy chain in the patient compared to controls and other SMA patients.

Conclusions: This case highlights the importance of rapid diagnosis of newborns to allow further treatment decisions to be made. Up to 30% of HLHS patients have associated conditions and the combination with SMA has been previously described, whether this is more than the coincidence of two relatively common conditions is unclear. A severe SMA phenotype has been previously seen in other patients with a splice site variant in intron 7.

Keywords:
Spinal Muscular Atrophy, Splice site variant, Hypoplastic left heart syndrome, Muscle Biopsy

EPNS21-286
Neuromuscular

Oral or poster

A case report of the precision treatment of a child with a Singelton Merton Interferonopathy with Ruxolitinib

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Objective: The Singleton and Merten Interferonopathy Type 1 is a rare autoimmune disorder caused by a mutation in the IFIH1 gen. This mutation leads to a overstimulation of the interferon pathway that causes a variety of symptoms. During the last years a drug Ruxolitinib became available to modulated the interferon signaling pathway.

Methods: We present the case of an nine year old child with a Singelton Merten interferonopathy. The child initially developed initially only with a slow gross motor function development and a muscular weakness. From the age of five years further symptoms appeared. He developed an osteoporosis, an acroosteolysis and a severe psoriasis. A genome analysis showed a pathogenic IFIH1 variant, metabolic testing in Leucocytes showed a pathologic interferon pathway activation pattern. Based on theroretical considerations a treatment with the Januskinase 1 and 2 inhibiter Ruxolitinib was iniated.

Results: Within days of treatment the Psoriasis improved significantly, the interferon signature normalized and the muscular weakness improved significantly.

Conclusions: This case report highlights the enormous potential of precision medicine for children with autoimmune disorders. By first identifying the exact genetic cause for the over stimulation of the immune response and then determining the metabolic status and identifying treatment markers one can design a patient tailored treatment approach. This approach - when successful - minimizes the treatment side effects and promises to over new treatment opportunities to many patients.

Keywords:
Singleton and Merten Interferonopathy Type 1, Aicardi-Goutières Syndrom

EPNS21-287 Poster only
Neuromuscular

Pooled safety data from the risdiplam clinical trial development programme

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Objective: Risdiplam (EVRYSDI®) is a centrally and peripherally distributed, oral survival of motor neuron 2 (*SMN2*) pre-mRNA splicing modifier approved by the European Commission for the treatment of patients aged ≥ 2 months, with a clinical diagnosis of Type 1, 2 or 3 SMA or with 1-4 *SMN2* copies. The aim of this analysis is to determine the long-term safety of risdiplam in patients with spinal muscular atrophy (SMA) who have participated in the risdiplam studies.

Methods: Safety data were pooled from three studies within the risdiplam clinical development programme:
• FIREFISH (NCT02913482) assesses safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and efficacy of risdiplam in infants with Type 1 SMA (aged 1-7 months at enrolment)
• SUNFISH (NCT02908685) assesses safety, tolerability, PK, PD and efficacy of risdiplam in patients with Types 2/3 SMA (aged 2-25 years at enrolment)
• JEWELFISH (NCT03032172) assesses safety, tolerability, PK and PD of risdiplam in patients with SMA (aged 6 months-60 years at enrolment) who previously received RG7800 (RO6885247), nusinersen (SPINRAZA®), olesoxime or onasemnogene abeparvovec (ZOLGENSMA®).

Results: Pooled analyses from FIREFISH Parts 1 and 2, SUNFISH Parts 1 and 2 and JEWELFISH showed no treatment-related safety findings leading to withdrawal in 465 patients for up to 38.9 months (data cut-offs: 14 November 2019, 15 January 2020 and 31 January 2020, respectively). Differences in adverse event (AE) profiles between Type 1 and Types 2/3 SMA populations were driven by the severity of the underlying disease, and the AEs/serious AEs (SAEs) reflected illnesses common in the respective age groups. There was a decline in SAE rates over time in Type 1 SMA, which may be indicative of the therapeutic benefit of risdiplam.

Conclusions: Pooled safety data across the risdiplam studies suggest risdiplam has a positive benefit-risk profile. This analysis adds to the understanding of the long-term safety profile of risdiplam.

Keywords:
Spinal muscular atrophy, risdiplam, clinical trial

EPNS21-298
Neuromuscular

Oral or poster

Application of gene therapy in patients with spinal muscular atrophy - own experience

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Objective: Spinal muscular atrophy (SMA) is a progressive degenerative disease of motor neurons leading to muscle wasting. It is a genetically determined disease caused by a mutation in the SMN1 gene, responsible for the production of the SMN protein, which is essential for the proper functioning of the motor neurons. The first preparation approved for the treatment of SMA was nusinersen (Spinraza). It is an antisense oligonucleotide that binds to the splicing inhibition sequence of intron 7. Allowing other therapeutic options, such as Zolgensma gene replacement therapy (GRT) (AVXS-101, onasemnogene aberparvovec), increases patients' chances of improving quality and life expectancy with this incurable neurodegenerative disease. Zolgensma (AVXS-101, onasemnogene aberparvovec) uses as vectors adenoviruses type 9 (AAV9) to deliver, complementary to SMN1, unmutated DNA to the motoneurons.The drug crosses the blood-brain barrier and is administered only once as an hourly intravenous infusion. This one administration is sufficient to obtain the systemic synthesis of the SMN protein, which begins several hours after the use of the drug. The purpose of this presentation is to present the results of the application of gene therapy in 24 patients with spinal muscular atrophy treated at the Department of Children's Neurology of the University Children's Hospital in Lublin (Poland).

Methods: Single intravenous administration of Zolgensma as a 60-minute infusion.
Functional assessment of patients in the CHOP -INTEND and Hammersmith scales the day before the application of gene therapy and 4 weeks after the application of the drug

Results: Improvement in functional scales was observed in all patients after four weeks of follow-up
Improvement in respiratory function was also seen in most patients

Conclusions: The use of gene therapy, especially in patients with less severe symptoms of spinal muscular atrophy, allows for improvement in functional scales, improvement of respiratory functions and achievement of milestones.

Keywords:
spinal muscular atrophy, gene therapy

EPNS21-303 Poster only
Neuromuscular

Updated demographics and safety data from patients with nonsense mutation Duchenne muscular dystrophy receiving ataluren in the STRIDE Registry

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Objective: Duchenne muscular dystrophy (DMD) is a severe neuromuscular disorder caused by a lack of functional dystrophin. Ataluren promotes readthrough of an in-frame premature stop codon to produce full-length dystrophin and is indicated for the treatment of patients with nonsense mutation (nm) DMD. Strategic Targeting of Registries and International Database of Excellence (STRIDE; NCT02369731) is an ongoing registry providing real-world data on ataluren use in patients with nmDMD.

We aimed to describe the demographics of the STRIDE population and the interim safety results, as of the latest data cut-off date of January 31, 2021.

Methods: Data from enrolled patients are collected at the consent date; for patients who initiated ataluren as part of a commercial or early access program before enrollment, data for the period prior to enrollment are obtained retrospectively. Patients will be followed up for ≥ 5 years or until study withdrawal.

Results: As of January 31, 2021, 286 boys had been enrolled in STRIDE in 13 countries and received at least one ataluren dose. Total mean (standard deviation [SD]) exposure to ataluren was 1352 (517) days; equivalent to 1059 patient-years. Safety outcomes were consistent with the known safety profile of ataluren. Thirty-one of the 286 boys discontinued the study. Of the 286 boys enrolled who received at least one ataluren dose, 269 had genetically confirmed nmDMD. Most patients were Caucasian (194/269 [72.1%]) and the mean (SD) age at consent date was 9.9 (3.8) years (n=269). Mean (SD) age at first symptoms was 2.7 (1.7) years (n=244); at nmDMD confirmation it was 4.9 (2.7) years (n=260). Median time between first symptoms and nmDMD confirmation was 1.4 years (n=240). Most patients used concomitant corticosteroids (237/269 [88.1%]).

Conclusions: STRIDE is the first drug registry for nmDMD patients. The interim registry data suggest that ataluren has a favorable safety profile when used in routine clinical practice, which is consistent with that shown in clinical trials.

Keywords:
ataluren, nonsense mutation Duchenne muscular dystrophy

EPNS21-305 Poster only
Neuromuscular

Age at loss of ambulation in patients with DMD from the STRIDE Registry and the CINRG Natural History Study: a matched cohort analysis

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Objective: We examined if nonsense mutation Duchenne muscular dystrophy (nmDMD) patients receiving ataluren plus standard of care (SoC) in the Strategic Targeting of Registries and International Database of Excellence (STRIDE) Registry (NCT02369731) experienced a delay in age at loss of ambulation (LOA) versus DMD patients receiving SoC alone in the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (NCT00468832).

Methods: STRIDE is an ongoing, multicenter, observational registry providing data on ataluren use in nmDMD patients in routine clinical practice. Data were extracted on January 31, 2021. Propensity score matching identified STRIDE and CINRG patient cohorts (N=241) comparable in established predictors of disease progression: age at first symptoms; age at initiation of corticosteroid use; duration of deflazacort use; and duration of other corticosteroid use. Patients from CINRG who had received investigational drugs for DMD were excluded. Kaplan-Meier analyses were used to estimate age at LOA.

Results: The mean (standard deviation) ages at first symptoms in the STRIDE and CINRG cohorts (N=241 per cohort) were 2.7 (1.7) and 2.8 (1.5) years, respectively. Most patients (STRIDE vs CINRG) received corticosteroids for ≥12 months (79.7% per cohort), with a similar proportion receiving deflazacort (43.6% vs 45.2%) or other corticosteroids (41.5% vs 43.2%). In the STRIDE cohort, 24.9% (60/241) of patients lost ambulation compared with 52.7% (127/241) of patients in the CINRG cohort. The median (95% confidence interval) ages at LOA (STRIDE vs CINRG) were 17.9 (14.4, non-estimable) and 12.5 (11.6, 13.5) years, respectively. Kaplan-Meier analyses showed that ataluren plus SoC delayed age at LOA compared with SoC alone ($p<0.0001$).

Conclusions: These interim registry data show that treatment with ataluren and SoC in routine clinical practice slows disease progression in nmDMD patients.

Keywords:
ataluren, nonsense mutation Duchenne muscular dystrophy, loss of ambulation

EPNS21-306 Poster only
Neuromuscular

Pulmonary function in patients with Duchenne muscular dystrophy from the STRIDE Registry and CINRG Natural History Study: a matched cohort analysis

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Objective: We investigated if nonsense mutation Duchenne muscular dystrophy (nmDMD) patients receiving ataluren plus standard of care (SoC) in the Strategic Targeting of Registries and International Database of Excellence (STRIDE) Registry (NCT02369731) experienced a lesser decline in pulmonary function versus DMD patients receiving SoC alone in the Cooperative International Neuromuscular Research Group (CINRG) Natural History Study (NCT00468832).

Methods: STRIDE is an ongoing, multicenter, observational registry providing data on ataluren use in nmDMD patients in routine clinical practice. Data were extracted on January 31, 2021. Propensity score matching identified STRIDE and CINRG patient cohorts (N=241) comparable in established predictors of disease progression: age at first symptoms; age at initiation of corticosteroid use; duration of deflazacort use; and duration of other corticosteroid use. Patients from CINRG who had received investigational drugs for DMD were excluded from this analysis. Kaplan-Meier analyses were used to estimate ages at % predicted forced vital capacity (FVC) <60% and <30%.

Results: The mean (standard deviation) ages at onset of first symptoms (STRIDE vs CINRG; N=241 per cohort) were 2.7 (1.7) and 2.8 (1.5) years, respectively. Most patients (STRIDE vs CINRG) received corticosteroids for ≥12 months (79.7% per cohort), with a similar proportion receiving deflazacort (43.6% vs 45.2%) or other corticosteroids (41.5% vs 43.2%). Median (95% confidence interval [CI]) ages at % predicted FVC <60% (STRIDE vs CINRG) were 17.6 (16.2, non-estimable) and 15.8 (15.1, 16.5) years, respectively (p=0.0051). Median (95% CI) ages at % predicted FVC <30% were non-estimable for STRIDE patients (only 0.5% [1/192] of patients reached % predicted FVC <30%) and 25.4 (20.6, 29.4) years for CINRG patients (p=0.0085).

Conclusions: These interim registry data suggest that treatment with ataluren and SoC in routine clinical practice slows disease progression in nmDMD patients.

Keywords:
ataluren, nonsense mutation Duchenne muscular dystrophy, pulmonary, forced vital capacity

EPNS21-308 Poster only
Neuromuscular

Comparison of North Star Ambulatory Assessment score change in nmDMD patients receiving ataluren: STRIDE Registry vs phase 3 clinical trial

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Objective: We investigated whether nonsense mutation Duchenne muscular dystrophy (nmDMD) patients receiving ataluren in real-world practice in the STRIDE Registry (NCT02369731) experienced lesser declines in North Star Ambulatory Assessment (NSAA) total, linear and shift scores vs patients receiving ataluren/placebo in a phase 3 clinical trial (Study 020; NCT01826487).

Methods: The NSAA comprises 17 items, scored to document progressive loss of function. STRIDE patients were assessed by first 48-week score change (difference between their first '48-week assessment' [between 40 and 72 weeks] and their first assessment); Study 020 patients were assessed by change over 48 weeks. The proportion of STRIDE patients who lost the ability to perform NSAA items over the first 48 weeks was compared with Study 020 patients in a shift analysis; item failure was recorded by a shift from a score of 2 (able) or 1 (impaired) to 0 (unable).

Results: In Study 020, ataluren-treated patients experienced a lesser mean decline in NSAA total and linear scores vs placebo-allocated patients over 48 weeks (total score [95% confidence interval [CI]: ataluren, −2.7 [−3.5, −1.9]; placebo, −3.7 [−4.5, −2.8]; linear score [95% CI]: ataluren, −6.3 [−8.3, −4.2]; placebo, −8.4 [−10.4, −6.4]). STRIDE patients consistently experienced a mean (95% CI) decline in NSAA total and linear scores of −1.97 (−2.90, −1.05) and −4.54 (−6.75, −2.33) respectively, over their first 48-week assessments. The proportion of patients who lost the ability to perform NSAA items was greater for Study 020 placebo-allocated patients than ataluren-treated STRIDE and Study 020 patients.

