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EMJ Neurology

Review of EAN 2023

Editor's Pick

Orthostatic Hypotension and Concomitant Paraneoplastic Syndromes: A Case Report

Interview

Exclusive interviews with Erich Schmutzhard, László Csiba, Ambra Stefani, and László Oláh

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ean congress

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Helsinki 2024

June 29 – July 2

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First Announcement

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Welcome letter

Koutsouki

Evgenia Koutsouki
Editor

Dear Readers,

Welcome to the latest edition of *EMJ Neurology*, covering highlights from the last year in the field. This edition includes an insightful review of the 9th Annual Congress of the European Academy of Neurology (EAN) which took place in Budapest, Hungary, from 1st–4th July. Among the highlights from this year's congress was the opening lecture given by Thomas Südhof, Stanford University, California, USA, who delved into conceptual understanding of synapse loss, neuroinflammation, and neuronal cell death in Alzheimer's disease.

This edition includes fascinating interviews with five important thought leaders from across the discipline. Four prominent members of EAN's teaching course sub-committee and local organising committee shared their expert perspective with EMJ. They focused on how the academy advances neurology, prioritises patient care, optimises research collaboration, and disseminates best clinical practice.

I am proud to share our Editor's Pick: a case report exploring an intriguing incidence of paraneoplastic autonomic neuropathy, despite a negative work-up of aetiology for orthostatic hypotension. The case highlights the importance of accurate identification, and the need for additional study into the association between paraneoplastic syndromes and malignancies.

Our team has handpicked a selection of highly relevant abstracts presented at EAN, which we have summarised in this journal. These explore essential topics including brain injury, trigeminal neuralgia, Parkinson's disease, and stroke.

Finally, I would like to take this opportunity to thank our Editorial Board, contributors, interviewees, and peer reviewers who made this journal possible. I hope you find this issue engaging, interesting, and insightful.

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Foreword

Dear Colleagues,

Welcome to our latest issue of *EMJ Neurology*, featuring a collection of peer-reviewed articles, insightful interviews with field experts, and a review of the 9th Annual European Academy of Neurology (EAN) Congress 2023, held in Budapest, Hungary, from 1st–4th July. The review provides a concise yet informative summary of the most significant highlights and key discussions presented throughout the congress.

The articles in this issue explore a diverse array of subjects. One notable contribution by Sharma et al. discusses a presentation of Pott's spine, a form of secondary tuberculosis with a significant prevalence in India. Alongside their case presentation, the authors analyse various manifestations of Pott's spine documented in existing literature.

My Editor's Pick is entitled 'Orthostatic Hypotension and Concomitant Paraneoplastic Syndromes: A Case Report'. Delving into the intriguing encounter with an elderly male patient, this case report unravels the presence of paraneoplastic autonomic neuropathy, despite a negative work-up for the aetiology of orthostatic hypotension, underscoring the importance of accurate identification.

Orthostatic hypotension, prevalent among the elderly, and linked to falls and trauma, necessitates further investigation when traditional treatments prove ineffective. Despite the strong association between paraneoplastic syndromes and malignancies, research remains limited, highlighting the need for future studies to offer potential insights into symptomatic management and disease progression, to ultimately enhance quality of life.

EMJ had the pleasure of speaking with prominent members from the teaching course sub-committee and local organising committee for EAN 2023, who offered a glimpse into their academic journeys, and imparted invaluable perspectives on how the EAN fosters collaboration among neurologists across Europe to enhance the quality of patient care, and reduce the burden of neurological diseases.

I would like to thank all of the individuals who have contributed to this issue of *EMJ Neurology*. Their dedication and expertise have truly elevated this issue. I sincerely hope that our esteemed readers thoroughly enjoy delving into the available content; may it not only captivate their interest, but also enrich their understanding of the ever-evolving field of neurology.

László Vécsei

Professor of Neurology and Head of the Neuroscience Research Group, Department of Neurology, University of Szeged, Hungary

EAN 2023

Review of the 9th Annual European Academy of Neurology (EAN) Congress 2023

Location:	Budapest, Hungary
Date:	1st–4th July 2023
Citation:	EMJ Neurol. 2023;11[1]:10-16. DOI/10.33590/emjneurol/10304204. https://doi.org/10.33590/emjneurol/10304204.

The 9th Annual Congress of the European Academy of Neurology (EAN) unfolded in the city of Budapest, Hungary, spanning 4 insightful days between 1st–4th July 2023. Paul Boon, Ghent University, Belgium, commenced the opening ceremony by extending a heartfelt welcome to all participants. Drawing attention to Budapest's historical significance as one of the capitals of the Austro-Hungarian dual monarchy, Boon underscored the city's allure as an additional attraction, complementing the exceptional science and education to be offered during the congress. Boon expressed gratitude to colleagues from the Hungarian Neurological Society (HNS), and all those involved in the organisation of the congress.

This year's EAN congress exhibited an impressive line-up of 460 invited speakers, accompanied by a record-breaking submission of 2,318 abstracts, as well as 2,000 eLearning materials. The scientific core of the EAN was represented by over 3,000 panel members across 28 scientific panels, showcasing a notable increase of 30% in panel members since early 2022. Additionally, the EAN is currently involved in 32 ongoing research projects and guidelines. These key figures speak to the EAN's commitment to fostering scientific advancements and collaborations.

Recognising the growing community of the EAN, Boon expressed their appreciation for the organisation's substantial membership, which stands at an impressive 45,000 members, hailing from 27 countries. Boon specifically celebrated the rapid growth of young neurologists, including residents and research fellows, acknowledging their pivotal role as the future of the field, stating: "The future is with us [...] You are our future, and we are very happy to have you here."

> **"The EAN envisions itself as the home of neurology, dedicated to advancing high-quality patient care."**

Exploring the EAN's vision, mission, and core pillars, Boon expressed that the EAN envisions itself as the home of neurology, dedicated to advancing high-quality patient care, with a mission to alleviate the burden posed by neurological diseases. The organisation's framework rests upon four fundamental pillars: science, education, membership, and advocacy. Importantly, the EAN is committed to operating within a broader network.

Drawing attention to the Brain Health Strategy, Boon underscored the fact that a significant portion of the population may not currently exhibit any neurological disorders, but could still be susceptible to future diagnoses. In an effort to consolidate their knowledge and insights on the prevention of neurological disorders, the EAN has compiled a publication, entitled 'The

"Boon highlighted the Brain Health Mission, a collaborative initiative aimed at prioritising brain health."

EAN Brain Health Strategy: One brain, one life, one approach', which Boon enthusiastically recommended for all neurologists to peruse. The publication serves as a valuable resource, encompassing diagnosis, treatment, and prevention strategies.

Boon highlighted the Brain Health Mission, a collaborative initiative aimed at prioritising brain health. As part of this mission, the inaugural Annual Brain Health Summit was successfully launched on 19th May 2023 in Vienna, Austria. The summit serves as a platform for inclusive discussions and joint efforts to elevate brain health as a key priority. Notably, the Brain Health Mission seeks to engage members of the European Parliament (EP) and patient organisations in an ongoing dialogue, aiming to influence the health policies of the European Union (EU).

Recognising the prevailing imbalance favouring larger specialities, the EAN is taking proactive steps to address this. They aim to bridge existing research gaps by undertaking a comprehensive European neurological research agenda that encompasses all sub-specialities, which will outline their top seven neurological areas of focus. These priorities encompass a wide variety of topics, including neuro-infections, neuro-immunological diseases, multiple sclerosis, headache/pain, epilepsy, Alzheimer's disease and dementias, stroke, and movement disorders.

Claudio Bassetti, University Hospital Bern, Switzerland, introduced Thomas Südhof, Stanford University, California, USA, who delivered the opening lecture, titled 'Towards a cell biology of Alzheimer's disease'. Südhof delved into conceptual questions surrounding Alzheimer's disease, and shared practical insights from a cell biology project conducted in their laboratory. They discussed puzzles within the field, and offered potential approaches to their solutions, emphasising the importance of a conceptual understanding of synapse loss, neuroinflammation, and neuronal cell death in Alzheimer's disease through a cell biology lens. Südhof also highlighted the need for a focus on better trial designs, recognising that the ultimate definitive 'experiment' lies in a positive clinical trial outcome.

Following the lecture, Boon proceeded to introduce the honorary EAN members for 2023, namely Thomas Brandt, Munich University Hospital, Germany, and Jes Olesen, University of Copenhagen, Denmark, who are renowned for their notable contributions in their respective areas of expertise.

Boon then extended an invitation to the President of the HNS, László Csiba, Debrecen University, Hungary. Csiba welcomed the attendees and provided an overview of the HNS' focus, which includes postgraduate teaching, patient information, and grants, as well as important updates on guidelines, diagnosis, and therapy advancements. Csiba described Budapest as a city of bridges, and emphasised Hungary's strategic geographical location, positioning the HNS as a bridge between East and West Europe. They expressed the HNS's desire to strengthen cooperation with the EAN, particularly in the field of education.

The EAN congress showcased the commitment to advancing the field of neurology, fostering collaborative efforts, and providing a vibrant platform for the exchange of knowledge. EMJ had the pleasure of participating in this congress, and is eagerly anticipating the next edition, scheduled to take place on 29th June–2nd July 2024 in Helsinki, Finland.

The current issue of *EMJ Neurology* provides concise summaries of pertinent press releases and abstracts presented at EAN, complemented by informative features focusing on the latest EAN guidelines, as well as the concept of neurodiversity in brain organisation. Notably, this issue also includes insightful interviews with members of the EAN teaching course sub-committee and local organising committee, including the Chair of the Local Organising committee, László Csiba. We encourage you to continue reading for further insights from this year's congress.

The Global Impact of Brain Conditions on Health Loss

NEW data from the Global Burden of Disease (GBD) study reveals that brain conditions contribute to more than 15% of all health loss. The findings from this ongoing study were presented at the 9th Annual Congress of EAN, in Budapest, Hungary.

Brain conditions contribute significantly to morbidity and mortality across the globe, and cause a high financial burden for both patients and healthcare systems. The most recent results from the GBD study highlight that in 2021, brain conditions resulted in 406 million disability-adjusted life years (DALY) of health loss. This was similar to the health loss associated with cardiovascular disease (402 million DALYs), and much higher than the health loss related to cancer (260 million DALYs). Furthermore, the GBD study revealed that diagnoses including stroke and Alzheimer's disease have increased by 98% and 178%, respectively, since 1990.