Conclusions: These results demonstrate that ataluren delays decline in performance of NSAA items in nmDMD patients vs placebo, indicating that ataluren delays disease progression.

Keywords:
ataluren, nonsense mutation Duchenne muscular dystrophy, North Star Ambulatory Assessment

EPNS21-309 Poster only
Neuromuscular

Comparing the change in 6-minute walk distance in nmDMD patients receiving ataluren: STRIDE Registry compared with phase 3 clinical trial

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Objective: We investigated whether nonsense mutation Duchenne muscular dystrophy (nmDMD) patients receiving ataluren in real-world practice in the STRIDE Registry (NCT02369731) experienced a similar decline in 6-minute walk distance (6MWD) vs patients receiving ataluren in a phase 3 clinical trial (Study 020; NCT01826487). The 6-minute walk test assesses distance walked on a flat surface in six minutes as a measure of ambulation and endurance, allowing progressive loss of function to be recorded.

Methods: STRIDE patients (n=42) were assessed by their first 48-week change (the difference between their first '48-week assessment' [between 40 and 72 weeks] and the first assessment); Study 020 patients (ataluren [n=45] and placebo-controlled [n=50] groups) were assessed by change over 48 weeks. Only ambulatory patients with a 6MWD of ≥300 to ≤400 m at first assessment were included in the analysis. For patients who lost ambulation during the 48-week periods, 6MWD was imputed as 0 metres (m) on the day ambulation was lost.

Results: The mean (95% confidence interval [CI]) first baseline 6MWD assessment for STRIDE patients (349.7 [341.4, 358.0] m, n=42) was comparable to that for patients in Study 020 ataluren and placebo groups (ataluren, 356.7 [348.9, 364.5] m, n=47; placebo, 354.5 [346.3, 362.8] m, n=52). The mean (standard deviation [SD]) age at first assessment for all patients was comparable (STRIDE ataluren, 9.6 [3.1], n=42; 020 ataluren, 8.9 [1.8], n=47; placebo, 9.0 [1.5], n=52).

STRIDE patients experienced a mean (95% CI) decline in 6MWD of −3.5 (−20.9, 13.8) m over their first 48-week assessments, thus performing better than ataluren-treated Study 020 patients (−28.3 [−45.1, −11.5] m), whereas placebo-allocated patients experienced a greater decline in 6MWD (−75.5 [−105.7, −45.3] m).

Conclusions: These results demonstrate that in both the real-world and clinical trial setting ataluren delays decline in motor function in nmDMD patients vs placebo, demonstrating that ataluren delays disease progression.

Keywords:
ataluren, nonsense mutation Duchenne muscular dystrophy, 6-minute walk distance

EPNS21-311 Poster only
Neuromuscular

Comparison of change in ability to perform timed function tests in nmDMD patients receiving ataluren: STRIDE Registry vs phase 3 clinical trial

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Objective: We investigated whether nonsense mutation Duchenne muscular dystrophy (nmDMD) patients receiving ataluren in real-world practice in the STRIDE Registry (NCT02369731) performed similarly in timed function tests (TFTs) vs patients receiving ataluren in a phase 3 clinical trial (Study 020; NCT01826487). TFTs included time to: run/walk 10 metres (m), climb four stairs, descend four stairs and stand from supine; each measuring progressive loss of function.

Methods: STRIDE patients were assessed by change over 'first 48 weeks' (the difference between their '48-week assessment' [between 40 and 72 weeks] and their first assessment); Study 020 patients (for both ataluren and placebo-controlled groups) were assessed by change over 48 weeks. Only ambulatory patients were included in the analysis. Patients who lost ambulation during the 48-week periods had their times to complete a TFT imputed as 30 seconds (s).

Results: In Study 020, ataluren-treated patients experienced a smaller mean increase in time (s) to perform TFTs vs placebo-allocated patients over 48 weeks (run/walk 10 m [95% confidence interval [95% CI]: ataluren, 2.3 [1.3, 3.3], n=109; placebo, 3.5 [2.3, 4.7], n=110; climb four stairs: ataluren, 2.7 [1.6, 3.7], n=105; placebo, 4.5 [3.0, 5.9], n=103; descend four stairs: ataluren, 2.2 [1.1, 3.2], n=106; placebo, 4.0 [2.4, 5.5], n=100; stand from supine: ataluren, 3.8 [2.7, 5.0], n=101; placebo, 3.9 [2.5, 5.3], n=96). STRIDE patients consistently experienced smaller mean increases in time (s) to perform TFTs than placebo-arm Study 020 patients (run/walk 10 m [95% CI]: 1.3 [0.6, 2.0], n=113; climb 4 stairs: 0.4 [−0.3, 1.0], n=73; descend 4 stairs: 0.3 [−0.1, 0.8], n=59; stand from supine: 1.7 [0.6, 2.8], n=93) over their first 48-week assessments.

Conclusions: These results demonstrate that in both the real-world and clinical trial setting ataluren delays decline in performance of TFTs in nmDMD patients vs placebo, indicating that ataluren delays disease progression.

Keywords:
ataluren, nonsense mutation Duchenne muscular dystrophy, timed function tests

EPNS21-316
Neuromuscular

Oral or poster

Baseline Characteristics and Initial Safety Results in RESPOND: A Phase 4 Study of Nusinersen in Children with Spinal Muscular Atrophy (SMA) Who Received Onasemnogene Abeparvovec

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Objective: Onasemnogene abeparvovec (OA) is an adeno-associated viral (AAV) vector gene therapy for SMA. Preclinical data show incomplete transduction of neurons by the vector. Nusinersen has the potential to increase SMN protein in untransduced motor neurons. We report baseline (BL) characteristics of participants and initial safety in RESPOND (NCT04488133), an ongoing study of nusinersen in children with SMA previously treated with OA.

Methods: This prospective, multisite study is enrolling children ≤ 36 mos who have ≥ 1 *SMN2* copy, are nusinersen-naïve and have suboptimal clinical response to OA administered ≥ 3 mos previously. Enrolled children receive the approved 12mg nusinersen regimen of 4 loading doses followed by maintenance doses every 4 mos. Suboptimal clinical response (investigator-determined) includes ≥ 1 of these domains: motor function, respiratory support, swallowing/feeding ability and other.

Results: As of 16 August 2021, 9 children (median [range] age 16.4 [5-30] mos) were enrolled; 1 discontinued (parent/guardian choice). Most (8/9) had 2 *SMN2* copies. BL mean±SD Hammersmith Infant Neurological Examination (HINE)-2 total score was 8.1±5.3. At BL, all children demonstrated suboptimal clinical status in ≥ 2 domains; motor and respiratory function were most common. Median (range) duration on nusinersen and safety follow-up period was 64 (1-183) days. Most common adverse events (AEs) were infections (4 children, 7 events [ear infection, viral gastroenteritis, parainfluenza virus infection (PIV), pneumonia, upper respiratory tract infection (URTI), viral URTI]) and vomiting (2 children). Two children had serious AEs (SAEs): PIV (2 AEs in 1 child) and URTI. No deaths or post-lumbar puncture syndrome AEs occurred.

Conclusions: BL characteristics showed suboptimal clinical status in multiple domains including motor and respiratory functions despite OA treatment. Initial safety findings indicate no AEs or SAEs were considered related to nusinersen.

Funding: Biogen

Keywords:
spinal muscular atrophy, nusinersen, onasemnogene abeparvovec, study design, clinical trial

EPNS21-317
Neuromuscular

Oral or poster

VARS2-related disorder mimicking a congenital myasthenic syndrome in a neonate

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Objective: Neurological differential diagnosis of neonatal respiratory failure associated with hypotonia is broad.

Methods: Case report

Results: A male term neonate presented respiratory insufficiency shortly after birth, requiring invasive ventilation. He had no dysmorphisms, contractures or fasciculations, had normal DTRs but variable axial hypotonia and alternating periods of active movements with global inactivity. Eyes were mostly closed for the first weeks but no ophtalmoparesis, ptosis or facial palsy was observed when open. He was thoroughly studied by ENT and Pneumology. Neonatal cardiosonography revealed slight interventricular sept hypertrophy. CK and thyroid hormones were normal, AChR, MusK and LRP4 autoantibodies were negative. Brain and cervical spine MRI, motor NCS and EMG were normal (SFEMG and repetitive stimulation were not performed). Extubation was not successful due to rapidly progressive respiratory distress and severe lactic acidosis. Considering a congenital myasthenic syndrome, SC neostigmine was started, with clear improvement of global muscle activity. Severe cholinergic effects occurred, requiring advanced resuscitation and atropine. Switching to oral piridostigmine and dosage reduction was successful with progressively less severe adverse effects. Oral salbutamol was added and transition to non-invasive ventilation was possible. After two weeks of stability, acute decompensation occurred, requiring invasive ventilation and hypertrophic cardiomyopathy with large pericardic effusion was detected. After drainage, non-invasive ventilation was resumed but lactic acidosis became systematically present. On day 60, exome sequencing identified two apparently compound heterozygous variants in VARS2 gene.

Conclusions: This patient with VARS2-related disorder had a definite response to acetilcholinesterase inhibitors and salbutamol. We suggest this mitochondrial encephalocardiomyopathy should be included in the differential diagnosis of neonatal respiratory failure with variable muscle tone.

Keywords:
respiratory failure, neonate, myasthenia, VARS2 gene

EPNS21-33
Neuromuscular

Oral or poster

Recurrent stroke-like episodes as a unique presentation of children with X linked hereditary motor and sensory neuropathy

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Objective: Background: Hereditary motor and sensory neuropathy (HMSN), also known as Charcot Marie Tooth (CMT) disease, has many subtypes with type A1 being the most common. Patients with HMSN typically present with slowly progressive weakness, sensory disturbances, and gait dysfunction. Central nervous system symptoms are very rare.

Methods: Case: A 14-year-old male presented with an acute history of right facial drooping, slurred speech, right arm tingling, and a sense of weakness. All symptoms self-resolved within hours. 2 days later he had a recurrence of prior symptoms. MRI did not show evidence of typical vascular territory stroke yet demonstrated T2/FLAIR hyperintensities in centrum semiovale bilaterally and splenium of the corpus callosum with restricted diffusion but no contrast enhancement. He spontaneously recovered and his MRI subsequently normalized. He presented again a year later with similar clinical and radiological manifestations, again to achieve full recovery. Genetic testing was then done and showed a pathogenic mutation in GjB1 consistent with X-linked CMT disease.

Results: Discussion: X-linked CMT (CMTX1) is the second most common form of HMSN. Males are more commonly affected. Peripheral symptoms dominate but central symptoms may occur. The disease is linked to various mutations in the GJB1 gene in the X chromosome. Axonal neuropathy dominates the neurophysiological studies, in contrast with the prototype CMT type 1A which has predominantly demyelinating features. CNS presentation can manifest as high altitude triggered encephalopathy with abnormal brain MRI. Intellectual disability, hearing impairment, and optic atrophy have been reported. Patients with CNS X-CMT can be misdiagnosed with vascular stroke or demyelinating disorders.

Conclusions: We report a unique presentation of X-CMT with recurring stroke-like episodes. It is plausible to screen for X-linked CMT in children who present with recurrent stroke-like episodes in the lack of typical vascular tertiary distribution.

Keywords:
Carcot Marrie Tooth, Encephalopathy, stroke-like episodes

EPNS21-348
Neuromuscular

Poster only

RAPSYN-related congenital myasthenic syndrome in Turkey, a case report

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Objective: Congenital myasthenic syndromes (CMS) are hereditary diseases that result from defects in the presynaptic, synaptic or postsynaptic areas of the neuromuscular junction. RAPSYN-related postsynaptic CMSs are striking with their relatively good response to treatment. We aimed to present a male case who presented with gait disturbance at the age of 20 months and was diagnosed with CMS due to RAPSYN gene defect.

Methods: The clinical and the next-generation sequencing (NGS) results are being discussed.

Results: The patient was born at the 36th gestational week via C/S weighing 2700 grams. Normal intrauterine movements and a suspicion of polyhydramnios was reported prenatally. He was followed-up in the neonatal intensive care unit due to difficulty in sucking and flexion deformities in the hands for 29 days. He had a history of recurrent pneumonia in the early infancy. The development of his motor, language and personal social skills was age-appropriate. On neurological examination, he had a long face and open, tent-like, mouth suggesting facial weakness. He had a gait with bending his knees although without prominant contractures. Creatine kinase levels, metabolic scan, brain magnetic resonance imaging, echocardiography and CRLF1 gene analysis were found to be normal. In the gene panel for neuromuscular diseases, a probable pathogenic variant (c.271C>T, p. Arg91 Cys) was detected in the RAPSYN gene. He has been treated with pyridostigmine.

Conclusions: The most common types are COLQ-related synaptic and CHAT-related presynaptic disorders in the Turkish population. Our case is remarkable being the first Turkish case reported in the literature and emphasizing the importance of NGS in the diagnosis of neuromuscular diseases, which can have a treatment option.

Keywords:
Congenital myasthenic syndromes, neuromuscular junction disorders, facial weakness, gait disturbance, next-generation sequencing

EPNS21-386 Oral or poster
Neuromuscular

THE FIRST DATA ON CLINICAL AND GENETIC CHARACTERISTICS OF DUCHENNE MUSCULAR DYSTROPHY IN KAZAKHSTAN

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Objective: The study of this pathology is relevant, since due to insufficient circumspection of general practitioners, pediatricians and pediatric neurologists, on average, the diagnosis of DMD in Kazakhstan is made in children closer to 6-8 years old, when the functional potential of muscle tissue is practically exhausted.

Methods: The study was carried out within the framework of a grant. The blood was taken for molecular genetic analysis of the DMD gene from children with clinical signs of DMD (57) and without symptoms, undergoing medical genetic counseling as siblings of probands (4), The sequencing and MLPA analysis of DMD gene was carried out in the German laboratory.

Results: Between November 13, 2018 and May 31, 2021 a total of 61 boys from 0 to 18 years old were examined, the diagnosis was confirmed in 37 (60.7%).
The average age of genetic diagnosis verification was 7.6 years, with a range from 2 months to 15 years.
Clinical symptoms included muscle weakness (26 / 70.3%), calf muscles pseudohypertrophy (23 / 62.2%), waddling gait (18 / 48.6%), Gowers's sign (22 / 59.5%), scoliosis (7 / 18.9%), lordosis (12 / 32.4%) and a history of multiple fractures (1 / 2.7%).

The following genetic spectrum of DMD gene mutations was obtained: missense (2 / 5.4%), monoexon deletion (4 / 10.8%), deletion of several exons (11 / 29.7%), nonsense (1 / 2.7%), multiple exon duplication (2 / 5.4%), frameshift (7 / 18.9%), substitution (2 / 5.4%), stop-codon (7 / 18.9%), combined mutation (combination of stop-codon with missense (1 / 2.7%).

Conclusions: A prolonged age of detection of the genetic defect at DMD is noted. It is necessary to effectively maintain the current level of knowledge of general practitioners, pediatricians and neurologists on the problem of neuromuscular diseases.

Keywords:
DMD, diagnostics

EPNS21-391
Neuromuscular

Poster only

Parental illness intrusiveness and depressive symptoms in caregivers of children with Duchenne Muscular Dystrophy

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Objective: Duchenne Muscular Dystrophy (DMD) is a rare neuromuscular disorder that only occurs in boys and is characterized by progressive muscular weakness. Although it is widely known that DMD has a wide ranging impact on patients and caregivers, research specifically focusing on parental experiences and well-being is still in its infancy. Therefore, this study aimed at a better understanding of particular difficulties in the everyday lives of parents. Parental illness intrusiveness (i.e. a parent's perception that the illness of one's child interferes with one's personal life) was examined in caregivers of children and adolescents with DMD. Associations between parental illness intrusiveness, parental depressive symptoms, and patient characteristics were explored in this population.

Methods: A total of 23 caregivers (74% mothers, Mage=47.3) of 23 patients with DMD completed questionnaires on their own experienced illness intrusiveness (Illness Intrusiveness Scale), depressive symptoms (CES-D), and overall quality of life (VAS-scale).

Results: Mothers reported significantly more illness intrusiveness than fathers [42.78 (SD=18.58) versus 23.00 (SD=3.16); $F(1,21)=6.54$, $p=.018$]. A substantial subset of caregivers (39.1%) met cutoff criteria of 16 or more on the CES-D which reflects an increased risk for depressive disorders. Depressive symptoms correlated negatively with overall quality of life in caregivers ($r=-.79$, $p<.001$), and positively with parental illness intrusiveness ($r=.45$, $p=.030$). Patient age did not correlate with parental illness intrusiveness or depressive symptoms.

Conclusions: Although preliminary, these findings illustrate the significant burden that caregivers of boys with DMD can experience and the importance of assessing parental illness-related experiences, such as illness intrusiveness. Future work, focusing on both mothers and fathers and assessing larger samples is needed to compare these results with results from parents confronted with other pediatric chronic illnesses.

Keywords:
parents; duchenne muscular dystrophy; illness intrusiveness; caregivers

EPNS21-395 Poster only
Neuromuscular

USE OF CORTICOSTEROIDS IN HEREDITARY NEUROPATHY WITH PRESSURE PALSIES

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Objective: Hereditary neuropathy with pressure palsies (HNPP) is a rare entity in childhood. It is caused by deletions/duplications of the gene encoding peripheral myelin protein-22(PMP22). HNPP can be diagnosed by suggestive clinical and electrophysiologic findings.

Methods: Treatment is not established but the use of corticosteroids in acute exacerbations could be a good option.

Results: A previously healthy 12-year-old male. After a long car trip from Seville to Valladolid (approximately 600 km), he developed left foot drop, an inability to lift the forefoot due to weakness, and paresthesias in the same leg. Two days later he came to the Emergency department. In the neurological examination, there was weakness in four extremities: reduced strength of the distal musculature in both arms (4/5) and in the right leg (4/5). In his left leg, he had paralysis of the muscles involved in lifting the front part of the foot (1-2/5) and hyperalgesia. Nerve conduction study demonstrated demyelination and secondary axonal changes in both median, ulnar and right peroneal territories. Nerve conduction velocity was blocked at the site of compression (left peroneal nerve). Family history investigation revealed that paternal grandfather had a high-stepping walk. Both parents are healthy. Whole-spine and cerebral magnetic resonance imaging (MRI) were normal. Cerebrospinal fluid was acellular. Genetic test identifies a deletion involving PMP22 gene. We decided to start corticosteroids 2mg/kg/día (max, 60 mg) and supplementation with a vitamin B complex including vitamin B1, B6 and B12. After two months he could lift the forefoot completely.

Conclusions: Corticosteroids and vitamin B complex for treating peripheral neuropathy could be a good option in all cases in which nerve conduction velocity has been delayed at the site of compression or even with conduction block. Corticosteroids can help reduce inflammation. Secondary effects should be controlled. Additionally, vitamin B is generally well-tolerated.

Keywords:
Weakness, neuropathy, chilhood, corticosteroids

EPNS21-428 Oral or poster
Neuromuscular

DMD care UK: Improving Standards of Care for Duchenne Muscular Dystrophy across the UK

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Objective: To improve Duchenne muscular dystrophy (DMD) care provision across the UK by reaching expert-consensus and facilitating implementation of UK-relevant standards of care (SoC) based on international guidelines. To identify gaps in evidence and support research efforts to better understand most effective interventions in a clinical care setting.

Methods: Through a network of expert working groups (WGs) DMD Care UK works with clinicians and patient representatives to interpret international care guidelines in a UK-context.
Each WG identifies current practice across the North Star network of neuromuscular centres from a clinician and patient perspective. Through consensus-building and consultation, using evidence and expert-opinion each drafts guidelines.
These are submitted for endorsement from national professional bodies. An awareness and education programme highlights each guideline to the clinical and patient community. Practice will be measured again at the end of the project to show impact.
Research proposals will be submitted to funders to address evidence gaps. Funding will be sought for resource needs. Data will be collected to make a case for sustainability.

Results: DMD Care UK has established 6 fully active WGs so far. Key results include:
UK Bone and Endocrine guidelines released and endorsed
Accompanied by family information leaflets, webinars for clinicians and patients
Agreed adrenal crisis management planning across the UK
Psychosocial WG secured funding to recruit 2 clinical psychologists and neuro-psychiatry time to address chronic shortage of provision and expertise for mental health and wellbeing care in DMD
Emergency Care App for patients in testing phases
Further guidelines in consultation

Conclusions: The bone and endocrine WG has demonstrated the successful project methodology. This will be repeated over the coming 18 months for other areas of care, so improving provision in accordance with International Standards and improving consistency and equity of access across the country.

Keywords:
Standards of Care; Duchenne muscular dystrophy; Psychosocial; Bone health; Endocrinologgy

EPNS21-436 Oral or poster
Neuromuscular

The Increased Incidence of Peroneal Nerve Palsy in Children - an Unexpected Sequel of Lifestyle Changes during the Covid-19 Pandemic?

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Objective: Between 2020 and 2021 a rise in the number of children presenting with peroneal nerve palsy (PNP) was noticed. The aim of this study was to analyse this clinical observation and to explore the possible causes for this occurrence.

Methods: This retrospective study included 32 patients diagnosed with PNP from 2013 to 2021. Since our hospital is the only tertiary paediatric neurological centre in the country, most patients with PNP are referred to our institution for further diagnosis and treatment. All data was obtained from the electronic hospital records. Chi-Square test was used for statistical analysis.

Results: The mean incidence of PNP in children from 2013-2019 was 2.29 per year. In contrast, the mean incidence of PNP during 2020-2021, the period of the Covid-19 pandemic, rose significantly, and was 8.0 per year ($p < 0.05$). When analysing the patients as a group, gender was equally represented, median age was 13.9 years, and 71.9 % patients had PNP on the right side. 3 patients have tested positive for Hereditary neuropathy with liability to pressure palsies - two had PNP due to compression and one due to an unknown cause. Of the 16 patients with onset during Covid-19 pandemic, 6 (37.5 %) were male and 10 (62.5 %) were female, median age was 14.5 years, and right leg was involved in 62.5 % of patients. The causes of PNP during Covid-19 pandemic were compression in 9 (56.25 %), weight loss in 2 (12.5 %), nerve straining in 1 (6.25 %), soft tissue injury in 1 (6.25 %), and unknown causes in 3 (18.75 %) patients.

Conclusions: This study found a statistically significant rise in PNP occurrence in children during 2020-2021. The predominant causes in these patients were nerve compression or straining potentially due to a more sedentary lifestyle with long hours of schooling and a less active lifestyle due to Covid-19 pandemic
restrictions.

Keywords:
Peroneal nerve palsy, Covid-19 pandemic, children, sedentary lifestyle

EPNS21-437 Poster only
Neuromuscular

Nusinersen therapy in Kazakhstan. Clinical and genetic characterization of patients, functional assessment and safety profile

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Objective: Description of nusinersen intrathecal injections safety profile in terms of the first SMA therapy experience in Kazakhstan.

Methods: 9 SMA patients received of nusinersen from June to Sept 2021 at Hospital in Almaty. Loading doses of nusinersen were injected intrathecally in accordance with prescribed regimen. Inhalation or local anesthesia was used. In the presence of spine deformation visualization tools were used to navigate the injection procedure. Motor function assessment, routine laboratory tests, were performed prior to therapy initiation.

Results: 9 patients have been admitted to inpatient clinic (5 females, 4 males). 6 children were type 2, 3 were type 3. Genotype profile: homozygous deletion of SMN1 exon 7 (1), homozygous deletion of SMN1 exons 7 and 8 (6), compound-heterozygous mutation (2). Age range of patients varied from 2,11 to 15,1 years. CHOP INTEND score of 2 type 2 patients (under 2 years) was 36 and 23. RULM scores of 4 type 2 patients were16,16,9,23. RULM scores for 3 type 3 patients were: 32,13,31. Inhalation and local anesthesia (cream or injection) were used. In total, 36 loading dose injections were conducted, amongst those 25 were standard, 1 complex spine injection was done with the aid EOM control. The following adverse reactions were reported after the first dose injection in 5 patients: headache, vomiting, dizziness, rise in body temperature. Second dose: 3 patients reported headache, dizziness, back pain, rise in temperature. Third dose: only 1 patient reported symptoms of lumbar radiculopathy. Fourth dose: 1 patient has developed local edema. Adverse reactions not related to the injection procedure included severe respiratory infection (1), pneumonia (1). No adverse reactions were reported by 3 patients throughout all loading dose injections.

Conclusions: Safety profile of nusinersen injections was in alignment with previously reported clinical data. Therapy effectiveness evaluation will be assessed before injection of the 5th dose and after 12 months of therapy.

Keywords:
SMA, children, nusinersen, functional assessment, safety profile

EPNS21-44
Neuromuscular

Poster only

An Assessment of the Knowledge, Attitudes, and Practices of Pediatricians and Pediatric Residents in Spinal Muscular Atrophy

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Objective: Aim:This study aims to investigate the knowledge levels and attitude of pediatricians and pediatric residents towards spinal muscular atrophy (SMA).

Methods: Materials and methods: A questionnaire consisting of 27 questions which investigates the knowledge level and attitude concerning genetic and laboratory characteristics in addition to follow up and management features of SMA using Google forms (Google LLC, Mountain View, CA, USA) and their answers were evaluated.

Results: Results:48.4% pediatricians, 15.1% fellows, 36.6% pediatric residents responded to the questionnaire. 73.1% of the participants knew that a deletion in exon 7-8 was the cause of SMA in more than 95% of the patients, 89.2% knew that it was characterized by a progressive loss in the motor neurons of the anterior horn, 92.5% knew that SMA classification was made based on the onset time of symptoms and genetic features and 98.9% believed that SMA subtype could define the prognosis. 8.6% participants answered that genetic workup was not necessary for the definitive diagnosis of SMA, 96.8% stated that the most important cause of mortality was the involvement of accessory respiratory muscles.

Conclusions: Conclusion: This study has revealed that physicians possess a satisfactory level of knowledge concerning the symptomatology, diagnostic algorithm, and follow up features of SMA disease.

Keywords:
spinal muscular atrophy, pediatricians

EPNS21-441
Neuromuscular

Oral or poster

Gene therapy for Spinal Muscular Atrophy under Global Managed Access Program: Experience by one centre in the United Arab Emirates

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Objective: Onasemnogene abeparvovec-xioi was approved as the gene therapy for Spinal Muscular Atrophy (SMA) by FDA in 2019. Through the Global Managed Access Program (GMAP) launched by the manufacturer, patients can get it free in the countries where it has not received regulatory approval.

Methods: We analysed the data of eight patients who received onasemnogene abeparvovec-xioi through GMAP in our centre in the United Arab Emirates (UAE) until October 2021. We were the first centre to offer this therapy in the UAE. Out of these, four children were followed up till October 2021.

Results: Out of the eight children who received onasemnogene abeparvovec-xioi, five were type 1 and three were type 2 SMA. None was a citizen of the UAE while four were residents in the UAE. Two travelled from Iran, one from Ethiopia and one from Nepal to receive the treatment as there are no recognised centres to deliver the gene therapy in their respective countries. Two children had tracheostomy and received 24 hours BiPAP. With the help of the paediatric pulmonologist, the ventilation was weaned down to a total of 16 hours a day before the gene therapy administration. The four children who travelled to the UAE were followed up for three months following the gene therapy by the multidisciplinary team. Periodic CHOP-intend and Hammersmith Infant Neurological Examination (HINE) scorings were done in all the children whilst in Dubai. The transition of their care to the local paediatric neurologists in their respective countries was done via Zoom meetings and emails. The four children who were followed up until October 2021 showed a significant increase in their CHOP-Intend scores (paired t value-8.2053; p=0.0037) and HINE scores.

Conclusions: We present the data of all the children with SMA who received onasemnogene abeparvovec-xioi in our centre under GMAP.

Keywords:
gene therapy, SMA, Managed Access Program

EPNS21-480
Neuromuscular

Oral or poster

Safety and Efficacy of High-Dose Clonidine in the Management of Pediatric Movement Disorder

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Objective: Clonidine is an alpha-2 agonist reported to be beneficial for paediatric movement disorders. We aimed to describe our experience with high-dose clonidine.

Methods: The aetiology of movement disorders, clonidine regimen, associated adverse drug reaction and response of two children on high-dose clonidine were described.