A key contributor to the disease burden of brain conditions is the ageing population, with projections that there will be >50 million people aged 65–79 years by 2050. The GBD study has been co-ordinated by the Institute for Health Metrics and Evaluation since 2007.

Epidemiologist and Client Services Engagement Manager, Shayla Smith, Institute for Health Metrics and Evaluation, University of Washington, Seattle, USA, remarked: "We expect the burden to increase in the coming years, creating new challenges for health systems, employers, patients, and families."

To date, a preliminary analysis has estimated that income loss for patients living with brain conditions is 1.22 trillion USD, and the direct healthcare cost is 1.14 trillion USD. Given these costs and concerns regarding an ageing population, Smith commented: "Data such as that derived from our study, and associated efforts, are critical to informing evidence-based planning and resource allocation."

Novel therapeutics could play a role in reducing this burden of disease. Smith discussed that improved prevention and treatment strategies for brain conditions to help reverse the anticipated increase in health loss are a goal for the future, and concluded that further research is needed to understand the best way to maintain brain health.

"In 2021, brain conditions resulted in 406 million disability-adjusted life years (DALY) of health loss."

Brain Fog Examined in Novel Study

THE FIRST digital study carried out on a large scale has examined the correlates of subjective brain fog, which causes difficulty concentrating, focusing, and accurately following conversations. This is a condition that has been reported increasingly since the COVID-19 pandemic began, and which can have a profound effect on wellbeing, productivity, and mental health, including raised levels of anxiety and depression. The condition is often intermittent, and affects a large demographic of individuals, including the young.

"The first digital study carried out on a large scale has examined the correlates of subjective brain fog."

The study, by researchers from London, UK, included 25,796 participants, all of whom described their lifestyles, comorbidities, and brain fog symptoms using a smartphone application designed to collect data remotely. Researchers studied links between 29 different variables against the self-reported presence of brain fog, using both machine learning and univariate methods. These variables included functional deficits, cognitive scores, and lifestyle factors. The Mindstep app, designed by a team of National Health Service (NHS) doctors in the UK, was used to collect data between 15th September–18th November 2022.

Research presented at the 9th Annual Congress of EAN in Budapest, Hungary, revealed that the highest overlap of brain fog comes with long COVID, migraine severity scores, and history of concussions. In the cohort, 7,280 (28.2%) reported brain fog symptoms (average age: 35.7 years; majority female), and a lower sleep quality was also associated with their comorbidities. The machine learning training accuracy was found to be 84%, with a cross-validated accuracy of 74%.

Lead author Ali Alim-Marvasti, University College London (UCL) Queen Square Institute of Neurology, UK, and Mindstep, commented: "Our conclusion is that brain fog is best defined as a difficulty to focus and concentrate, and this may affect activities of daily living, including completing paperwork, planning ahead, and mental arithmetic." They went on to describe the possibility of using machine learning in future to further explore this condition: "With further prospective data, extreme gradient-boosted algorithms show promise in identifying individuals at risk of subjective brain fog."

Whether the Weather Impacts Migraine

MIGRAINE is impacted by weather variations, according to research presented at the 9th Annual Congress of EAN by Costanza Sottani, Policlinico Gemelli Hospital, Rome, Italy. Characterised by recurrent attacks, migraine is a relapsing/remittent pleomorphic disorder that can be triggered or precipitated by numerous factors.

The aim of this study was to confirm if meteorological parameters influenced migraine attacks over a 2-year period. Sottani and colleagues collected clinical data of 1,742 patients who presented with migraine with and without aura at the emergency department (ED). The data was collected between March 2010–March 2012, and it was correlated with data from the Italian National Weather Service for the same period.

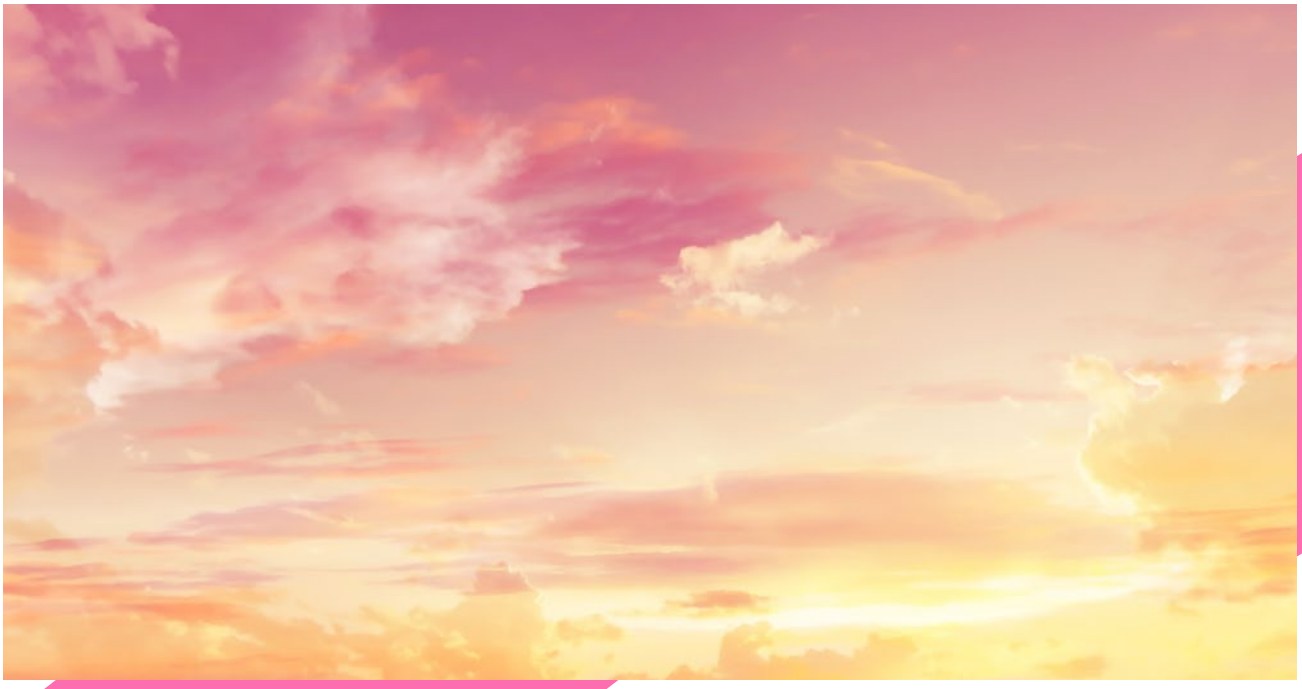
"As migraine is typically managed in a non-emergency setting, these ED visits are particularly important."

The results indicate that a subgroup of patients with migraine is very sensitive to meteorological variations, with an increase of temperature the day before presenting at the ED directly correlating with the number of admissions. Humidity level from 2 days before the migraine attack is also directly linked to admissions, and atmospheric pressure 2 days prior is also inversely correlated.

As migraine is typically managed in a non-emergency setting, these ED visits are particularly important. Sottani explained that this could mean that the attack is more severe, presents with different characteristics, or the patients' regular medication is not working.

The researchers believe that weather variation could interfere with neuronal excitability of the trigeminal-vascular system, or at least the structures linked to it, which leads to migraine attack. However, Sottani noted: "It could be possible that quantitative variations of trigger factors may enhance the response of migraineurs to environmental stimuli."

The fact that ED admissions could be correlated with weather variation for 2 years "reflects the fact that is it not about absolute values or specific degrees, but really about the sudden changes," said Sottani. While this study only focused on weather conditions, Sottani noted that it reasonable to think that global warming could have a negative impact on patients with migraine and other neurological conditions.



Artificial Intelligence Can Predict Brain Changes in Alzheimer's Disease

ARTIFICIAL intelligence (AI) is able to predict future brain changes up to 6 years after initial assessment of Alzheimer's disease through images obtained in fluorodeoxyglucose (FDG)-PET examinations, according to a study presented at the 9th Annual Congress of EAN. While previous studies have showed that AI could use baseline neuroimaging information to predict clinical symptomatic changes of neuropsychiatric disorders, data on predicting longitudinal metabolic changes in the brain are sparse.

A team from Germany and Iceland trained an algorithm on the first two FDG-PET scans through a convolutional neural network to predict the third scan in patients over 55 years with Alzheimer's disease. The algorithm, which predicted metabolic reduction, which reflects neuronal activity, "was able to anticipate future signal decline, i.e., metabolic reduction, reflecting loss of neuronal activity," stated Elena Doering, German Center for Neurodegenerative Diseases (DZNE), Göttingen, Germany. The tool also predicted significant signal decline in the second year in regions prone to Alzheimer's, including the posterior cingulate cortex, and the bilateral inferior temporal and parietal regions.

"Such an algorithm would allow physicians to read an anticipated 'future' FDG-PET brain scan as they would in their normal routine, but years in advance," stated Doering, which would help improve patient care. The team hopes their work will carry two clinical benefits: allowing for individual prediction of brain pathological changes over time, and improving early diagnosis or providing reliable prognosis. The data may also help the understanding of the natural course of the disease. Doering explained predictions over more extended periods of time may become available as databases increase. "Another potential application of our algorithm could be to predict drug efficacy within clinical trials, even without the need for longer follow-up or repeated imaging examinations," concluded Doering.

"A team from Germany and Iceland trained an algorithm on the first two FDG-PET scans through a convolutional neural network."

New EAN Guidelines: Diagnosing HyperCKaemia, Managing Amyotrophic Lateral Sclerosis, and Addressing Neurogenic Dysfunction

Authors:	Jivitesh Newoor, EMJ, London, UK

Citation:	EMJ Neurol. 2023;11[1]:17-20. DOI/10.33590/emjneurol/10305297. https://doi.org/10.33590/emjneurol/10305297.

DURING the 9th Annual Congress of the European Academy of Neurology (EAN), 1st–4th July 2023, a highly important session entitled 'Meet the New EAN Guidelines' featured the most recent guidelines developed by EAN over the past year. These guidelines, currently in the pipeline, are carefully prepared by ad hoc Task Forces following a well-established procedure.