Results: 15-year-old girl (50kg) was admitted to intensive care unit (ICU) on day 8 of viral associated encephalopathy with seizures. She was started on clonidine infusion on day 10 of illness for intrusive dystonia (DSAP Grade 4). Gradual escalation from 2mcg/kg/h to 5.9mcg/kg/h reduced the generalised dystonia, preventing progression into status dystonicus. She was later started on a short course of thiopentone for super-refractory status epilepticus. Clonidine was weaned from day 25 of illness over five days to 1mcg/kg/h, and converted to the transdermal route. Her dystonia remains well controlled (DSAP Grade 2). Hypotension, transient bradycardia and rashes reported were conservatively managed.

4-year-old girl (20kg) was admitted to ICU for sepsis and multi-organ dysfunction, leading to hypoxic ischemic encephalopathy. Clonidine infusion was started on day 9 of illness at 0.5mcg/kg/h for sedation, which was gradually titrated to 6mcg/kg/h due to mixed lower limb spasticity and dystonia (DSAP Grade 3). Clonidine was converted to the transdermal route when the patient was stable. This was weaned off over the next twelve months in view of good control of her muscle tone (DSAP Grade 2). Hypotension reported were managed and reversible.

Conclusions: There is a paucity of information of the usage of high-dose clonidine for children with severe dystonia or spasticity. The use of high-dose clonidine in both patients reduced the severity of dystonia. Doses up to 6mcg/kg/h was tolerated, with transient bradycardia and hypotension (IV route), and rashes (transdermal route). Future larger and prospective paediatric studies are needed.

Keywords:
clonidine, paediatric, movement disorders, dystonia, spasticity

EPNS21-489
Neuromuscular

Oral or poster

Adeno-Associated Virus Serotype 9 Antibody Titers in Patients with SMA Pre-screened for Treatment with Onasemnogene Abeparvovec - Real World Data

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Objective: Spinal muscular atrophy (SMA) is characterized by progressive weakness of skeletal and respiratory muscles. This study aimed to evaluate the prevalence of pre-existing anti adeno-associated virus serotype 9 antibody (AAV9-Ab) titers among infantile-onset SMA diagnosed infants pre-screened for treatment with AAV9-based onasemnogene abeparvovec, and to explore whether clinical and/or demographic characteristics are correlated with AAV9 Ab test results.

Methods: This is a retrospective multicenter study of children diagnosed with 5q SMA younger than two years of age. The obtained data included demographic data, SMA type, SMN2 gene copy number, onset date, and results of AAV9-Ab test and of SMA prior treatments.

Results: Thirty-four patients were enrolled; six patients had positive results of AAV9-Ab (titer>1:50) in the initial screening, 15 patients were re-tested for AAV9-Abs, of whom, three patients had seroreverted [1.5-4.5 months] between the two AAV9-Abs tests. One patient had seroconverted (5.5 months after the first AAV9-Abs test). The remaining 20 patients presented matching titer results in the two tests. No demographic/clinical factors were correlated to high AAV9-Abs titers (P>0.05).

Conclusions: We recommend AAV9-Ab re-tests to be performed until the age of 8 months, or, if 1.5 to 4.5 months have passed after the initial AAV9-Abs test.

Keywords:
Spinal muscular atrophy, adeno-associated virus serotype 9, onasemnogene abeparvovec, gene therapy, survival motor neuron.

EPNS21-498
Neuromuscular

Poster only

New insights in agrin-associated congenital myasthenic syndrome

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Objective: Agrin-associated congenital myasthenic syndrome (CMS) is a rare cause of CMS. CMS 8 is caused by variants in AGRN encoding for a proteoglycan essential for the differentiation and maintenance of the neuromuscular junction. Herein, we present genetic and muscle morphology, clinical course and treatment response of a pediatric patient and review the literature.

Methods: The clinical phenotype and treatment outcome, along with the results from the electrophysiology, muscle biopsy and genetic investigations are presented.

Results: This 17-year-old female developed a waddling gait by the age of three years. Repetitive nerve stimulation at 3 Hz showed a generalized neuromuscular transmission defect with decrementing response of 7-25%. Fiber atrophy was evident on muscle biopsy. Exome sequencing revealed two novel compound heterozygous missense variants in AGRN; p.(Pro1240Leu) and p.(Gly1707Ser). Treatment with pyridostigmine was started at the age of six years and its aggravating effect, with increased muscle weakness and fatigue, was masked for many years by concomitant treatment with salbutamol and/or ephedrine. The disease had a slowly progressive course with loss of ambulation at the age of 14 years. Marked clinical improvement was obtained when medication with pyridostigmine was stopped and salbutamol with add-on ephedrine was continued. 3,4-DAP had no effect. More than 30 patients with CMS 8 have been described in the literature with variable genetic background and clinical courses, the majority responded well to salbutamol and some of them were remarkedly helped by ephedrine. The effect of pyridostigmine was diverse.

Conclusions: Genetic and electrophysiological investigations are important not only for timely diagnosis but also for correct treatment in rare forms of CMS.

Keywords:
Congential myasthenic syndrome. AGRN, treatment

EPNS21-506
Neuromuscular

Oral or poster

Diagnostic challenges for floppy baby syndrome: severe congenital myotonic dystrophy type 1.

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Objective: to illustrate the algorithm of differential diagnosis of the floppy baby syndrome using the example of severe congenital myotonic dystrophy type I.

Methods: The newborn female was born to a 28-year-old, gravida I woman at 30 6/7 weeks of gestation by vaginal delivery. Pregnancy was complicated by polyhydramnios and reduced fetal movements. Apgar score was 3 at first minute and 5 at fifth minute. Heart rate and blood pressure were normal, bur the infant had poor spontaneous respiratory effort which led to mechanical ventilation.
Dysmorphic features: equinovarus bilateral talipes, high-arched palate, micrognathia.
Neuromuscular examination showed severe generalized muscle weakness, muscular hypotonia, severe decreasing of generalized movements, facial diplegia, absent of suck, Moro reflexes. Deep tendon reflexes were absent.
Notable remark of chest examination was unilateral diaphragmatic paralyses (right).
The results of cardiac and abdominal examination were normal. No signs of infection or metabolic disease were found.
The creatine kinase level in the blood test was 64.6 U / L (normal).
Electromyography observed primary muscular damage.
Within the diagnostic process the mother was intensively examined, and her neurological state showed: delayed grip relaxation after shaking hands, «warm-up» phenomenon.

Results: The diagnosis of severe congenital form in a child and classic adult form in her mother was confirmed by molecular genetic testing of CTG repeats in the DMPK gene.

Conclusions: Floppy baby syndrome is usually a diagnostic challenge due to the many rare and genetic causes of hypotonia. A stepwise approach starts by classifying the hypotonia as peripheral or central and neurological assessment of child's parents in order to eliminate myotonic phenomenon. The algorithm significantly facilitates and accelerates the diagnostic process, which we showed in this clinical case.

Keywords:
neonatal form of Steinert myotonic dystrophy, muscle hypotension, respiratory insufficiency, clinical observation.

EPNS21-507 Oral or poster
Neuromuscular

Early onset Amyotrophic lateral sclerosis (ALS): A diagnostic challenge

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Objective: Diagnosis of children with suspected ALS can be challenging. We present a case with suspected ALS with both upper and lower motor neuron involvement

Methods: Description of a clinical case with suspected early onset ALS with both upper and lower limbs involvement.

Results: We present an 8 year old boy who was referred at the age of 4 years due to toe walking and waddling gait. He was born at term with no other concerns. His mother also was a toe walker and had Achilles tendon lengthening. She does not have a diagnosis and currently remains asymptomatic. There was no other family history of note. The patient was unable to run and had difficulty with stairs. His distal lower limb weakness progressed with a loss of ambulation at 5 years. His upper limbs were also affected. His respiratory function declined to the point of needing non-invasive ventilation. He developed a mild cardiomyopathy, a scoliosis, tongue fasciculations and slurred speech. He also developed distal spasticity with clonus in his lower limbs. Normal investigations included: neurometabolic testing, CSF neurotransmitters, abdominal ultrasound, brain and spine MRI. Nerve conduction study showed an anterior horncell/motor neuropathy. Muscle biopsy showed chronic neurogenic changes. Whole exome sequencing revealed a de novo variant of unknown significance at the SPTCL2 gene, NM_00483.3: c.8GAp.(Glu20Lys), associated to hereditary motor sensory neuropathy type 1C, which did not fit the phenotype of our patient. His condition was more compatible with a non 5 q spinal muscular atrophy/ALS phenotype with mutations identified at the SPTCL1 gene. Biochemical essays in fibroblast culture are pending.

Conclusions: Mutations at the SPTCL1 gene have been associated with childhood ALS. We propose an overlapping mechanism between SPTCL1 and SPTLC2 genes. However, the functional impact of the mutation needs to be proved.

Keywords:
Neuromuscular, Amyotrophyc Lateral Sclerosis, Whole exome sequencing.

EPNS21-515 Poster only
Neuromuscular

''NUSINERSEN'' A TURNING POINT IN THE HISTORY OF SPINAL MUSCULAR ATROPHY. EXPERIENCE IN A TERTIARY HOSPITAL

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Objective: The use of gene therapies is changing the management of spinal muscular atrophy (SMA). The aim of our study was to describe the epidemiological and clinical characteristics of patients treated with Nusinersen in our hospital and the preliminary results of efficacy/safety of the treatment

Methods: Retrospective review of patients affected by SMA on treatment with nusinersen since its approval in Spain in March 2018

Results: 20 patients under follow-up. Age between 2 months-16 years at the beginning of treatment. 12 males/8 females. Type II was the most frequent (65%), followed by type I (25%). 7 patients had 2 copies SMN2, 12 had 3 copies, 1 had 4. The median age of symptomatic onset is 7 months (RIQ:4-12) and of treatment initiation is 4 years (RIQ: 19 months-11 years). The mean number of doses received was 10.95 (SD: 2.35) by non-image-guided lumbar puncture, except for four cases. All have completed the induction phase. 2 patients reported post-puncture headache. 1 case required insertion of intrathecal catheter with reservoir due to difficulties in administration. None showed analytical alterations in blood/LCR. The median follow-up after initiation of nusinersen is 34 months (RIQ:24-40). From the family subjective point of view, 100% of cases improve (significant 58%, the rest partial). Clinically, by means of pre-treatment and in-treatment motor function scales (CHOP INTEND, HINE, RULM and/or HFMSE), 75% show improvement (slight 30%; significant 45%), the rest remain stable, only one case progresses. 75% have scoliosis in different degrees, 5 of them underwent surgery. 65% have non-invasive respiratory support, except for one tracheotomized case. 20% require nutritional support (3 cases by gastrostomy, 1 by nasogastric tube)

Conclusions: Despite the limitations of the observational study design, our data provide evidence of the safety and efficacy of nusinersen in children with SMA, with clinically meaningful improvements in motor function and quality of life, especially with early detection

Keywords:
SMA, Spinal Muscular Atrophy, Nusinersen, Neuromuscular Disease

EPNS21-534 Poster only
Neuromuscular

Administration by lumbar intrathecal catheter of nusinersen in a patient with spinal muscular atrophy type 2 (ame2)

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Objective: Nusinersen is an antisense oligonucleotide approved for spinal muscular atrophy (SMA). SMA patients very often develop scoliosis which makes intrathecal access difficult. This prevents initiation of treatment in some patients which has led to the search for alternative routes. This article presents our experience with a subcutaneous intrathecal catheter system connecting a titanium port for safe drug delivery to the spinal cord in a patient with difficult intrathecal access.

Methods: Single case from a tertiary hospital with a multidisciplinary approach by neurosurgeons, radiologists, paediatricians and anaesthesiologists.

Results: A 15-year-old male patient with SMA type 2 (3 copies of the SMN2 gene), obesity and severe scoliosis underwent posterior T3-iliac spinal fusion. After a first dose administered by lumbar puncture, the second dose was unsuccessful due to the patient's complex anatomy. The placement of an intrathecal catheter with reservoir was agreed with the Neurosurgery Department by means of L5-S1 laminectomy and introduction of the catheter into the subarachnoid space after duratomy. Finally it is connected by tunneling to a subcutaneous reservoir implanted in the abdominal wall. The technique lasted 2 hours. The patient has completed all the loading doses and 8 more administrations (total follow-up of 35 months) without complications related to the reservoir. The administration did not require analgesia, sedation or airway precautions. Blood/cerebrospinal fluid controls were normal. He has presented an overall improvement in his baseline disease with better scores in the upper limb motor scales with respect to the pre-treatment assessment (RULM scale + 5 points, HFMSE + 3 points).

Conclusions: In our case, we opted for the placement of a lumbar catheter with a reservoir that allowed treatment to continue. This procedure is a safe option with a low complication rate for patients with advanced neuromuscular disease. In addition, it reduces the need for sedation and radiation exposure.

Keywords:
spinal muscular atrophy; nusinersen; intrathecal catheter

EPNS21-546 Poster only
Neuromuscular

Novel pathogenic ALG2 mutation causing congenital myasthenic syndrome: a case report

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Objective: *ALG2* mutations are extremely rare causes of congenital myasthenic syndromes (CMS). The clinical phenotype and treatment response is therefore not well described. We present a child with CMS caused by *ALG2* mutation.

Methods: Clinical- and electrophysiological evaluations together with genetic- and functional studies were performed.

Results: The child presented at birth with pronounced truncal hypotonia, proximal muscle weakness and a weak cry. Due to feeding difficulties a nasogastric tube was used until 8 weeks of age. Ventilatory support was never needed. Single fibre electromyography (SFEMG) showed neuromuscular transmission failure. Initial treatment with pyridostigmine from 3 weeks of age had no effect, but subsequent treatment with salbutamol improved both muscle weakness and neuromuscular transmission. Genetic analysis revealed a likely pathogenic variant c.1040del, p.(Gly347Valfs*27) and a variant of uncertain significance, c.239G>A, p.(Gly80Asp) in *ALG2*. Western blot in whole cell lysates of HEK293 cells transfected with p.Gly80Asp, or p.Gly347Valfs*27 expression constructs indicated that p.Gly347Valfs*27 is likely a null allele and p.Gly80Asp is pathogenic through marked reduction of ALG2 expression. A delayed acquisition of gross motor skills was observed throughout her first years, but her muscle strength continued to improve. At 27 months of age, ephedrine was introduced as an add-on treatment with a clear parentally reported improvement in functional outcomes, but also improved neuromuscular transmission on SFEMG. At the last clinical follow-up (34 months of age), she was able to sit without support, get up from prone to standing position, and move around by crawling and using a walker.