GUIDELINES ON THE DIAGNOSTIC APPROACH TO OLIGO- OR ASYMPTOMATIC HYPERCKAEMIA

Theodoros Kyriakides, University of Nicosia, Cyprus, discussed the evolution of hyperCKaemia investigation, noting that the 2010 European Federation of Neurological Societies (EFNS) guidelines relied on muscle biopsy as the diagnostic gold standard, despite its invasiveness and susceptibility to sampling errors. Currently, their objective is to gather information in a minimally invasive, highly sensitive, specific, and cost-effective manner. Notably, genetic diagnosis has become more feasible and desirable, owing to advancements in next-generation sequencing (NGS).

Who to Investigate

When evaluating hyperCKaemia, exploring non-neuromuscular and non-myopathic causes is recommended. Clinicians should also inquire about any family history of neuromuscular disease, hyperCKaemia, or malignant hyperthermia. To ensure accurate assessment, it is advised to repeat creatine kinase (CK) measurements after at least 72 hours, preferably after a week of abstaining from exercise, medications, or other factors that could elevate CK levels. Additionally, CK should be repeated twice, with 1-month intervals after the initial measurement.

"When evaluating hyperCKaemia, exploring non-neuromuscular and non-myopathic causes is recommended."

How to Investigate

In the diagnostic approach to hyperCKaemia, several tests are recommended to investigate the underlying causes. For suspected metabolic myopathy, a screening test including dried blood spot, acyl carnitine profiling, and measurement of resting/exercise lactic acid levels is advised. Nerve conduction studies and electromyography are recommended to identify any myopathic basis of hyperCKaemia. Muscle MRI can be used to assess abnormalities, guiding genetic testing based on observed patterns.

Genetic testing is recommended in specific scenarios, such as juvenile/adult onset, CK levels exceeding three times the upper limit of normal, myopathic electromyography findings, abnormal muscle MRI scans, and females with hyperCKaemia. For cases without known family mutations or individuals with characteristic

clinical phenotypes, targeted single gene analysis may be considered for paucisymptomatic or asymptomatic hyperCKaemia. NGS is preferred over sequential targeted DNA testing. In certain cases, a muscle biopsy may be necessary for comprehensive phenotyping and exploring the transcriptome to understand the consequences and mechanisms of variants detected through NGS blood testing.

GUIDELINES ON THE MANAGEMENT OF AMYOTROPHIC LATERAL SCLEROSIS

Philippe Van Damme, Katholieke Universiteit (KU) Leuven, Belgium, highlighted the unmet care needs in amyotrophic lateral sclerosis (ALS) management, owing to the limited availability of pharmaceutical interventions. Van Damme then presented the new ALS guidelines, which replace the previous guidelines on ALS in Europe that date back to 2012.

Recommendations

Concomitant frontotemporal dementia

The presence of concomitant frontotemporal dementia in ALS can impact decision-making. Therefore, it is crucial to assess the individual's capacity to make decisions, as well as provide consent, and evaluate the severity of frontotemporal dementia and cognitive problems. It is also important to consider the individual's acceptance and ability to cope with the treatment.

Multidisciplinary care

The guidelines offer specific recommendations regarding the composition of a multidisciplinary team, primarily based on the National Institutes for Health and Care Excellence (NICE) guidelines. An optimal team should consist of various professionals, including an ALS neurologist, respiratory specialist, nursing professional, mental health professional, social worker, speech/language pathologist, dietitian, and physical therapist.

Disease-modifying treatments

The panel recommends offering lifelong riluzole to all individuals with ALS at the time of diagnosis. Dose adjustments and re-evaluation should be considered in case of adverse events. The use of cell-based treatments outside of clinical trials is not recommended until positive Phase III trial data become available. However, temporary recommendations are made for two promising new drugs, edaravone and AMX0035, while awaiting the final outcome of Phase III

studies. Tofersen is recommended as a first-line treatment for individuals with ALS caused by pathogenic mutations in superoxide dismutase 1, with the acknowledgment of potential severe adverse events.

"The panel recommends offering lifelong riluzole to all individuals with ALS at the time of diagnosis."

Nutritional support

Although there are currently no ongoing randomised controlled trials specifically focusing on nutritional interventions, the guidelines recommend early and regular discussions about the potential option of gastrostomy as the disease progresses. These discussions should consider factors such as swallowing difficulties, weight loss, respiratory function, and feeding-related challenges. The guidelines highlight the benefits of early gastrostomy placement and emphasise the risks associated with delaying the procedure.

Respiratory symptoms

Initiating non-invasive ventilation is recommended for all patients with ALS who exhibit symptoms, signs, or laboratory findings suggestive of respiratory insufficiency. However, diaphragmatic pacing is not advised as a treatment for ALS.

Symptomatic treatments

Sodium blockers, such as ranolazine, quinine sulphate, mexiletine, and carbamazepine, can be considered for managing muscle cramps. Non-pharmacological approaches and physical therapy are recommended for spasticity. Cannabinoids, baclofen, tizanidine, dantrolene, or gabapentin should be considered to treat muscle stiffness, spasticity, or increased tone. Botulinum toxin may be considered for focal spasticity cases.

When treating sialorrhoea, additional symptoms or comorbidities (such as dysphagia, dysarthria, and depression) and potential adverse events should be considered. First-line treatment options include anticholinergics.

Dextromethorphan/quinidine may be particularly suitable for individuals with emotional lability or pseudobulbar affect. In severe cases of sialorrhoea unresponsive to pharmacotherapy or poorly tolerated, botulinum toxin can be considered. Radiotherapy may be an option if other treatments have failed.

Future Updates

The updated EAN guidelines on ALS management are expected to be published by the end of 2023, and will provide a comprehensive framework for ALS management and highlight areas requiring further research. Given the rapidly evolving treatment landscape and the evaluation of three additional drugs by the European Medicines Agency (EMA) in the coming year, Van Damme anticipates the necessity for future updates to the guideline.

MANAGEMENT OF NEUROGENIC LOWER URINARY TRACT AND SEXUAL DYSFUNCTION FOR THE PRACTICING NEUROLOGIST

Jalesh Panicker, University College London Hospitals (UCLH), UK, explained that these guidelines aim to provide evidence-based recommendations for the management of neurogenic urinary and sexual dysfunction specifically tailored for practicing neurologists. Currently, the guidelines previously established by various societies have had limited implementation in general neurological practice.

Assessment of Bladder Symptoms

Neurologists are advised to proactively inquire about bladder symptoms and conduct a targeted physical examination during the initial evaluation of such symptoms. Urinalysis should be conducted at the initial evaluation and as needed during follow-up visits, with urine culture reserved for suspected urinary tract infections. Completing a 3-day bladder diary is recommended. Measurement of post-void residual volume should be performed using non-invasive methods. Renal function tests, including blood urea and serum creatinine levels, are advised. Annual testing is recommended for individuals at risk of upper urinary tract damage. Prostate cancer screening may be offered to males over 50 years old. Urodynamics testing is not recommended initially, but should be considered for individuals at high-risk or those with atypical symptoms. Referral to specialists

is warranted for patients at risk of upper urinary tract damage, suspicion of concurrent primary urological pathology, poor treatment response, or significant side effects from first-line bladder symptom treatments.

Treatment of Bladder Symptoms

Neurologists should provide guidance on fluid intake and offer bladder retraining for individuals with urinary urgency and spontaneous voiding. Advice on pelvic floor exercises should be suggested to those experiencing urinary urgency and/or stress incontinence. Appliances can be offered to improve continence in select individuals. For individuals who do not respond well or cannot tolerate other treatments, tibial nerve stimulation may be offered, whilst taking patient preference into consideration. The benefits and potential risks and burdens of these interventions should be discussed.

Intermittent catheterisation should be offered as the first-line therapy to individuals unable to empty their bladder. In cases where long-term indwelling urinary bladder drainage is unavoidable, suprapubic catheter drainage is preferred over urethral catheterisation. Routine antibiotic prophylaxis is not recommended for catheter users. Symptomatic urinary tract infections in catheter users should be treated with antibiotics, guided by urine culture/sensitivity. Antibiotics are not routinely recommended to treat asymptomatic bacteriuria, except in specific circumstances. Antimuscarinic drugs should be offered to individuals experiencing urinary storage (overactive bladder) symptoms, and β3 receptor agonists may also be considered for such symptoms. However, there is insufficient evidence to recommend the use of cholinergic drugs to promote bladder emptying in individuals with detrusor underactivity. Desmopressin may be offered to those experiencing nocturia or nocturnal polyuria that significantly affects their quality of life.

Assessment of Sexual Symptoms

Neurologists should actively inquire about sexual problems and conduct targeted physical examinations during regular assessments. Screening laboratory tests, such as for vascular risk factors in males with erectile dysfunction, should be performed when clinically appropriate. Routine measurement of testosterone is not recommended unless hypogonadism is suspected. Instrumental diagnostic evaluations, such as pelvic neurophysiology and MRI, are not routinely needed for initial workup but may be considered in specific cases. Referral to specialists is advised for patients with specific concerns or conditions that impact sexual function.

Next Steps

Panicker emphasised the importance of neurologists managing symptoms and recognising when specialist referral is needed. While the guidelines do not encompass intricate assessments, they provide guidance on history-taking, basic bedside assessments, and the use of first-line oral agents, which are within the scope of practice for neurologists. The next steps involve the steering committee reviewing outcomes, making necessary modifications, and developing management algorithms, which will then be submitted for publication by the Guideline Production Group.

CONCLUSION

The newly introduced EAN guidelines, developed with rigorous methodologies, emphasise the importance of accurate assessments, personalised approaches, and the involvement of specialised teams to enhance decision-making and improve patient care. The guidelines also highlight the need for future updates and further research. ●

Neurodiversity in Brain Organisation

Authors: Evgenia Koutsouki, EMJ, London, UK

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IN A HIGHLY engaging session during the European Academy of Neurology (EAN) Congress 2023, discussing neurodiversity in brain organisation, Annakarina Mundorf, Medical School Hamburg, Germany, spoke about the role of laterality in neurological diseases, while Sebastian Ocklenburg, Medical School Hamburg, Germany, discussed asymmetries in clinical and non-clinical populations.

HEMISPHERIC ASYMMETRIES

Mundorf explained that it is widely accepted that, in most individuals, the left hemisphere is dominant for language processing and speech, and the right hemisphere is dominant for visuospatial functions. These asymmetries are reflected in the body as the hemispheres control the contralateral side of the body; therefore, damage of the left side leads to impairment of the right side of the body and vice versa. These inherent differences between hemispheres pose one question: do these differences render one hemisphere more vulnerable to pathology, or is it the case that external factors impact one hemisphere more, leading to stronger impairment of one hemisphere?

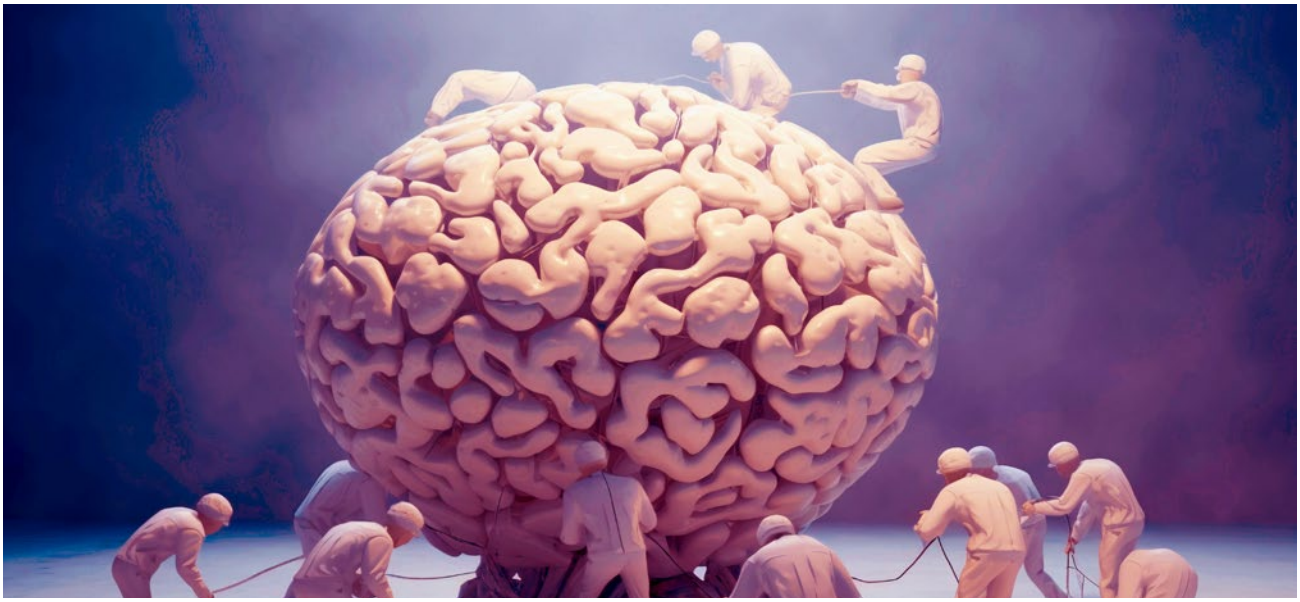
> **"In most individuals, the left hemisphere is dominant for language processing and speech."**

LATERALITY IN NEUROLOGICAL DISEASES

Studies have shown that in Alzheimer's disease (AD), the side of greater neurodegeneration and amyloid-β pathology always correlates with either poor verbal memory language impairment or visuospatial deficits. According to a recent study, no difference is shown in handedness. Even though earlier and faster grey matter atrophy and greater loss of neuronal connections are observed in the left hemisphere, there is no overall direction of asymmetry observed for asymmetric reductions in glucose metabolism, accelerated asymmetric cortical thinning, and asymmetric distribution of amyloid-β pathology. Studies in animal models of AD have demonstrated asymmetrical accumulation of fibrillar plaque burden and asymmetrical atrophy, predominantly associated with the right hemisphere.

Parkinson's disease also demonstrates laterality with unilateral motor symptom onset, such as asymmetry in arm swing before clinical diagnosis. Cognitive symptoms correspond to the side of symptom onset. Interestingly, more symptoms (and of higher severity) are observed on the side of dominant hand. In the brain there is loss of dopaminergic neurons contralateral to motor symptom onset and asymmetric distribution of α-synuclein aggregates. Studies in animal models have shown that symptoms are induced via right-sided lesions and findings are in line with the humans.

The evidence in multiple sclerosis is less clear; there is a unilateral limp weakness at onset in some, but not all cases, and no difference in handedness. Aerobic performance and metabolic asymmetries between limbs and inflammation of the optic nerve in one eye are observed, and there is asymmetric distribution of lesions early in disease with no indication of one particular hemisphere being affected. Grey matter loss is asymmetric, with loss predominantly in the left hemisphere, which is expected given that most people are right-handed. One animal model study



demonstrated reduced lateralisation of brain activation in motor areas compared to baseline.

In amyotrophic lateral sclerosis, there is unilateral limb weakness at onset in the dominant limb, motor symptoms get worse during progression of symptoms on side of onset, and there is concordance of side of onset and handedness in upper limb onset. However, there is no difference in handedness compared with the general population. Grey matter loss in contralateral hemisphere of side of symptom onset is observed in the brain. No animal models have investigated laterality yet.

CLINICAL IMPLICATIONS

For these neurological disorders, the side of symptom onset is often predictive of symptoms and severity, and reflects neurodegeneration in contralateral hemisphere, which is frequently left-sided. It is important to consider inherent asymmetries in lymphatic flow or unilateral dysfunction, as these could contribute to asymmetric disease pathogenesis.

Mundorf explained that it could be helpful during clinical examination to ask the patient about their dominant hand or limb preference, as this might give important information on symptom severity and the form of the cognitive impairments that would be expected. This could also help advance understanding of altered asymmetries in neurological diseases.

Going back to the question posed at the beginning, Mundorf explained that the hemispheric vulnerability theory is supported by genetic and epigenetic variations associated with asymmetry and disease, as well as by inherent neurochemical asymmetries and asymmetrical protein accumulation. The asymmetric onset of pathology is supported by the asymmetrical vagal nerve gut–brain path, where one hemisphere would be reached first. Overall, there is little research to help answer the question.

In their concluding remarks, Mundorf emphasised that separating the hemispheres in genetic, transcriptomic, imaging, and cell staining studies is important, as grouping tissue from both hemispheres may mask or dilute hemisphere-specific results. Mundorf explained that laterality matters, with the side of onset often correlating with hand and limb preferences, and is often predictive of the symptoms to be expected and symptom severity. The side of the symptom onset reflects neurodegeneration in contralateral hemisphere and is frequently left-sided.

AMYGDALA ASYMMETRIES IN CLINICAL AND NON-CLINICAL POPULATIONS

Introducing the structure and function of the amygdala, Ocklenburg explained that when it comes to fear processing in the brain, the most relevant activity is detected in the amygdala with an asymmetry in activity detected between the two brain hemispheres.

The amygdala is a core structure in the neuronal network that underlies emotional processing, and it is important in the evaluation and integration of sensory information, assigning emotional value to sensory information. This means that, for example, looking at a snake on a phone screen is not as fear-inducing as seeing a snake in the wild. The amygdala is frequently investigated in patients with relation to psychiatric disorders but also neurological disorders.

Ocklenburg explained that the amygdala consist of groups of distinct nuclei (13–15 depending on how they are characterised), grouped in three larger subdivisions: the basolateral nuclei, which are the input layer of the amygdala where the sensory information gets transferred in the amygdala; the cortical-like nuclei, which are structurally closer to the cortex; and the centromedial nuclei, which are the output layer of the amygdala, where information processed in the amygdala gets transferred to other brain regions. The two brain hemispheres are not equivalent functionally; in fact, many brain regions show hemispheric asymmetries, in parameters such as cortical thickness and surface area. For many higher cognitive functions, one hemisphere is faster and more accurate than the other in most of the population.

Studies indicate that the basolateral nuclei, specifically the lateral nucleus, show a rightward asymmetry and the rest of the amygdala are non-asymmetric. The lateral nucleus receives and integrates sensory inputs from the thalamus and the cortex and attaches emotional significance to sensory stimuli.

Ocklenburg went to explain prevailing models of how emotions might be organised in the brain, and went through a study that their group performed, demonstrating that the right amygdala dominates pain processing as well as fear processing. Ocklenburg explained that for conscious processing where a stimulus is given over time, the left amygdala seems to dominate, whereas for unconscious processing with short stimulus presentation, there is a right hemisphere dominance.

Based on these findings, Ocklenburg's group came up with the TEP model, interpreting hemispheric asymmetries in the amygdala: Temporal dynamics, meaning that there is left amygdala dominance for sustained stimuli and right amygdala processes for masked presentation; Emotional valence based on animal research pointing towards an important role of right amygdala in fear processing (but less important than previously thought); and Perceptual properties, meaning there is a leftward dominance for language stimuli and rightward dominance for pictorial stimuli.

"Grouping tissue from both hemispheres may mask or dilute hemisphere-specific results."

CLINICAL ASPECTS

A meta-analysis of several studies demonstrated a 5.2% reduction in amygdala volume on the left in patients with major depressive disorder, and a 7.4% reduction on the right showing greater degeneration in the right and a shift toward the left.

In neurodegenerative disorders, findings have shown that in Parkinson's disease there is a loss of dopaminergic neurons in the substantia nigra, and in AD there is an asymmetric neurodegeneration of subcortical structure. Shape asymmetries in the amygdala are predictive for disease progression, showing increase asymmetry with advanced disease stage, which reflects unilateral neurodegeneration stronger in AD than mild cognitive impairment. Neurogenetic studies have shown that genes that are functionally associated with AD had an influence on structural asymmetries in the amygdala showing that biological underpinnings of AD and amygdala asymmetry interact.