Conclusions: Functional studies can be crucial in helping us expand our knowledge about variants of unknown significance in CMS. Patients with CMS caused by *ALG2* mutations may manifest with infantile proximal muscle weakness and hypotonia and benefit from treatment with salbutamol and ephedrine.

Keywords:
Congenital myasthenic syndrome, ALG2, salbutamol

EPNS21-551 Poster only
Neuromuscular

The occurrence of symptoms in different stages of Duchenne Muscular Dystrophy and their impact on social participation

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Objective: As life expectancy improves for patients with Duchenne Muscular Dystrophy, new symptoms are likely to arise. This aims of this study are: 1) to explore the prevalence of a broad variety of symptoms in the various stages of DMD (with and without steroid use); 2) to explore the prevalence of common secondary diagnoses; 3) to evaluate the social participation level of patients with DMD older than 16 years of age; and to explore correlations between social participation and symptoms.

Methods: A cross-sectional self-report questionnaire, including questions on functional level and health status, as well as a standardized participation scale was distributed among Dutch patients with DMD.

Results: Eighty-four male patients with a mean age of 22.0 (SD 10.0) years were enrolled. The most prevalent and limiting symptoms were difficulty coughing (58%), coldness of hands (57%), contractures (51%), stiffness (49%), fatigue (40%), myalgia (38%), and low speech volume (33%). Prevalent secondary diagnoses included cardiac disease (14%), neurobehavioral diagnosis (13%), low blood pressure (13%), and arthrosis (5%). Social participation correlated negatively with coldness of hands (r -0.29, p 0.03), decreased intelligibility (r -0.40, p 0.003), and chewing problems (r -0.33, p 0.02).

Conclusions: The prevalence of a broad spectrum of symptoms and secondary diagnoses is high in patients with DMD, and some of these symptoms are correlated with social participation. Growing awareness of new symptoms and secondary diagnoses among patients, caregivers, and professionals can enhance their recognition, possibly facilitating prevention and early treatment.

Keywords:
Duchenne Muscular Dystrophy, aging, signs and symptoms, social participation, symptoms.

EPNS21-576 Oral or poster
Neuromuscular

Outcome of Croatian patients with spinal muscular atrophy (SMA) treated with nusinersen or risdiplam

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Objective: Comparison of treatment course and outcome of patients treated with risdiplam and nusinersen in Croatia.

Methods: Retrospective study, clinical exam, CHOP INTEND (Children's Hospital of Philadelphia infant test of neuromuscular disorders) HFMSE (The Hammersmith Functional Motor Scale Expanded), RULM (Revised Upper Limb Module), spirometry.

Results: Total of 34 patients (18 SMA (spinal muscular atrophy) 1, 4 SMA 2, 12 SMA 3) were treated with nusinersen between 2017 and 2021. At baseline, CHOP INTEND for SMA 1 on nusinersen was 18 (5 - 38) with the treatment onset at the age 3 months - 3.5 years. 8/8 patients required NIV (noninvasive ventilation) , after 3 years of follow up 1/8 required PIMV (permanent invasive mechanical ventilation). 3 patients required feeding support at baseline and during treatment. 2/8 patients acquired the ability to sit independently at 24-27 months. 8 SMA 1 on PIMV, aged 4.5 -13 years at baseline, CHOP 3 (1 - 10), treated with nusinersen for 18 months, on follow up CHOP 9 (4 - 14), 7 switched to risdiplam. Onset of nusinersen treatment for 12 SMA 3 patients was at the age of 4 - 17 years with mean HFMSE 52; and 58 after 2.5 years of follow up.
Total of 13 patients were treated with risdiplam; 1 SMA 1 3 months of age at baseline, CHOP INTEND 19, and 43 after 130 weeks. No breathing or feeding support were required at baseline nor during treatment, also achieved the ability to sit unassisted at 13 months.
Onset of risdiplam treatment for SMA 2 (8 patients) was at 11 years (3 - 14) with mean HFMSE 9 (2 - 23). After 2.5 years of follow up HFMSE was 5.5 (1 - 20). SMA 3 (3 patients) aged 17 -19 years achieved HFMSE 23 (4 - 38) at baseline. After 2.5 years of risdiplam therapy HFMSE was 26 (3 - 44).

Conclusions: No significant difference in efficiency of both disease modifying therapies (DMT) and no impact on breathing dysfunction were observed. Earlier onset of treatment enables higher motor milestones achievements regardless of DMT.

Keywords:
spinal muscular atrophy, treatment, nusinersen, risdiplam

EPNS21-584 Poster only
Neuromuscular

PHENOTYPIC CHARACTERIZATION OF A SERIES OF PATIENTS WITH CONGENITAL MUSCLE DYSTROPHY WITH PRIMARY MEROSIN DEFICIENCY (LAMA2 gene)

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Objective: We aimed to lay out the clinical course of the LAMA2-RD (CMD / LGMD) patients followed in our center through the last two decades in order to improve the knowledge of the disease, identify genotype-phenotype correlations and describe clinical management of patients, as well as to identify atypical phenotypes and potential biomarkers.

Methods: The retrospective study identified 38 children with LAMA2-RD. The cohort was divided into two groups based on maximum motor acquisition (ambulant/non-ambulant) and data was collected (clinical, molecular, histological and brain and whole body muscular MRI).

Results: Of the total number of 38 patients with LAMA2-RD (age range 1-41 years old) 55.27% were females. 21 patients had not acquired walking (68.4%). Atypical patients with mental retardation and/or brain malformation associated with refractory epilepsy were identified. The most severe complications were respiratory and orthopaedic: 59.3% of non-ambulant patients (vs 18.2% non-ambulant) required non-invasive ventilation. 25.9% of non-ambulant patients required a tracheostomy, all treated before 2010, and 18.5% of them were gastrostomized. 50% non-ambulant and 18.5% ambulant patients had spinal surgery. Muscle MRI showed a common pattern in both congenital and late onset patients and two young children showed inflammatory changes.

Conclusions: Survival, respiratory and orthopaedic prognosis were better in patients followed in the last decade. Proactive respiratory management (Intermittent positive pressure breathing - IPPB) and less invasive spinal surgical techniques as well as surveillance and treatment of bronchial compression caused by the spinal deformity are main management changes. The interest of whole-body muscular MRI consist of the diagnosis of walking forms, but also for the follow-up and outcome measure of future therapeutic trials.

Keywords:
congenital muscular dystrophy, LAMA2, respiratory, orthopaedic, whole-body muscular MRI

EPNS21-608 Oral or poster
Neuromuscular

Multicenter study of neuromuscular disease screening in children with elevated CK

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Objective: Introduction: An early diagnosis of patients with myopathies, clinically asymptomatic or paucissymptomatic with high creatine phosphokinase (CK), can allow a potentially treatment and appropriate care such as change in lifestyle/physical activity, a multidisciplinary approach and can even be potential candidates for clinical trials.
Objectives: Sensibilization of pediatric clinicians for myopathies and muscular dystrophies with elevated CK, allowing early detection of these disorders.

Methods: Methods: Prospective study between May 1, 2018, to April 30, 2020.
Project population: children aged between 1M and 18Y from 8 Pediatric Departments of participating centers of the north of Portugal and with high CK (1,5X normal values), asymptomatic or fatigue/myalgias. Acute conditions were not included. Children were referred to Pediatric Neuromuscular Diseases Centre at the CMIN/CHUPorto.
According to clinical evaluation in our Center, etiological investigation was guided.
A local visit and lecture were performed in each Pediatric Department, to present the project.

Results: Results: From 33 children observed, one was excluded (normal CK); 28 males. At first visit, the median age was 7Y (between 6M and 17Y).
All 7 patients with CK < 500UI/L, with later normalization, had normal clinical muscular examination; 1 due to use of isotretinoin. The patients with CK>500UI/L, 16 had a diagnosis, 7 dystrophinopathies, 5 myositis, 1 gammasarcoglycanopathy, 1 carnitine palmitoyl transferase 2 deficiency (CPT2), 1 myopathy not yet classified and 1 neuropathy. In this group, 9 patients without diagnosis maintained elevation of CK.

Conclusions: Conclusion: Awareness of these diseases was achieved. Patients are sent to the expertise center at an early stage. Half of patients, diagnosis was possible with an implication on care measures and treatment. Dystrophinopathies represent the larger group (21%). Although all patients with Ck<500, had no neuromuscular disease, a follow-up is needed until complete normalization

Keywords:
creatine phosphokinase; neuromuscular disease; dystrophinopathies

EPNS21-648 Oral or poster
Neuromuscular

Gene Therapy for long-term ventilated infants with Spinal Muscular Atrophy type one

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Objective: Long-term ventilated Spinal Muscular Atrophy (SMA) type 1 are eligible for gene therapy if only ventilated for 16 hours or less under Global Managed Access Program (GMAP).

Methods: Two SMA type 1 infants had a tracheostomy and required continuous ventilation around the clock referred to our long-term ventilation clinic in UAE for respiratory assessment and aiming to wean down continuous ventilation.

Results: Both patients were females, the first was referred at age of 11 months from Nepal and the second was a 9 months old Indian infant resident in UAE. Both were constantly receiving dry circuits, lacked synchronization with the ventilator, shown abnormal paradoxical breathing, poor chest expansion, and hypercapnia in blood gas.
To ensure adequate pressure for chest expansion and gas exchange without increasing the risk of barotrauma, the ventilator was upgraded to Astral 150 BiPAP for the first patient for better synchronization, and the ventilation mode was changed to Pressure Support with Safety Tidal volume (PS/SVt) with back up respiratory rate. Active humidification was added. A multidisciplinary approach targeting maximizing nutrition, regular respiratory physiotherapy to augment cough and strengthen respiratory muscle, and reducing oropharyngeal secretion was achieved. Gradual weaning off ventilator program started with 5 minutes twice a day, increased slowly on daily basis aiming for four hours off the ventilator twice a day while awake. The gene therapy was administered after the target ventilation weaning was achieved in 3 weeks for the first patient and in 8 weeks for the second one. Both patients who were followed up until October 2021 showed a significant improvement in spontaneous work of breathing and an increase in their CHOP-Intend scores and HINE scores.

Conclusions: We present our experience of infants with SMA and tracheostomy who received onasemnogene abeparvovec-xioi in our center under GMAP.

Keywords:
gene therapy, SMA, tracheostomy, ventilation

EPNS21-662
Neuromuscular

Oral or poster

Diagnostic delay in Serbian pediatric patients with spinal muscular atrophy

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Objective: Early diagnosis of spinal muscular atrophy (SMA) is crucial in the current therapeutic era. We aimed to investigate the diagnostic delay for Serbian children with different types of SMA.

Methods: This study included patients with a genetically confirmed diagnosis of SMA type 1, 2, and 3 followed-up at the two tertiary referral centres between 2000 and 2020. We analyzed the age of onset and genetic confirmation, and the diagnostic delay. The Kruskal-Wallis and Mann-Whitney test was used to compare the diagnostic delay for different SMA types.

Results: Of 106 eligible patients, 86 (81%) were included in the analyses. There were 16, 35, and 32 patients with SMA type 1-3, respectively. The median age of onset was 2.5 months (range 1-4 months), 7 months (range 3-18 months), and 24 months (range 12-120 months) for patients with types 1-3, respectively. The diagnostic delay was 23.8 months (range 0-144.6 months) for type 3, followed by 8.6 months (range 1.87-155.8 months) for type 2, and 2.2 months (range 0.47-9.83 months) for type 1, and was statistically different between the disease types.

Conclusions: Diagnostic delay is common in SMA, and it depends on the disease type. In our cohort, it was greatest for SMA type 3 which is in accordance with the literature. However, the diagnostic delay for patients with SMA type 1 and 2 is considerable. Therefore, it is crucial to reduce the diagnostic delay, especially for SMA type 1, so that the disease-modifying therapy can be initiated in a timely manner.

Keywords:
diagnostic delay, SMA

EPNS21-690 Poster only
Neuromuscular

Whole-exome sequencing identifies pathogenic mutations and phenotype influencing variants muscular dystrophy patients with limb-girdle weakness

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Objective: Limb girdle muscular dystrophies (LGMD) are a group of heterogeneous hereditary myopathies with similar clinical symptoms. Disease onset and progression are highly variable. Molecular diagnosis of LGMD patients is scarce in our place. We aimed to apply whole-exome sequencing (WES) to clinical practice for the genetic diagnosis of patients with limb girdle weakness.

Methods: WES was performed in 14 families with clinically diagnosed LGMD (10 families) and no deletions nor duplications Duchenne muscular dystrophy (DMD) patients tested with multiplex-ligation probe amplifications methods (4 families). Patients were ascertained retrospectively in a tertiary health center between 2017 and 2021.

Results: We identified likely pathogenic mutations in known myopathy genes for 6 of 10 families. The causative mutations were mostly in LGMD-associated genes; 1 families with congenital muscular dystrophy/LGMD R13 Fukutin-related (FKTN), 1 families with LGMD R1 calpain3-related (CAPN3), and 2 families with Duchenne muscular Dystrophy (DMD). Phenotype-influencing variant in splicing site were found in patients with limb girdle weakness caused by DMD gene mutation. A patient with distal weakness has a mutation in MPZ gene associated with Charcot Marie Tooth 1B. One patient with suspected fascio-scapulohumeral muscular dystrophy clinically has a mutation in DNA2 gene-related mitochondrial disorders.

Conclusions: With WES, we achieved a diagnostic success rate of 60% in our difficult-to-diagnose patients with LGMD. Accurate clinical examination is important for interpretation of WES, with many diagnoses requiring follow-up review.

Keywords:
LGMD, DMD, whole-exome sequencing, limb-girdle weakness

EPNS21-701
Neuromuscular

Oral or poster

Between peripheral and central: congenital myasthenic syndrome and congenital disorder of glycosylation

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Objective: The investigation of a complex neurological phenotype may mask the suspicion of a congenital myasthenic syndrome.