In their concluding remarks, Ocklenburg emphasised the importance of improving study design to disentangle alterations found in patients, which will help in unravelling neuronal implications and advance treatment options. ●

Focal Onset Seizures: New Treatment Options in The Clinical Practice

This symposium took place on 1st July 2023 as part of the 9th Congress of the European Academy of Neurology (EAN) in Budapest, Hungary

Chairpeople:	Bernhard J. Steinhoff[1]
Speakers:	Bernhard J. Steinhoff,[1] Mar Carreño[2] 1. Kork Epilepsy Center, Kehl, Germany 2. Hospital Clínic and Instituto Clavel, Barcelona, Spain
Disclosure:	Carreño is a speaker for GW Pharmaceuticals, Angelini Pharma, Eisai, and Neuraxpharm; received a research grant from Eisai; and is on advisory boards for Biocodex, UCB, Angelini Pharma, and Neuraxpharm. Steinhoff reports advisory and consulting honoraria from Angelini, Jazz/GW Pharmaceuticals, Precisis, and UCB; speaker's honoraria from Al Jazeera, Angelini, Bial, Desitin, Eisai, Jazz/GW Pharmaceuticals, Medscape, Teva Pharmaceuticals, UCB, and Zogenix; and research support from Eisai, Janssen-Cilag, Jazz/GW Pharmaceuticals, SK Life Sciences, UCB, Zogenix, Dr. Anneliese-Brinkmann Stiftung, and the European Union (EU).
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Meeting Summary

This symposium took place during the 2023 Congress of the European Academy of Neurology (EAN). Mar Carreño, Director, Epilepsy Unit, Hospital Clínic and Instituto Clavel, Barcelona, Spain, presented the definition of drug-resistant epilepsy (DRE), and stressed that uncontrolled epilepsy does not necessarily indicate DRE. Before a diagnosis of DRE is made in a patient not responding to medication, questions should be asked regarding the initial epilepsy diagnosis. Carreño discussed paroxysmal events that may mimic epilepsy, and presented three cases of misdiagnosed DRE that were subsequently correctly identified as cardiac syncope, a psychogenic event, and use of inappropriate medication in a patient with generalised epilepsy. The second part of Carreño's presentation focused on patients with confirmed DRE. They outlined the complications of DRE, including sudden unexpected death in epilepsy (SUDEP), which should be discussed with the patient. Carreño finished their lecture with a discussion of comorbid conditions, including neuropsychiatric comorbidities,

which affect one in three patients with epilepsy. Bernhard J. Steinhoff, Medical Director, Kork Epilepsy Center, Kehl, Germany, then discussed the clinical approach to patients with DRE, including treatment options, the range of anti-seizure medications (ASM), and the reasons for failure of first-line treatment, noting that the probability of achieving seizure freedom decreases with each failed ASM. Steinhoff explored the options of substitution monotherapy or combination therapy after failure of the first ASM, before describing cenobamate (CNB) add-on therapy. A randomised, placebo-controlled, dose-response trial showed that adjunctive CNB reduced focal (partial)-onset seizure frequency in a dose-related fashion. Several papers have been published providing real-world evidence to show that adjunctive CNB therapy is associated with improved seizure outcomes, and that the number of concomitant ASMs could be reduced. The symposium concluded with a question and answer session.

A Spectrum of Uncontrolled Epilepsies

Mar Carreño

Definition of Drug-Resistant Epilepsy

Carreño began by discussing the spectrum of uncontrolled epilepsies. They stressed that uncontrolled epilepsy does not necessarily indicate DRE, and noted that this is important in ensuring that the correct treatment is offered. According to the International League Against Epilepsy (ILAE), patients are considered to have DRE if they are not seizure free after administration of two appropriate ASMs as sequential monotherapies or as combination therapy.[1]

Sustained seizure freedom is defined as freedom from seizures for at least three-times the longest inter-seizure interval before medical intervention (determined for seizures occurring in the previous year), or 12 months, whichever is longer.[1] If duration of seizure freedom is <12 months, treatment outcomes should be classified as undetermined. If the patient has another seizure before the end of the 12-month period, the treatment is considered failed, even though the seizure frequency has reduced compared with baseline.[1]

Checking the Initial Diagnosis of Epilepsy

Before a diagnosis of DRE is made in a patient not responding to medication, Carreño suggested, based on their own experience, that the following questions should be asked regarding the initial diagnosis of epilepsy: is it a seizure or another type of paroxysmal event?; is it really the first seizure, or have other seizures occurred previously that went unnoticed? (this situation is very common with absence seizures and myoclonic seizures); is it an acute symptomatic seizure or an unprovoked seizure?; what is the risk of recurrence?; and, in cases where a diagnosis of epilepsy is highly likely, what type of epilepsy is it? This will determine the type of treatment required.

Carreño has observed in their own clinical practice that a number of paroxysmal events may mimic epilepsy. These include neurological conditions such as migraine (particularly migraine with aura), transient global amnesia, movement disorders (paroxysmal dystonia), parasomnias, and metabolic disturbances. In clinical practice, Carreño has found that the conditions that most frequently mimic epilepsy are psychogenic seizures and syncope.

As physicians rarely observe first seizures, the diagnostic process should include careful history-taking[2] with a reliable witness, especially if the patient reports loss of consciousness. If the patient is experiencing repeated episodes, it is important to establish if there are stereotypical features of epilepsy. Potential triggers should be identified, as these may be different in cases of syncope, for example. Physicians should check for signs and symptoms suggestive of epilepsy, including premonitory symptoms, aura, postictal confusion, drowsiness, headache, or myalgia. Home video recordings should be obtained when possible and reviewed. Postictal and interictal investigations, such as electroencephalogram

(EEG) and neuroimaging tests, should also be performed. Video EEG monitoring may be required.

Case of Cardiac Syncope

Carreño discussed the case of a 72-year-old female referred to Carreño's centre with DRE. The patient's seizures were classified as complex partial seizures, with oral automatisms and secondary generalisation causing repeated falls and several fractures. They underwent video monitoring, which revealed shallow breathing, loss of awareness, neck extension with open eyes, stiffness of the right arm, and movements of the mouth. The patient did not respond to treatment with carbamazepine (CBZ) and levetiracetam (LEV).

An EEG/ECG recorded during the episode demonstrated bradycardia followed by asystole. During asystole, the EEG showed a generalised flattening relating to hypoperfusion with muscle artefacts due to tonic extension of the body. The patient was discharged with a pacemaker, and antiepileptic drugs were discontinued. The patient did not have DRE or epilepsy.

Case of a Psychogenic Event

Carreño presented a second case of a male undergoing invasive monitoring with subdural electrodes. They had a partial seizure with head and eye movements and sustained deviation to the left, followed by deviation of the trunk, stiffening, and jerking of the left arm and face. The aetiology of the seizure was right frontal cortical dysplasia. The patient underwent surgery and was subsequently seizure free for 6 months.

After 6 months, the patient presented to the emergency department with recurrent seizures, despite compliance with medication. Monitoring demonstrated irregular jerking of the head, and head and trunk deviation to the left with preservation of consciousness. An EEG showed no change, suggesting a psychogenic event in a patient with prior epilepsy.

Case of Inappropriate Medication

Another potential reason for the mistaken diagnosis of DRE is inappropriate use of medication. A third case was presented, describing a 23-year-old female with seizure onset at 10 years of age. The patient reported head jerks, head deviation to the right, and generalised jerking. In addition, the patient had seizures with brief loss of awareness several times a week. An EEG had been performed in another centre, which showed left frontocentral focal epileptiform activity. Left frontocentral epilepsy was suspected, and the patient was referred to Carreño for presurgical evaluation. The patient was resistant to CBZ, oxcarbazepine, gabapentin, and lacosamide (LCM). The patient was admitted for video EEG, which showed interictal generalised interictal discharges.

The recorded seizure consisted of jerks and eye deviation to the left (rather than the right, as the patient had claimed), left face and arm jerks, and a generalised tonic phase followed by generalised clonic jerking. The corresponding EEG was generalised from the onset, and the patient was diagnosed with juvenile myoclonic epilepsy (JME). The patient had primarily been receiving sodium-channel blockers (SCB), which may worsen seizures in patients with JME. It was noted that focal features may be seen in seizures and EEG of patients with generalised epilepsies.

Seizure Aggravation by Use of Incorrect Anti-Seizure Medications

Certain drugs, especially SCBs such as CBZ, can both aggravate and induce new seizure types in absence epilepsy, JME, and other genetic generalised epilepsies.[3] In other epilepsies, CBZ may aggravate myoclonic, atonic, or atypical absence seizures. CBZ often causes new or more severe generalised paroxysmal abnormalities on an EEG, and this may correlate with seizure aggravation.[3]

Vigabatrin may aggravate absence seizures in childhood absence epilepsy, and may exacerbate or induce myoclonic seizures in myoclonic epilepsies.[3] Lamotrigine (LTG) may aggravate myoclonic seizures, while gabapentin may exacerbate absence epilepsy and myoclonic seizures.[3]

Importance of a Correct Diagnosis

A false positive diagnosis of DRE can have severe psychological and socioeconomic consequences

for the patient, including unnecessary driving restrictions and employment difficulties.[4] Patients may experience iatrogenic harm due to inadequate intake of ASMs. In addition, some life threatening conditions may be missed, including cardiac syncope for example.

Complications of Drug-Resistant Epilepsy

The second part of Carreño's presentation focused on patients with confirmed DRE. They pointed out that patients with DRE have seizures and numerous complications, which pose a significant healthcare challenge. Patients are at risk of injury and premature mortality.[5] The majority of deaths are epilepsy-related, and 40% are due to SUDEP.[6]

Sudden Unexpected Death in Epilepsy

SUDEP is 40-times more likely in patients with ongoing seizures than in those who are seizure free,[7] and is the most common cause of premature death among individuals with epilepsy.[8,9] Although the precise cause of SUDEP remains unknown, it is thought to include a central mechanism involving cardiac and respiratory dysfunction after a generalised tonic-clonic seizure (GTCS), and a brainstem mechanism involving adenosine and serotonin.[8] Consistent risk factors include poor seizure control; frequent GTCS, especially at night; and long-standing epilepsy.[9] Deaths are usually nocturnal and unwitnessed.[10]

In Carreño's experience, the most effective strategy for prevention of SUDEP is complete seizure control, but if the patient's epilepsy is uncontrolled, treatment with new ASMs should be attempted. They added that seizure precipitants should be avoided, and adherence to chronic treatment should be encouraged. Devices are recommended to detect and alert caregivers about the occurrence of nocturnal GTCS, as adequate supervision and stimulation may decrease the incidence of SUDEP.[11]

Comorbid Conditions

Comorbid conditions are more common in patients with epilepsy than in the general population.[12] Common comorbidities include cerebrovascular accidents, dementia, gastrointestinal and digestive disorders, migraine, musculoskeletal system disorders, depression, and anxiety.[12]

Neuropsychiatric Comorbidities

Neuropsychiatric comorbidities affect one in three patients with epilepsy.[13] Simple and standardised screening tools are available to diagnose neuropsychiatric comorbidities in patients with epilepsy, for example, the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E).[14] Neuropsychiatric comorbidities often complicate the diagnostic process, as depression, for example, may mimic seizures or adverse events caused by ASMs.[15] Neuropsychiatric comorbidities also influence the response to treatment.[16] The severity of depression correlates with a lower odds of achieving seizure remission.[12] Psychiatric disease is associated with premature mortality, increased risks of substance or alcohol abuse, increased risks of injury, and increased rates of suicide and SUDEP.[17]

Carreño recommended that in patients with psychiatric conditions, ASMs with potential psychiatric side effects should be avoided. They advised that when discontinuing mood stabilising agents, patients should be warned about psychiatric symptoms. In their experience, antidepressant and antianxiety drugs should be prescribed, such as selective serotonin reuptake inhibitors, taking into account possible interactions with ASMs.

Conclusions

Uncontrolled epilepsy cannot always be classified as DRE. In difficult cases, physicians should consider whether the diagnosis may be incorrect, or whether the patient may be receiving an inappropriate treatment. In patients with confirmed DRE, the impact of comorbid conditions should be considered. In particular, psychiatric conditions may lead to premature mortality and a reduced quality of life, and patients should be screened, treated, and referred for psychiatry assessment if current treatment is unsuccessful. At-risk patients should be made aware of the risk of SUDEP, and the importance of adhering to treatment.

The Clinical Approach

Bernhard J. Steinhoff

Treatment Options for Epilepsy

Steinhoff opened their presentation by stating that the ultimate goal of epilepsy treatment is apparent seizure freedom without any treatment-emergent adverse events. Steinhoff commented that current treatment options include lifestyle adaptation, which may be particularly difficult in adolescence; chronic ASM; epilepsy surgery; neurostimulation; and dietary therapies. Chronic ASM is the gold standard for almost all patients.

Anti-seizure Medications

The development of ASMs began in the 19th century with the first use of bromide to manage seizures.[18] Today, fourth-generation ASMs provide more options for patients, although questions remain over how these medications should be used to increase the proportion of patients achieving sustained freedom from seizures. In Steinhoff's opinion, the criteria for selecting first-line medication include the pharmacokinetics of the drug, its spectrum of efficacy, interactions with other medications, acute and long-term tolerability, and potential teratogenicity.

The SANAD II trial was designed to assess non-inferiority of LEV and zonisamide (ZNS) to LTG for the primary outcome of time to 12-month remission.[19] In the intention-to-treat analysis of time to 12-month remission versus LGT, LEV did not meet the criteria for non-inferiority but ZNS did.[19] In the per-protocol analysis, 12-month remission was superior with LTG compared with both LEV and ZNS.[19] The trial demonstrated that 12-month remission was superior with LTG compared with both LEV and ZNS in patients with focal epilepsy, indicating that LTG should remain a first-line treatment for this patient group.[19] The risk of taking ASM during pregnancy also needs to be considered, with the potential for congenital malformation following prenatal exposure.[20] The International Registry of Antiepileptic Drugs and Pregnancy (EURAP) registry showed a 10.3% rate of congenital malformations with valproic acid (VPA), and a dose-dependent risk increase among the children of females who had been exposed to ASM during pregnancy.[20] In contrast, the rate of malformations was 2.8% with LEV, with no dose-dependent risk increase.

Failure of First-Line Treatment

In Steinhoff's experience, the reasons for failure of first-line treatment include tolerability, for example, rash with LTG; irritability and sedation with LEV; and obesity, hair loss, and tremor with VPA. They said that after failure of first-line treatment, the physician should examine whether the initial diagnosis was incorrect, and the patient had instead experienced psychogenic seizures, syncope, or other paroxysmal events. In addition, Steinhoff stated that the physician should also check whether the classification of epilepsy was correct, as some ASMs may trigger, rather than prevent, seizures. For example, LTG may trigger myoclonic seizures, while CBZ, oxcarbazepine, and eslicarbazepine acetate (ESL) may trigger absence or myoclonic seizures. Steinhoff noted that adherence to medication should be checked and, in some cases, a drug with another mode of action could be tried. Another question, they added, is whether to proceed with alternative monotherapy, or with combinations of treatments.

The underlying cause of epilepsy is a major prognostic factor for recurrence.[21] An observational survey of 2,200 adult outpatients with partial epilepsy showed that seizure control (>1 year without seizure) was achieved in 82% of patients who had idiopathic generalised epilepsy, 35% of patients with symptomatic partial epilepsy, 45% with cryptogenic partial epilepsy, and 11% with partial epilepsy associated with hippocampal sclerosis.[21] In partial epilepsy, dual pathology (hippocampal sclerosis and another lesion) was associated with a low rate of freedom from seizures (3%).

Substitution Monotherapy or Combination Therapy After Failure of the First Anti-seizure Medication

Currently there are a number of ASMs that might be combined without drug interactions. According to the longitudinal observational study in people with epilepsy after failure of initial monotherapy reported by Hakeem et al.,[22] seizure outcomes were similar on substitution or combination therapy, and the type of ASM used, either alone or in combination, did not affect seizure outcome. Similarly, a prospective

observational study among children and adults with epilepsy in whom first monotherapy failed, showed that retention time, hospital admissions, days off work and off school, and quality of life did not differ between patients on monotherapy or combination therapy.[23] A further observational study also showed that the seizure remission rate and retention rate of substitution therapy were better than those of add-on therapy for patients with focal epilepsy whose first monotherapy failed.[24] The choice of substitution monotherapy or combination therapy therefore requires an individualised approach.

Achieving Seizure Freedom

Steinhoff next presented data to show that although around two-thirds of patients achieve seizure freedom with ASMs, the probability of success decreases with each failed treatment. For example, in 2000, Kwan and Brodie[25] demonstrated that among 470 previously untreated patients with newly diagnosed epilepsy, 222 (47%) became seizure free during treatment with their first ASM, and 14% became seizure free during treatment with a second or third drug. For 12 patients (3%), epilepsy was controlled with two drugs. Chen et al.[26] showed in 2018 that despite the availability of new ASMs with different modes of action, the probability of seizure freedom decreased with each subsequent ASM tried, and that more than one-third of patients have uncontrolled epilepsy.

The evidence concerning seizure freedom with add-on treatment is restricted to meta-analyses, with no direct comparative trials between the newer ASMs. A network meta-analysis of brivaracetam (BRV), CNB, ESL, LCM, and perampanel (PER) showed that all ASMs were associated with a higher responder rate than placebo, while BRV, CNB, ESL, and PER were associated with a higher rate of seizure freedom than placebo.[27] CNB ranked highest for efficacy, with a greater rate of ≥50% seizure frequency reduction than BRV, ESL, LCM, or PER.[27]

Villanueva et al.[28] investigated the number needed to treat to achieve a response or freedom from seizures among patients with DRE. The authors concluded that CNB may be the most effective ASM in all doses studied compared with third-generation ASMs, as well as the most efficient option at the daily defined dose for both 50% responder rate and seizure freedom.[28] Steinhoff noted that the study could contribute to informed decision-making regarding the selection of the most appropriate therapy for focal onset seizures (FOS) in adult patients with DRE.

Cenobamate Add-on Therapy

CNB has a dual mode of action, exerting its effects by reducing excitatory currents (mainly by inhibition of persistent sodium channels) and augmenting inactivated sodium channels.[29] It is also a positive allosteric modulator of the γ-aminobutyric acid type A-receptor at the nonbenzodiazepine binding site.[30] The long half-life of CNB permits once-daily dosing, which is beneficial for adherence.[31,32] On the other hand, the drug has a complex metabolism, and interactions with other drugs, including other ASMs, need to be considered.[32]

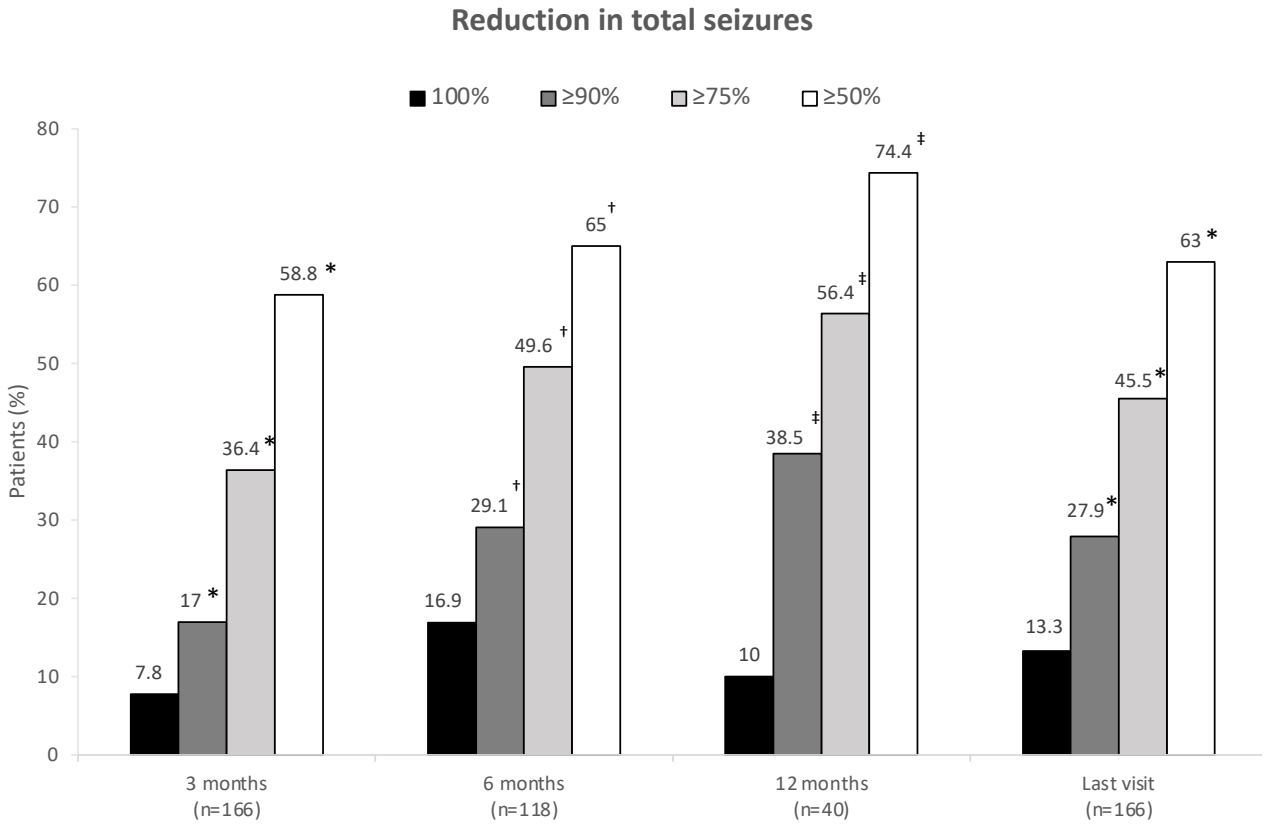
A randomised, placebo-controlled, dose-response trial in patients with uncontrolled focal seizures showed that adjunctive CNB reduced focal (partial)-onset seizure frequency in a dose-related fashion.[33] Freedom from seizures was achieved by 21% of patients in the CNB 400 mg group, 11% in the CNB 200 mg group, 4% in the CNB 100 mg group, and 1% of those on placebo.[33] Several papers have also been published presenting real-world evidence to show that adjunctive CNB is associated with improved seizure outcomes.[34-36]

Real-World Evidence with Cenobamate

A multicentre, retrospective, observational study was conducted to assess the safety and effectiveness of CNB in patients with refractory epilepsy in a real-world setting.[36] The study included 170 patients from the Early Access Programme in Spain, which enrolled patients with no other therapeutic alternative. Participants had taken an average of 12 previous ASMs, 36 patients had undergone vagus nerve stimulation therapy, and 34 had received resective surgery. Patients were taking an average of three concomitant ASMs. Mean CNB dosages/day were 176 mg, 200 mg, and 250 mg at 3, 6, and 12 months, respectively.