Methods: Case report

Results: Ten-year-old girl, with no relevant family or gestational history, who presented at the age of 17 months with developmental delay, global hypotonia, hyperlaxity and slight right hemiparesis. She acquired gait at 25 months and had language development delay. Brain MRI revealed multifocal white matter changes and reduced volume of the right corticospinal tract on tractography. CMV PCR on neonatal blood was negative. There was a slight elevation of creatine kinase. From the age of 3 years, parents noticed tiredness, falls, difficulty in controlling her head and dysphagia that soon appeared fluctuating along the day and from day to day. In the following years, limb girdle weakness became apparent. The first EMG (38 months) raised the suspicion of myopathy. Muscle biopsy and mitochondrial respiratory chain studies were inconclusive. At 49 months, however, a repeat EMG found decrement on repetitive stimulation. The NGS gene panel for congenital myasthenic syndromes subsequently found 2 variants of undetermined significance on DPAGT1 gene in compound heterozygoty. Transferrin isoelectric focusing was altered, confirming the pathogenicity of these variants, and confirming the double diagnosis of congenital myasthenic syndrome and congenital disorder of glycosylation. Currently, the patient presents a developmental language and motor coordination disorder, slight bilateral facial palsy, nasal dysphonia, global hypotonia, hyperlaxity and limb girdle weakness and is treated with ephedrine with favourable response.

Conclusions: This case illustrates how the availability of genetic diagnosis is blurring the distinction between central and peripheral nervous system pathology for complex phenotypes. The key for this diagnosis was the development of fluctuation of clinical weakness.

Keywords:
congenital myasthenic syndrome, congenital disorder of glycosylation, DPAGT1 gene

EPNS21-704
Neuromuscular

Poster only

Neuromuscular diagnoses uncovered by unexpected anaesthesia complications

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Objective: Patients with non-specific neuromuscular symptoms often undergo surgical procedures before diagnosis is established and may be at risk of life-threatening complications if peri-anaesthetic complications are not anticipated.Our aim was to identify patients whose neuromuscular diagnosis was only made following an unexpected adverse anaesthetic event, and to identify features that could have aided its anticipation

Methods: Patients were included as part of a retrospective study based on the presence of a complication following an anaesthetic procedure that led to the identification of a neuromuscular diagnosis

Results: 2 patients identified.First patient was 2-year-old girl with history of bilateral hip luxation and clubfeet who developed a severe Malignant Hyperthermia (MH) reaction during general anaesthesia for elective hip surgery.In retrospect,she had a history of hypotonia and delayed motor milestones,both parents suffered myalgia and muscle cramps.Subsequently 2 RYR1 variants were identified in trans,she was found to have central cores on muscle biopsy.The second patient was an almost 3-year-old boy admitted for a suspected "rhabdomyolysis" after recent onset muscle pain and hyperCKaemia.Following general anaesthesia with sevoflurane for soft tissue debridement for extravasation he developed further muscle breakdown with extreme hyperkalemia leading to a secondary cardiac arrest and hypoxic-ischemic injury.A diagnosis of Anaesthesia-Induced Rhabdomyolysis (AIR) was made, and a mutation in the dystrophin gene subsequently identified.

Conclusions: These cases highlight that patients with undiagnosed neuromuscular disorders usually have pre-existing features that should alert to their potential anaesthetic risk.Awareness of such features in patients undergoing surgical procedures is crucial amongst medical professionals.We aim to identify similar cases illustrating the link between undiagnosed neuromuscular disorders and adverse anaesthesia events, to prevent or reduce their occurrence in future.

Keywords:
Malignant hyperthermia, general anaesthesia, neuromuscular, rhabdomyolysis

EPNS21-706 Poster only
Neuromuscular

A case study of a very severe SMA type 1 with an unexpected outcome months after treatment with Nusinersen

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Objective: To present a case study of an infant with SMA type 1 in whom active early treatment has led to a surprising unexpected outcome. To reflect on the variables that could have played a role in his outcome.

Methods: Retrospective case study of a patient from our tertiary Neuromuscular Service.

Results: Male infant born at 37w, had antigravity movements following birth (as evidenced in parental videos).Between 2-4 weeks of age, progressive deterioration of movements. Hospital admission at age 4weeks,CHOP-Intend was 3/64 with minimal spontaneous movements of limbs, no antigravity power, feeding difficulties, marked diaphragmatic breathing and frequent desaturations. He was ventilated because of respiratory failure. Clinically suspected SMA type 1 was confirmed on genetic testing (2 copies of SMN2).Treatment with Nusinersen started at 5weeks of age.4 loading doses completed as per protocol. He remained mechanically ventilated for 3 months, extubated at 4 months and 10 days of age (1 month after loading doses completed) onto NIV - ultimately required only during sleep. Profound weakness and need for continuous mechanical ventilation led to consideration of treatment withdrawal, tracheostomy and palliative options. Progressive improvement of his condition allowed him to receive Onasemnogene abeparvovec (gene therapy for SMA) at 7months of age. CHOP-intend pre-gene therapy was 40/64.He is currently (9months old) able to sustain a supported seated position with good head control and is starting to manage some oral tastes.

Conclusions: Our case study highlights that severity at presentation for SMA type 1 might not be the only factor affecting outcome. Other variables ought to be considered. Patients treated under the age of 3 months, despite their severity, might have an unpredictable outcome. Caution at clinical decision making is needed. Respiratory improvements lag behind motor improvements. Disease-modifying treatments have highly variable outcomes and determining factors remain poorly understood.

Keywords:
SMA type 1, SMN2, nusinersen, onasemnogene abeparvovec, disease-modifying treatments

EPNS21-708 Poster only
Neuromuscular

Long-term efficacy of nusinersen in hungarian pediatric SMA patients

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Objective: Spinal muscular atrophy (SMA) is caused by a homozygous deletion in survival motor neuron (SMN) 1 gene. Nusinersen is an antisense oligonucleotide, which can increase the production of SMN protein. In Hungary, it is available from April 2018. Our aim is to summarize our experiences regarding the efficacy of nusinersen in a long-term follow up, including data about life quality.

Methods: Data on 76 SMA patients, starting nusinersen therapy in Hungary between April 2018 and July 2021, were retrospectively collected. The motor functions were evaluated at baseline, before the 4th and before all following injections. For assessing life quality, data from Quality of Life (QOL) and Pediatric Quality of Life (PedsQL) questionnaires were analyzed at baseline and after 1 year.

Results: 19 patients were type 1 (0.39y-17.98y,), 37 patients were type 2 (1.29 y-17.96y,), 31 patients were type 3 (1.87y-18.01y).
In SMA1 patients we saw a 20.75 (12-24) point average improvement Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders scale after two years of treatment (p=0,125). In case of SMA2 patients we found an average 8.24 ((-5) - (+18)) point increase from baseline (p<0.0008) with Hammersmith Functional Motor Scale Expanded. The increase in 6 minute's walk test was on average 48,79 meters (min-max (-20,6) - (+228,5)) in SMA3 patients.
In SMA2 patients we proved significant correlation between SMN2 copy number and the level of improvement by the time of 9th injection. The influence of the age at start and severity of disease on the therapy response was significant. No significant worsening was detected in life quality, it remained stable even in severe cases or pourly responding patients.

Conclusions: Nusinersen was proved to be effective in all SMA types, the improvement in motor functions remained stable even after 3 years. There were no decline in life quality, neither in patients, who reacted less for the treatment.

Keywords:
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EPNS21-709
Neuromuscular

Oral or poster

HOMOZYGOUS C.7447A>G MUTATION IN COL6A3 GENE ASSOCIATED TO A DISTAL PHENOTYPE WITH AXONAL NEUROPATHY

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Objective: Recently, it has been reported that young adults carrying homozygous c.7447A>G mutation in COL6A3 gene present with a milder phenotype as expected to collagen VI-related limb-girdle syndrome. We present four pediatric cases with the same gene variant in homozygous state with a clinical presentation of mild distal weakness.

Methods: A retrospective study of four cases with an initial diagnosis of axonal neuropathy and mutations in COL6A3 gene in a single centre.

Results: The four patients were unrelated boys with 6, 9, 12 and 15 years old at last evaluation. They all presented with abnormal gait before 3 years of age, characterized by muscle weakness in distal lower limbs, mostly in lateral peroneal muscles without muscle atrophy. Mild ankle contractures were found in all of them. Tendon reflexes were normal. Creatine phosphokinase levels showed a wide range from 275 to 2550 U/L. Electroneurogram revealed normal nerve conduction but low amplitudes in all cases, and electromyography showed no abnormalities. Muscle MRI did not reveal any specific alterations in all of them. Clinical exome sequencing did not uncover any gene mutations related to the phenotype. Whole genome sequencing was performed in all the cases and revealed the c.7447A>G mutation in a homozygous state in the COL6A3 gene in all the cases. Parents were all heterozygous for the variant. The families were unrelated but all of them came from the same region. Haplotype studies are on course to reveal a mutation founder effect in this population.

Conclusions: The clinical presentation of early onset lower limbs distal weakness in a toddler, and the finding of low amplitude in EMG, would be related to collagen VI-related limb-girdle syndrome related to the variant c.7447A>G in homozygous state. Low amplitude with normal nerve conduction should not be associated to an axonal neuropathy phenotype in these cases.

Keywords:
COL6A3, axonal neuropathy

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Neuromuscular

SMA: New Treatments. Are We Ready?

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Objective: New treatments for Spinal Muscular Atrophy are now available, including Nusinersen, Risdiplam and Zolegensama. Given their significant financial cost, access is limited. Evidence suggests that greater benefit is gained with earlier commencement of treatment.
Are we making the diagnosis early enough to maximise benefit from new treatments. Can we identify barriers to earlier diagnosis?

Methods: We have reviewed the diagnosis pathway of all children diagnosed with SMA in a large UK Neuromuscular centre over a 10-year period. Time from initial symptoms to genetic diagnosis was collected, and compared between the clinical phenotypes of SMA 1, 2 &3. Particular barriers to or delays in achieving a diagnosis were captured. 27 patient pathways were analysed.

Results: 27 patient pathways were analysed in the last 10 years. Patients with genetically confirmed SMA were included. Earlier diagnosis was possible in patient with SMA 1, but many patients were diagnosed after 6 months of age.
The mean time for diagnoses for SMA type 1 in the period of 2010-2015 was 2.3 months compared to the period 2016-2021 was 11.3 months overall mean age of diagnosis was 6.2 months in the last 10 years.
Diagnosis of SMA 2 is usually in the second year of life with mean age of diagnosis 23 months.
Diagnosis is most delayed in Patients with SMA 3 with mean age of diagnosis of 39months.

Conclusions: Diagnosis of SMA is frequently delayed, even in those with severe symptoms. Neurone survival correlates with age. Evidence shows that outcomes are best when patients are treated early. Given the expense of the drug, this is also the most cost-effective strategy. A pre-symptomatic diagnosis is unusual in the UK unless there is a family history and New-born screening is not available in the UK. A greater awareness of newer treatments may help clinicians consider earlier testing for SMA. New-born screening would seem the cost-effective way to utilise these new and expensive treatments, while also gaining maximum clinical benefit.

Keywords:
spinal muscular atrophy

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Poster only

Congenital Myasthenic Syndrome: Case Report of 2 Siblings with CHRNE Mutation

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Objective: Congenital myasthenic syndromes (CMS) are rare diseases caused by neuromuscular conduction disorder. It is divided into three groups as presynaptic, synaptic and postsynaptic according to the location of the defect in the neuromuscular junction. Clinical findings are variable depending on the underlying molecular defect. In this report, two siblings diagnosed with congenital myasthenia will be presented.

Methods: An 11-year-old girl and her 6-year-old brother presented with complaints of droopy eyelids and limitation of eye movements since the neonatal period. There was a second degree consanguinity between their parents. Mild weakness, an increase in complaints in the evening was described. Neurological examination revealed bilateral ptosis and weakness in the facial muscles. EMG examination revealed findings consistent with myopathic appearance due to motor end plate dysfunction. Anti acetylcholine antibodies were negative.

Results: In the molecular examination performed with the pre-diagnosis of congenital myasthenic syndrome, homozygous c.905C>G p.P302R variant was detected in the 8th exon of the CHRNE gene in both siblings. Ptosis regressed significantly with the pyridostigmine treatment.

Conclusions: The CHRNE gene mutations cause muscle nicotinic acetylcholine receptor deficiency and is responsible for the etiology in approximately 50% of patients with congenital myasthenia gravis. CHRNE-associated congenital myasthenia syndrome should be considered in the preliminary diagnosis in cases who present with ptosis and have a positive response to pyridostigmine treatment.

Keywords:
Congenital Myasthenic Syndrome, CHRNE, pyridostigmine

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Neuromuscular

Oral or poster

MYOTONIA CONGENITA; SINGLE CENTER EXPERIENCE

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Objective: Myotonia congenita is a rare disease of nondystrophic myotonias due to mutations in the CLCN1 gene encoding the voltage-dependent chloride channel.

Methods: Demographic, clinical, genetic, and electrophysiological features of 5 patients from 3 different families diagnosed with myotonia congenita were retrospectively analyzed.

Results: The mean age of 4 male (80%) and 1 (20%) female patients with Becker phenotype was 15.7 years (12-19 years). The age of onset of symptoms was seven years (4-12 years), and the age at diagnosis was 14.5 years (11-17 years). The admission complaints were muscle pain. While all of the patients described the warm-up phenomenon, three (60%) had worsening symptoms with cold. Muscle hypertrophy, action, and percussion myotonia were observed in all of them. The parents of patients were cousins. The mean CK value was measured 128 IU/L (91-178). Myotonia was seen in 4 patients who underwent needle electromyography. A c.1129C>T(p.Arg3777Ter) mutation in the CLCN1 gene was detected in 3 patients, two of whom were siblings, and a c.127C>T(p.Gln43Ter) mutation was found in the other two patients who were also siblings. Symptoms improved in 4 patients (80%) with mexiletine and one (20%) with carbamazepine.

Conclusions: Phenotypic diversity can be observed even in patients from the same family with the same mutation. In our series, the time between symptom onset and diagnosis was long. Although the patients' symptoms decreased under treatment, it was noted that the symptoms exacerbated with the discontinuation of the drug.

Keywords:
myotonia congenita, child

EPNS21-96 Poster only
Neuromuscular

Osmotic stress-associated Sodium/Myo-Inositol co-transporter is upregulated in skeletal muscle of the mdx mouse

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Objective: Duchenne Muscular Dystrophy (DMD) leads to contraction-induced muscle damage, and recent evidence suggests osmotic stress is an aggravating factor. As the cell's protective response to osmotic stress involves increased uptake of the osmolyte myo-inositol, we studied the expression of its transporter sodium/myo-inositol co-transporter SLC5A3 in the mdx mouse model for DMD. We focused on mice, between 4 and 26 weeks old, as muscle tissues experience most active degeneration/regeneration at younger ages.

Methods: Male C57BL/10ScSn-Dmdmdx/J (mdx) and C57BL/10SnJ control mice were sacrificed at age 4, 8, 12, and 26 weeks. The tibialis anterior was H&E stained and five sections per animal were analyzed for percentages of healthy, regenerating and necrotic fibers. Expression levels of SLC5A3 were evaluated at the mRNA level by quantitative PCR, and at the protein level by quantitative western blotting. Protein data underwent a log-transformation and was analyzed by the mixed model approach. Immunofluorescent stainings were carried out to characterize inflammatory cells.

Results: Necrosis was most pronounced in the tibialis anterior of 12-week-old mdx mice (9.2%) and declined by age 26 weeks (3.1%). While mRNA levels were equal to controls, SLC5A3 protein was significantly upregulated in tibialis anterior and gastrocnemius of mdx mice at all ages ($p<0.01$), most explicitly in tibialis anterior at age 4 weeks (454-fold) and in the gastrocnemius at 12 weeks (437-fold). In the diaphragm, protein levels were significantly different at age 4 ($p=0.006$; 2.1-fold) and 12 weeks ($p<0.001$; 3-fold). Necrotic fibers stained positive for SLC5A3, whereas no apparent colocalization with macrophage markers F4/F80 or CD206 was observed.

Conclusions: This study revealed a significant upregulation of SLC5A3 in mdx muscle fibers. From our results, we propose that SLC5A3 activation coincides with muscle degeneration/regeneration processes and might represent an appropriate response of muscle cells to restore osmotic homeostasis.

Keywords:
Duchenne muscular dystrophy, mdx, osmoregulation, SLC5A3

EPNS21-99
Neuromuscular

Oral or poster

Study Design of IV Efgartigimod in Juvenile Generalized Myasthenia Gravis

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Objective: Generalized Myasthenic Gravis (gMG) is a rare, chronic, and debilitating autoimmune disease with a substantial disease and treatment burdens. Immunoglobulin G (IgG) autoantibodies are key mediators of gMG pathophysiology. Efgartigimod is a human IgG1 antibody Fc-fragment that blocks FcRn; thereby decreasing IgG recycling and reducing pathogenic IgG autoantibody levels. ADAPT, a phase 3 trial in adults with gMG, showed efgartigimod was efficacious and well tolerated. The incidence of juvenile gMG is considerably lower than in the adult population (1 to 5:1,000,000). Randomized clinical trial data as well as treatments are limited and medical need for effective and safe treatments remain high. Here we present the study design evaluating efgartigimod in pediatric patients with juvenile gMG. The primary aim of this study is to confirm age-appropriate dose of efgartigimod and provide evidence for the treatment response.

Methods: The study recruits 12 patients, 2-17 years of age in a staggered way, starting with the older age group (12-17 years). Patients must have a confirmed diagnosis of gMG class II, III and IVa, the presence of anti-acetylcholine-receptor-antibodies and be on stable background therapy. Patients start with 1 infusion of efgartigimod and a 5 week-follow up period before proceeding to the efficacy confirmatory part with 4 weekly infusions.

Results: Pharmacokinetics, pharmacodynamics, clinical response and safety are assessed. In children >6 year of age, MG-ADL and modified QMG are utilized, while a detailed neurological assessment is employed to assess response in very young children =<6 years. Fatigue will be assessed using NeuroQoL - pediatric fatigue score.

Conclusions: The unique design of this study will provide data to support PK/PD modelling to confirm age-appropriate dose and evaluate efficacy and safety of efgartigimod in pediatric MG patients. Efgartigimod may potentially become new effective and safe treatment option.

Keywords:
Myasthenia gravis, clinical trial, efgartigimod

EPNS21-358 Oral or poster
Neuro-Oncology

Dysembryoplastic Neuroepithelial Tumor in Noonan syndrome

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Objective: Noonan syndrome (NS) is an autosomal dominant developmental disorder. It is one of the RASopathies and is associated with an increased risk of oncogenesis. Dysembryoplastic neuroepithelial tumor (DNET) is a benign CNS tumor previously reported in few cases of NS. Our case report demonstrates the diagnostic and treatment challenges in patients NS and DNET.

Methods: A girl with refractory epilepsy was referred for epilepsy surgery at Oslo University Hospital (OUS) at the age of two years.

Results: She had gradually increasing seizures up to 20 tonic and atonic daily. A T2 hyperintense lesion in the frontal lobe was detected on MRI and was interpreted as focal cortical dysplasia or low-grade glioma at the left premotor area with extension deep in the white matter reaching the lateral ventricle. Several anti-seizure medications were tried including oxcarbazepine, sodium valproate, topiramate, levetiracetam, clonazepam and acetazolamide. PET scan showed reduced uptake of FDG in the left precentral gyrus, probably DNET. Diffusion tensor imaging and tractography demonstrated close proximity to cortico-spinal tract (CST) at corona radiata and the deep part traverses the CST. Subtotal resection was performed to avoid the hand area in the motor cortex. Histopathological examination showed typical findings of DNET, but could not rule out diffuse glioma. Complete seizure control was achieved for two years before recurrence of seizure and behavioral problems ascribed to frontal lobe residual tumor. The surgical challenge is the location at perirolandic area lateral to the precentral hand knob area and she should be awake and cooperative during surgery. Genetic work-up showed that she is heterozygous for a PTPN11 mutation.

Conclusions: Screening with MRI should be included in the guidelines for children with Noonan syndrome particularly those who are eligible for growth hormone therapy for short stature. Caution should be taken in our patient due to evidence of mild increase in the size of the residual tumor.

Keywords:
Noonan, DNET, Growth hormone, epilepsy surgery, RASopathy

EPNS21-381 Poster only
Neuro-Oncology

Optic pathway gliomas (OPG) and non-OPG gliomas in a paediatric Neurofibromatosis type 1 (NF1) population: a single-center experience

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Objective: To describe the natural history of children with Neurofibromatosis type 1 (NF1) presenting oncological complications (gliomas), referred to the referral center of our region, with particular attention to patients who have developed a second glioma and identification of any predisposing factors.

Methods: A retrospective study was conducted on NF1 patients with gliomas who were diagnosed and followed up by our Institution between January 2010 and March 2021.

Results: 43 patients were identified out of the 211 NF1 patients followed by our center during the study period. A total of 60 gliomas were diagnosed, of which 28 (46.6%) were OPG and 32 (53.4%) were non-OPG. The mean age at first glioma diagnosis was 5.08 years for OPG gliomas (0-11 years) and 10.9 for non-OPG gliomas (3-16 years). Only 13 (21.6%) of the gliomas had signs and/or symptoms at diagnosis. Among non-OPG gliomas there was a prevalence of infratentorial localization (63.6%) compared to supratentorial (36.4%). Eight patients were treated with chemotherapy, of which 6 developed a second glioma. The mean time to second glioma onset in these patients was 6.25 years (1.2-17 years). The association between chemotherapy and occurrence of second glioma was statistically significant ($p<0.001$).

Conclusions: Our experience confirms the need for close clinical and neuroradiological follow-up in the NF1 paediatric population due to the frequent absence of sign or symptoms of OPG and non-OPG complications. Our results also suggest a possible increased risk of developing neoplastic lesions in patients previously treated with chemotherapy. These data need to be further investigated.

Keywords:
neurofibromatosis, gliomas, OPG, NF1, chemotherapy

EPNS21-421 Poster only
Neuro-Oncology

Brain Magnetic Resonance Imaging Findings of Pediatric Hemophagocytic Lymphohistiocytosis Could be Diagnostic and Life Saving

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Objective: Hemophagocytic lymphohistiocytosis (HLH) is a rare and fatal disease, and may also present with central nervous system (CNS) findings at the beginning without specific diagnostic criteria. Brain magnetic resonance imaging (MRI) findings are diverse, also can be diagnostic. We aimed to emphasize the importance of brain MRI findings in the early diagnosis of this fatal disease.

Methods: MRI findings, clinical presentations, treatment response, and prognosis of seven patients with HLH were described.

Results: There were seven pediatric patients who were initially diagnosed with HLH with neurological findings without systemic signs of HLH. Four as primary, two as secondary, and one of them were diagnosed as possible primary HLH. All patients had contrast-enhancing diffuse cerebellar and brainstem lesions; also contrast-enhancing patchy periventricular and callosal cerebral lesions were observed. The patients were followed up with these MRI findings, with pre-diagnoses of toxic, metabolic, infectious, vascular, and demyelinating diseases. Not all patients met the HLH diagnostic criteria due to incomplete systemic/laboratory findings; therefore, only two were immediately directed for hematopoietic stem cell therapy. Four died shortly after admission, one patient could not be followed up after HLH treatment, two patients who fulfilled the HLH diagnostic criteria underwent hematopoietic stem cell transplantation and survived.

Conclusions: Brain MRI findings, especially in the presence of neurologic findings, allow for early diagnosis, which can be life-saving. These common features in brain MRI findings should be evaluated with this suspicion and included in HLH diagnostic criteria.

Keywords:
hemophagocytic lymphohistiocytosis; brain MRI findings; diagnosis

EPNS21-462
Neuro-Oncology

Poster only

Everolimus for Cerebellar Tubers in Tuberous Sclerosis Complex

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Objective: Tuberous sclerosis complex (TSC) is a neurocutaneous syndrome that can affect multiple organ systems. The patients with TSC have characteristic skin lesions, seizures, and cellular overgrowth or hamartomas in the heart, brain, and kidneys. It is an autosomal dominant or sporadic multisystem disorder that results from mutations in either TSC1 or TSC2. Everolimus, an inhibitor of mTORC1 and an analog of rapamycin, is a water-insoluble small molecule. Preliminary studies have shown that mTOR inhibition is associated with improvements in the manifestation of tuberous sclerosis including subependymal giant cell astrocytomas, angiomyolipomas (benign renal tumours), and facial angiofibromas.

Methods: We present a case of 8-year and 6-month-old boy with TSC who has drug-resistant epilepsy and mental retardation. He was born after uneventful pregnancy and delivery, with non-consanguineous marriage of his parents. His developmental milestones were reported as normal. On the physical examination at the age of 1-year, he had a few adenoma sebaceum on the face and hypopigmented macules on the trunk. Cardiac evaluation revealed rhabdomyosarcoma and renal evaluation revealed angiomyolipoma. The brain magnetic resonance imaging (MRI) at the age of two years demonstrated supratentorial cortical tubers, subependymal nodules, mild cerebral atrophy and cerebellar tubers. On the follow up MRI two years later, there is an increase in the size of cerebellar tubers. Everolimus treatment was started at the age of eight, and a significant reduction in the size of the cerebellar tubers was observed after everolimus treatment.

Results: We observed a significant reduction in the size of the cerebellar tubers with everolimus treatment.

Conclusions: Everolimus therapy was associated with marked reduction in the size of giant cerebellar tubers and may be a potential alternative treatment to neurosurgical resection in some cases.

Keywords:
Tuberous sclerosis complex, cerebellar tubers, Everolimus treatment

EPNS21-468
Neuro-Oncology

Oral or poster

Neurological complications in children after bone marrow transplantation

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Objective: Analysis of incidence, structure and severity of causes of neurological complications (NC) in pediatric bone marrow transplantation (BMT) Department in Morozov Children's hospital (Moscow, Russia).

Methods: Retrospective descriptive analysis of 87 cases in BMT Department during the period of 2018-2020.

Results: The general incidence of NC was 9,2 % (8/87) of all of BMTs. Median age of patients was 8,8 years. NC occurred on median 43,4 posttransplant day (PTD) (from 3 to 162). Pre-engraftment NC were detected in 25% and associated with drug toxicity. The early post-BMT NC (before +100 PTD) were observed in 62,5% and included toxic and infections complications. The late post-BMT NC (after +100 PTD) were revealed in one patient 12.5%. According to the Common Terminology Criteria for Adverse Events (CTCAE), NC were classified as grade (G)2 - 37,5%, G3 - 25%, G4 - 25% and G5 - 12,5 %. The clinical structure of cases was the following: 12,5% were treated for Human Herpesvirus 6 (HHV6) encephalitis and toxic leukoencephalopathy (LE) simultaneously, 25% - for toxic LE alone, 25% for HHV-6 encephalitis alone, 12,5 % - for posterior reversible encephalopathy syndrome caused by ciclosporin A intake, 12,5 % - for metabolic Wernicke's encephalopathy (WE) and 12,5 % - for immune encephalitis (IE), developed 6 months after BMT. 62,5% patients recovered. 3 children (37,5 %) died: the girl with NC G4 due to relapse of leukemia, the boy who survived WE died due to systemic infection, another boy died due to IE G5.

Conclusions: The severe NC are very important causes of morbidity and mortality in post-BMT period. The G of NC according CTCAE correlates with chances for recovery. The mild NC could be prevented. Repeat viral load, drug concentration monitoring and competent neurological examination can be useful for severe NC.

Keywords:
bone marrow transplantation, leukoencephalopathy, encephalitis

EPNS21-488 Poster only
Neuro-Oncology

A rare complication of neurofibromatosis type 1

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Objective: Plexiform neurofibromas are benign peripheral nerve sheath tumours and are a significant complication of neurofibromatosis type 1 (NF1), which can occur in 30 - 50% of these patients. Malignant transformation of plexiform neurofibromas is very rare in childhood and is estimated to occur in 2 to 5% of all NF1 individuals. Selumetinib is an inhibitor of MEK1 + MEK2 protein that has an important role in MAPK signalling pathway related to tumour growth, which has been shown to reduce tumour size in 70% of patients. Selumetinib has been approved for use in paediatric patients older than 2 years for treatment of symptomatic inoperable plexiform neurofibromas.