Results of the study confirmed the efficacy data from pivotal clinical trials (Figure 1).[36] In a post

Figure 1: Real-world data demonstrates the effectiveness of cenobamate.[36]



*n=165

†n=117

‡n=39

Proportion of patients with a reduction in the frequency of total seizures following cenobamate treatment. Reductions in seizure frequency are displayed as a 100% reduction from baseline or a ≥90%, ≥75%, or ≥50% reduction since the previous patient visit. Patients with a ≥50% reduction from the previous visit are considered responders at that timepoint.

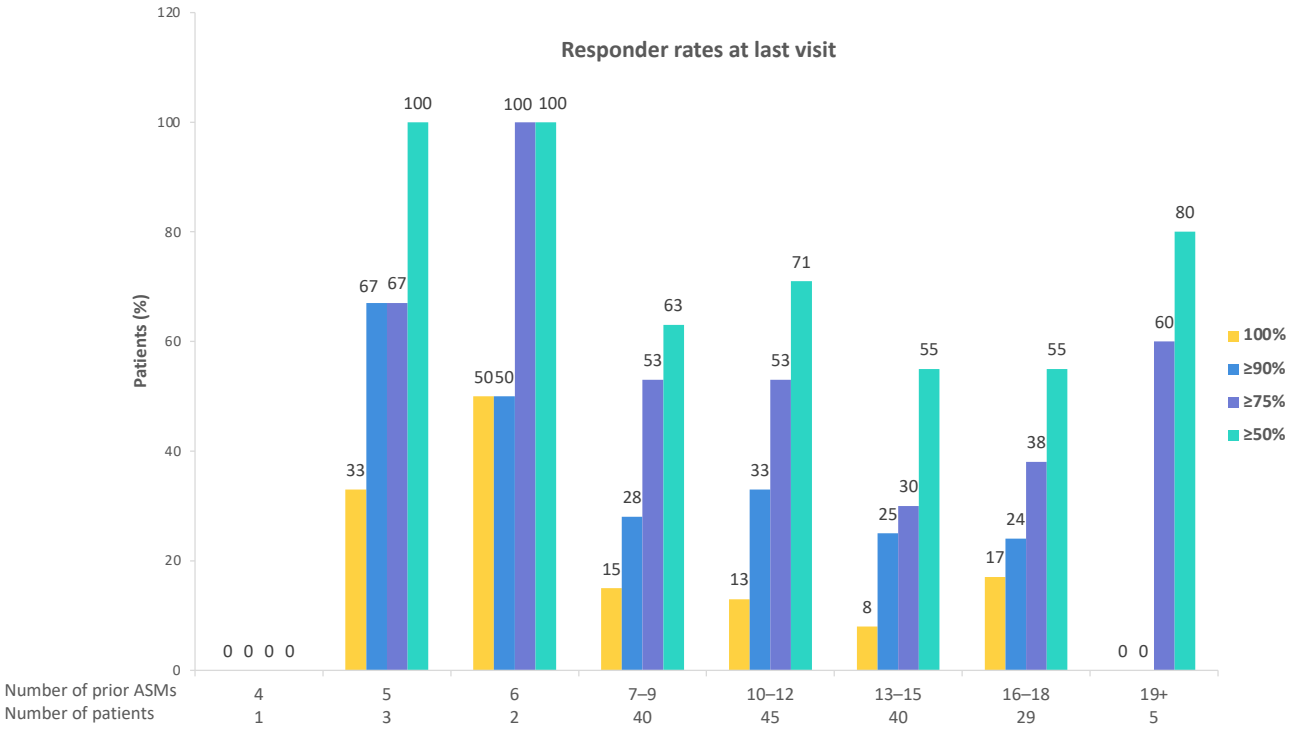
Adapted from Villanueva et al.[36]

hoc analysis, 18.1% of patients were continuously seizure free during follow-up for at least 3 months, and 19.5% of patients were continuously seizure free during follow-up for at least 6 months.

When the effectiveness of CNB was examined according to the number of previous ASMs, the high response rate in patients who had already taken at least six ASMs, which is considered absolute drug resistance, could suggest a breakthrough response in this patient profile (Figure 2). Although only a small number of patients received early treatment, the data suggest improved efficacy when CNB is initiated earlier in the course of the disease.

This real-world study also demonstrated that in patients who benefitted from CNB, there was a trend towards reduction in baseline medication (Figure 3).[36] Some 44.7% of patients reduced the number of concomitant ASMs required, with primary reasons including the efficacy of CNB, and the avoidance of pharmacodynamic side effects due to drug interactions. SCBs and clobazam were the most commonly reduced

Figure 2: Effectiveness of cenobamate by number of previous anti-seizure medications.[36]



Responder rates at last visit.

Proportion of patients with an improvement in seizure frequency at the last visit by the number of prior ASMs. Reductions in seizure frequency are displayed as a 100% reduction from baseline, or a ≥90%, ≥75%, or ≥50% reduction since the previous patient visit. Patients with a ≥50% reduction from the previous visit are considered responders at that timepoint.

Adapted from Villanueva et al.[36]

ASM: anti-seizure medication.

ASMs. CNB increases the serum concentration of the main metabolite of clobazam, which may cause side effects.

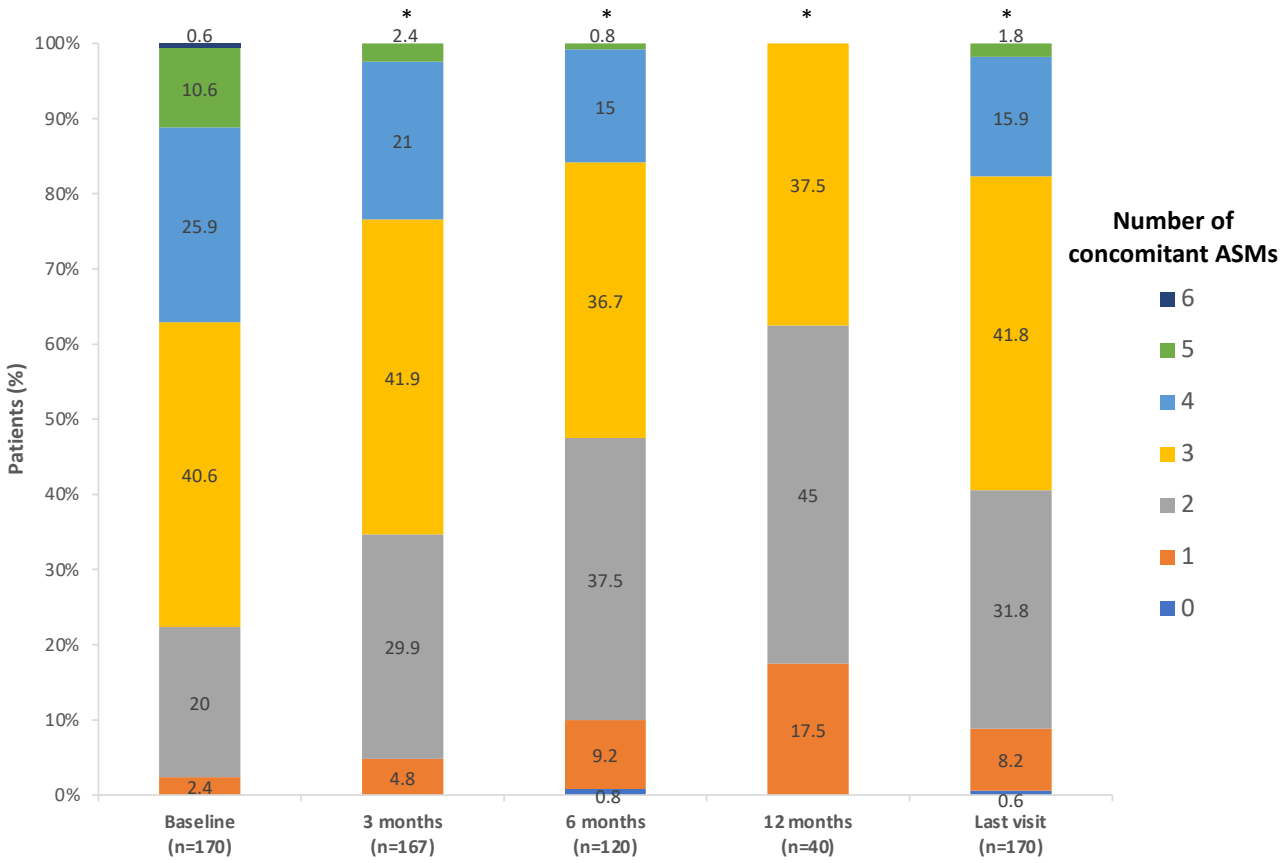
The percentage, type, and severity of adverse events in this real-world study were similar to those reported in clinical trials.[36] The main adverse events with add-on CNB were central nervous system-related, with somnolence occurring in 35.9% of patients and dizziness in 26.5%. Retention rates also reconfirmed the data from clinical trials.[36] At 12 months, the retention rate was 87%, supporting the clinical benefit of CNB in adults with uncontrolled FOS.