Methods: We report on two paediatric individuals with NF1 who developed rare malignant peripheral nerve sheath tumours (MPNST) during childhood, which were treated with selumetinib.

Results: The first individual is a young boy with NF1 who developed a MPSNT of his forearm at nine years of age, which caused significant pain. He was trialled on selumetinib but there was no reduction in tumour size. He underwent complete surgical excision of the lesion and remains stable. The second individual is an 11 year old girl with NF1 and a history of plexiform neurofibromas of thoracic and lumbar paraspinal region and right pelvis. She reported significant pain, discomfort and difficulty walking, which was significantly disrupting her life. She was trialled on selumetinib, but showed no response in symptom reduction after 9 months. She developed MPSNT of her pelvis plexiform neurofibroma on repeat biopsy after selumetinib trial. She underwent chemotherapy, radiotherapy and followed by complete resection of this lesion.

Conclusions: MPNST are rare in children, but as this case report highlights, they can cause significant symptoms including intolerable pain and discomfort. While our sample size is small, we report very limited benefit from the use of selumetinib in these patients.

Keywords:
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EPNS21-529 Poster only
Neuro-Oncology

Paediatric CNS tumors - the epidemiological study of patient and tumor characteristics

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Objective: Primary central nervous system (CNS) tumors are the most common solid tumors in children. The incidence varies by country from 1.12-5.14/100.000 children. The aim of this study was to evaluate all children who were diagnosed with a CNS tumor in the period of 2007-2018 in a single referral centre in the country and to describe their tumor characteristics.

Methods: For purpose of this retrospective epidemiological study, the electronic health records and medical charts were utilised to search for patients who had malignant or benign neoplasms of the brain or other parts of CNS according to ICD-10. Data on patients age, gender, clinical symptoms, tumor histology and tumor locations were collected from medical records.

Results: 182 children and adolescents were included, with a mean age of 7.9±4.5 years (range 0-18 years) at the time of diagnosis. CNS tumors were more common in males (53%). Of all patients, 62% had gliomas, 15% had embryonal brain tumors (medulloblastoma presenting 12%), 7% had ependymomas, 3% had craniopharyngioma and 13% had other types of tumors. Among glioma patients, 74% had a low grade tumor: among these 30% of the diagnosis was based on radiological characteristics (7 patients had neurofibromatosis type 1, 3 had tuberous sclerosis, in 4 patients tumor was located in region inaccessible for surgery and in 11 tumors was found incidentally). Ten patients had diffuse intrinsic pontine glioma (DIPG) and 9 had glioblastoma. Biopsy was done in only one patient with DIPG. Clinical presentation data were obtained in 121 patients:40% presented with signs of increased intracranial pressure, 42% had focal neurological signs, 12% had seizures and the rest presented with fatigue or failure to thrive.

Conclusions: Our cohort included all children and adolescents with malignant and benign CNS tumors in the country in a twelve-year period. The results of our study resemble those reported in other similarly designed studies elsewhere in the world.

Keywords:
epidemiology, CNS tumors, childhood

EPNS21-642 Poster only
Neuro-Oncology

Diagnostic pitfalls in a case of bilateral papilloedema

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Objective: "Optic disc swelling" is a general term that can have several causes. Careful history and examination are needed to differentiate them. Optic neuritis refers to inflammation of the optic nerve due to a demyelinating or infectious disease. The term "papilledema" is reserved for optic disc swelling due to raised intracranial pressure. Conditions causing papilledema include intracranial masses, head trauma, meningitis, spinal cord lesions, impairment of cerebral sinus drainage and idiopathic intracranial hypertension.
Objective: To establish an urgent practical approach for the onward investigations and the subsequent management of patients with papilledema.

Methods: A 11-year-old girl, with type I diabetes, is found with bilateral papilledema at her routine ophthalmologic screening. Her clinical records were analyzed and clinical course, MRI features and outcome after treatment were reviewed.

Results: After the incidental discovery of papilledema, the full clinical examination showed no neurological deficits or other clinically significant findings. Brain MRI showed tetraventricular hydrocephalus without transependymal reabsorption and without any intracerebral lesion. Without any intracerebral cause of hydrocephalus, the possibility of a lower obstructive cause was investigated. Spinal MRI revealed an extramedullary, intradural spinal tumor(T11 - L4). A microsurgical resection was performed. Lumbar puncture was delayed due to tumor location, but CSF was collected during surgery.

Conclusions: Patients presenting with bilateral papilledema need urgent and careful multidisciplinary assessment to exclude life-threatening causes. The mechanism involved in papilledema was most likely here not directly linked to the compressive mechanism of the spinal tumor, but to subarachnoid hemosiderin accumulation due to tumor bleeding. Leptomeningeal hemosiderin deposits were discovered on MRI on the surface of the cerebellum and around the spinal cord, with secondary impairment of CSF circulation and drainage.

Keywords:
papilledema, spinal tumor, MRI

EPNS21-681 Poster only
Neuro-Oncology

Unusual Stroke Mimics: Methotrexate Induced Reversible Stroke Like Neurotoxicity and Leukoencephalopathy

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Objective: Intrathecal administration of methotrexate (MTX) is quite useful in the treatment of pediatric hematological cancers. Methotrexate may rarely cause neurological side effects. Herein, we report a patient with B-ALL presenting with reversible neurological symptoms; central facial palsy, hemiplegia and encephalopathy after intrathecal methotrexate (IT-MTX).

Methods: .....

Results: An 11-years old girl was diagnosed with NCI high risk B-ALL without central nervous system involvement. On 15th day of consolidation phase of COG AALL1732 protocol, she presented with arrest of motor behavior, blank stare, right-sided facial paralysis, right hemiparesis, change in consciousness and aphasia, 6 hours after receiving 6th IT-MTX. Brain magnetic resonance image (MRI) revealed bilateral lesions with restricted diffusion in the centrum semiovale and corpus callosum. The coagulation parameters were unremarkable. We suggested that these findings were consistent with MTX neurotoxicity. Levetiracetam, aminophylline and calcium leucovorin were administered. The symptoms were fluctuating and migratory. On the sixth day, the neurologic symptoms resolved completely. We continued to consolidation treatment as previously planned without any further neurological adverse effects. Brain MRI findings improved partially at 3 months.

Conclusions: MTX-induced neurotoxicity is usually characterized with transient events but rarely severe outcomes can be observed like necrotising encephalopathies. This event may be difficult for clinicians to distinguish from stroke. For this, there are some clues: symptoms were fluctuating and migratory and finally ameliorated, brain MRI was not consistent with stroke, fibrin/fibrinogen degradation product and D-dimer were normal. Leucovorin, aminophylline, amiodorone,edaravone and D-mannitol can be used in the treatment of MTX-induced neurotoxicity. MTX-induced neurotoxicity should be kept in mind in patients with hematological malignancy receiving IT-MTX presenting with a stroke-like episode.

Keywords:
Methotrexate, Neurotoxicity, Leukoencephalopathy

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Neuropsychiatry

Genetic and clinical characteristics in a group of Romanian patients with autism spectrum disorders

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Objective: Autism spectrum disorders (ASDs) are severe neurodevelopmental disorders characterized by complex genetic architecture and clinical heterogeneity. The combined strategy of genomic profiling by chromosomal microarrays and targeted testing for monogenic defects led to higher genetic diagnostic yield.
We report the results of array-based genomic comparative hybridization (array-CGH) and methylation specific multiplex ligation-dependent probe amplification (MS-MLPA) testing, in a group of 106 ASDs patients.

Methods: 106 children (78 males, 28 females) with ASDs as the main phenotypic feature, were included in this study. The clinical evaluation included neurological, psychiatric, and psychological evaluations completed with specific investigations (EEG, neuroimaging studies, biological tests). All patients were investigated with array-CGH; MS-MLPA was used in male patients to assess for the methylation pattern of FMR1 and AFF2 genes.

Results: Most children had a complex phenotype which included, beside autism, intellectual disability (149 children), dysmorphic features (130 cases), muscle hypotonia (119 cases), epilepsy (16 patients). Eighteen pathogenic and 40 likely pathogenic CNVs were detected; the pathogenic variants varied in size from 28 Kb to 16.8 Mb. Many of these CNVs involve well-described syndromic regions, such as deletions of 3q13.31, 2q23.1, 11q24, and duplications of 1q21.1, 22q11.2, 17p11.2). Two samples had an abnormal methylation status of FMR1 gene indicative of a full mutation for Fragile X syndrome.

Conclusions: New phenotypic data and molecular characterization of rare / unreported genomic variants may contribute to the delineation of rare clinical entities associated with autism. Our study emphasizes the utility of an integrated genetic and clinical evaluation strategy in ASDs patients, especially in cases with a complex phenotype.

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Keywords:
autism, phenotype, genomic variants

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Update on the TANDem project: Empowering families to identify, measure and manage Tuberous Sclerosis Complex Associated Neuropsychiatric Disorders (TAND)

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Objective: Tuberous sclerosis complex (TSC) is a multi-system genetic disorder with many TSC-associated neuropsychiatric disorders (TAND) that significantly impact the quality of life of individuals with TSC and their caregivers. The clinician-administered TAND checklist (TAND-L) has improved assessment for TAND, but many individuals and families worldwide have difficulty accessing appropriate clinicians, and TAND remains under-identified and under-treated. The TANDem project was set up to 1) develop a self-completed, quantified version of the TAND checklist (TAND-SQ) implemented and validated in a smartphone app, 2) generate consensus guidelines for identification and management of TAND, and 3) establish a global TAND consortium. We present updates on the TAND-SQ and development of consensus clinical guidelines for TAND.

Methods: The TAND-L checklist was adapted to a self-completed checklist and Likert scales added to quantify the severity of concerns. Working groups composed of clinicians and family stakeholders reviewed targeted literature and current clinical practices to create consensus summary statements and recommendations for each TAND cluster. These were reviewed, rated, and refined by all stakeholders through an iterative consensus-building process.
RESULTS: We present the TAND-SQ that will be implemented and validated as a smartphone app to identify and monitor TAND. We also present the consensus summary statements and recommendations for different TAND clusters.

Results: We present the TAND-SQ that will be implemented and validated as a smartphone app to identify and monitor TAND. We also present the consensus summary statements and recommendations for different TAND clusters.

Conclusions: The TANDem project will empower the worldwide TSC community through an easily accessible digital solution to identify and manage TAND and improve quality of life of those with TSC and their caregivers. TANDem provides an example for other genetic disorders with complex neuropsychiatric profiles.

Keywords:
TAND, TANDem, TSC, digital, app

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Neuropsychiatry

Tourette syndrome (TS) as a risk factor for Incident interictal epileptiform discharges (IEDs) in children with ADHD

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Objective: We studied whether TS comorbidity influenced the IEDs occurrence at the time of ADHD assessment. In addition, we studied whether IEDs and TS influenced initial use of methylphenidate (MPH) and epileptic seizures (SZ) risk.

Methods: Method: Over a period of 6 years 505 children diagnosed with ADHD, age 5-14 years, performed routine awake EEG at ADHD assessment. The children were divided into two groups according to confirmed or not confirmed diagnosis of TS. EEG findings were coded as either EEG with IEDs or without IEDs. Groups of patients with and without TS were compared. ADHD IV rating scale score was used to assess effectiveness of treatment. At least one control EEG was done on children with IEDs during at least five years (5-10 y,) follow-up. Measure outcomes: TS occurrence, IEDs occurrence, MPH use, SZ risk.

Results: Among 505 children, 31 (6.1%) cases were diagnosed with TS. IEDs occur more often in children diagnosed with both ADHD and TS (5, 16.1%), than in ADHD children without TS (22, 4,6%).
In the ADHD-TS group, 4 (80%) children were treated with MPH with positive response in reducing of ADHD symptoms in 3 (75%). There was not statistic significant difference in using of MPH between the groups. At 5 years' follow-up, none of the patients with IEDs developed epilepsy.

Conclusions: IEDs occur more often in children with ADHD and TS comorbidity. The groups with and without TS had similar initial use, and positive response to MPH. Temporarily occurrence of IEDs does not increase SZ risk during 5 years follow up.

Keywords:
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Neuropsychiatry

Suggestive Seizure Induction technique in a pediatric PNES population related to neurocognitive and psychological profile: a pilot study.

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Objective: To investigate seizures induction techniques response in a pediatric population affected by psychogenic non epileptic seizures (PNES) and the relationship between neurocognitive and psychological profiles.

Methods: We recruited patients referred to our Unit who received a diagnosis of clinically established PNES in the last year. Enrolled patients underwent video-EEG recording that included a seizures induction standardized protocol:bitemporal compression, verbal suggestion, diapason stimulation,saline buffer,hyperpnea and intermittent light stimulation (ILS).Patients also carried out neuropsychiatric evaluation.

Results: The sample consisted of 12 patients (9 females and 3 males) aged between 12 and 17 years old (mean 15.08).Seizure phenotype was mostly generalized tonic-clonic seizures with loss of consciousness (7/12 patients, 58,3%).7 patients (GROUP A, 58.3%) presented seizures during induction tests and seizures were inducted by two techniques in three of them. In particular,bitemporal compression activated seizures in a patient (8.3%),verbal suggestion in 4 patients(33,3%),saline buffer in 5 patients (41,6%), ILS in 2 patients.Patients who did not present seizures (GROUP B, 41,7%) during the test reported somatic complaints in each technique (headache, paresthesias, visual impairment, chest pain). Neuropsychological tests showed a mild intellectual disability in one patient (8,3%), borderline intellectual functioning in two patients (16,6%) and 4 patients (33,3%) received diagnosis of Learning Disorder.Regarding cognitive profiles, GROUP A had a mean IQ of 85 (versus a mean of 94 in GROUP B) and lower verbal comprehension index compared to perceptual reasoning index (mean VCI=90 vs mean PRI=102,28).Psychopatological evaluation showed higher scores in the Dissociation Questionnaire in GROUP A compared to GROUP B.

Conclusions: Results showed a possible role of lower verbal ability and a higher dissociation proneness in young PNES patients who respond to suggestion techniques.

Keywords:
PNES, suggestion, dissociation, cognitive profile

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