Case of Cenobamate Therapy

Steinhoff presented the case of a board-certified neurologist who was born in 1969, and had been involved in a car accident at 13 years of age. They had a right temporal epidural haematoma followed by a left temporal abscess, hemiparesis, aphasia, and hemianopia. The patient had impaired attention and memory, but was still able to obtain a high school diploma and graduate from university. Following the onset of epilepsy in 1994, the patient experienced drug-resistant structural FOS with focal aware acoustic and olfactory seizures, focal unaware seizures, focal to bilateral tonic-clonic seizures, and intermittent depressive episodes with suicidal ideations.

The patient demonstrated ideal adherence to medication, with a history of 11 ASM drugs: CBZ,

Figure 3: Reduction of concomitant anti-seizure medications with cenobamate.[36]



Proportion of patients receiving concomitant ASMs following cenobamate treatment.

Bars show the proportion of patients receiving 0–6 concomitant ASMs at each timepoint.

*p<0.001 versus baseline.

Adapted from Villanueva et al.[36]

ASM: anti-seizure medication.

VPA, LTG, topiramate, LEV, LCM, ZNS, phenytoin, ESL, PER, and BRV. An MRI demonstrated that the risk of resective epilepsy surgery would have been extremely high; therefore, surgery was not pursued. An interictal EEG showed intermingled spikes over the left temporal region. The patient is now receiving CNB 350 mg per day, and both citalopram and LEV have been discontinued. During an observation period of >2 years, they have had less than one focal aware acoustic seizure per month. The patient has no abnormal ECG or laboratory findings, and their quality of life has improved.

Conclusions

Steinhoff concluded by remarking that there are a number of options available today to overcome the burden of DRE. Clinical trial evidence has demonstrated that adjunctive CNB reduces seizure frequency in a dose-related fashion. In addition, real-world evidence has demonstrated that adjunctive CNB is associated with improved seizure outcomes, and a reduction in the number of concomitant ASMs.

Question and Answer Session

Bernhard Steinhoff and Mar Carreño

The symposium concluded with a question and answer session. Carreño was asked why they would prescribe citalopram or sertraline as opposed to the other selective serotonin reuptake inhibitors for the treatment of depression in patients with epilepsy. Carreño explained that these medications are well-tolerated, widely available, and effective in patients with a combined profile of anxiety and depression.

Steinhoff was asked about surveillance of patients taking CNB. They said that their laboratory measures levels of CNB and other ASMs in order to understand potential drug interactions in individual cases. Steinhoff's hospital also measures liver enzyme concentrations, although elevations are infrequent. They also perform ECGs, but noted that no cardiological problems have been found in more than 500 patients with add-on CNB.

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A Spotlight on Friedreich Ataxia: Optimising the Patient Journey from Diagnosis to Disease Management

This industry symposium took place on 1st July 2023 as part of the 9th Congress of the European Academy of Neurology (EAN) in Budapest, Hungary

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Speakers:	Mathieu Anheim,[3] Paola Giunti[4]

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Meeting Summary

This symposium was held on the first day of the European Academy of Neurology (EAN) Congress, with four main objectives: to raise awareness of Friedreich ataxia (FA) as a rare, progressive neurodegenerative disorder; to summarise the patient journey from identifying first symptoms in childhood and adolescence to reaching an accurate diagnosis; to discuss the burden of living with FA and highlight the benefit of improved communication and collaboration between members of the multidisciplinary team on reducing this burden on patients and their

caregivers; and to summarise current management options within the field of FA and provide an overview of emerging therapies and active clinical trials.

The symposium was chaired by Sylvia Boesch, a neurologist and senior staff member at the Medical University of Innsbruck, Austria, and Head of the Centre for Rare Movement Disorders, Innsbruck, Austria, who presented an overview of rare diseases in general and of FA. Mathieu Anheim, a neurologist at the Movement Disorders Unit, University Hospital of Strasbourg, France, followed with a description of the aetiology and symptomatology of FA. Lastly, Paola Giunti, a professorial research associate in the Department of Clinical and Movement Neurosciences, University College London Queen Square Institute of Neurology, Faculty of Brain Sciences, University College London, UK, explained the best approach to FA management, including a summary of clinical trials for emerging therapies in FA.

Introduction

Sylvia Boesch

Boesch explained that in the European Union (EU), a rare disease is defined as a disease that affects less than one person in 2,000. Between 6,000–8,000 different rare diseases affect an estimated 30 million people in the EU.[1] In the USA, a rare disease can be defined as a disease or condition that impacts fewer than 200,000 people.[2] Of all rare diseases, ≤5% are estimated to have approved treatments, known as 'orphan' therapies,[3] yet 3.5–5.9% of the global population (263–446 million people) are affected with a rare disease at any one time.[2]

Based on their own clinical experience, Boesch described the unmet needs in rare neurological disease as a lack of available diagnoses; relatively unavailable, and ineffective treatment; a lack of research to develop treatment; poor disease awareness; and limited financial resources.[4,5]

FA is a rare neurodegenerative disorder that affects one in 20,000–50,000 individuals in Europe, and a total of approximately 22,000 people globally.[6,7] Anheim explained that FA is the most common inherited ataxia.[8] Disease onset typically occurs in childhood or adolescence, between 5–15 years of age,[7] and the condition affects multiple body systems including the central nervous system, peripheral nervous system, musculoskeletal system, heart, and pancreas.[9]

The disorder is characterised by progressive neurological and non-neurological symptoms, including effects on ambulation, speech, swallowing, hearing, and vision, as well as cardiomyopathy and skeletal abnormalities.[10-12] Loss of ambulation and the need for a wheelchair typically occur between 25–30 years of age, leading to loss of autonomy and an increasing requirement for assistive care.[9,10,13] As FA progresses, it results in an increasing need for complex multidisciplinary care.[13]

Introducing Friedreich Ataxia: Discover the Journey to Diagnosis and the Burden of Illness

Mathieu Anheim

FA is an autosomal recessive disease caused by mutations in the *FXN* gene.[14] In most cases (96%), the mutation is a homozygous GAA triplet expansion in intron 1; triplet repeats over 66 are considered pathogenic, and the expansion number correlates with age of onset and disease severity.[10,15-18] A minority of patients (4%) carry a heterozygous GAA expansion and a point mutation on the other allele.[10] Anheim emphasised that, in their experience, *FXN* GAA triplet-repeat expansion cannot be identified through targeted gene panels or whole exome sequencing, and that specific testing for these expansions is required.

Mutations in *FXN* in FA lead to reduced levels of functional frataxin,[19] a protein involved in mitochondrial iron homeostasis and the assembly

and transfer of iron–sulfur clusters to various mitochondrial components.[8,19,20] A reduced level of frataxin results in impaired mitochondrial function and increased sensitivity to oxidative stress.[8,19] This leads to the clinical features of FA, characterised by progressive degeneration of the peripheral nervous system and central nervous system, cardiomyopathy, and ataxia. [8,9]

In Anheim's clinical experience, the first signs of FA occur in the peripheral nervous system, with the loss of dorsal root ganglia, degeneration of the posterior column of the spinal cord, and peripheral neuropathy. Anheim explained that patients tend to present with a loss of tendon reflexes and ocular symptoms.

The neurological symptoms of FA include combined ataxia, cerebellar dysarthria (muscle-related speech difficulty), absent tendon reflexes, hypopallesthesia (a decreased ability to perceive vibration), sensory neuropathy, extensor plantar reflexes, and square wave jerks (involuntary, horizontal, saccadic intrusions that interrupt eye fixation).[11,21] Anheim explained that cerebellar ataxia progressively worsens in FA, evidenced by worsening instability when closing the eyes, and an impaired heel-shin test due to hypermetria.[22] Notably, MRI of the brain shows mild to no cerebellar atrophy in FA.[21,23] Extra-neurological signs of FA include hypertrophic cardiomyopathy, scoliosis, diabetes, optic neuropathy, hearing loss, and pes cavus (abnormally high plantar longitudinal arch).[21]

Anheim noted that in their clinical experience, clumsiness and unsteadiness worsen as the condition progresses. More advanced stages are severely disabling in many activities of daily living, with increased wheelchair use, marked dysarthria, and swallowing difficulties.

Differential diagnosis of FA can be supported by electroneuromyography to identify the type of neuropathy present; the recessive ataxias can be divided into those without peripheral neuropathy, those with both sensory and motor neuropathy, and those with sensory neuropathy alone (for which FA is the prototype).[22] Anheim stressed that, in their experience, the differential diagnosis should not neglect treatable entities, such as ataxia with vitamin E deficiency, which can be treated with vitamin E supplementation; Refsum disease, which can be treated with phytanic acid; cerebrotendinous xanthomatosis, which can be treated with cholestanol; and others. In particular, Anheim highlighted that ataxia with vitamin E deficiency often mimics the clinical picture of FA.

Overall, FA is associated with a poor prognosis.[13] The mean duration of the disease is 15.0–20.0 years, and the mean age of death is 36.5 years (12.0–87.0 years).[13] The primary cause of death in patients with FA is cardiac dysfunction, most commonly from congestive heart failure or arrhythmia.[24]

Patients with FA require multidisciplinary clinical care,[25] and Anheim stressed the importance of co-ordination, collaboration, and communication between the disciplines involved. Anheim explained that spasticity can be managed with baclofen or botulinum toxin injections, neuropathic pain with gabapentin or pregabalin, urinary emergencies with oxybutynin, and cardiomyopathy with β-blockers or aldosterone antagonists. In Anheim's experience, orthopaedics is important for the management of scoliosis, and referral to cardiology, ophthalmology, audiology, and speech/physical/occupational therapy should be considered as needed.[25] Anheim also advocated assessment by dual-energy X-ray absorptiometry to detect osteoporosis, screening for fasting blood glucose and HbA1c on a yearly basis, and offering genetic counselling.[25]

Anheim emphasised the take home message that *FXN* mutations should be specifically searched for as soon as an autosomal recessive cerebellar ataxia with an FA-compatible phenotype is detected.[21] Anheim noted that this phenotype would include progressive worsening of combined ataxia arising in a young patient, with optional findings such as scoliosis, pes cavus, cardiomyopathy, lack of tendon reflexes, or bilateral extensor plantar reflexes.

The Therapeutic Landscape: Navigating Disease Management and an Outlook on Key Clinical Trials

Paola Giunti

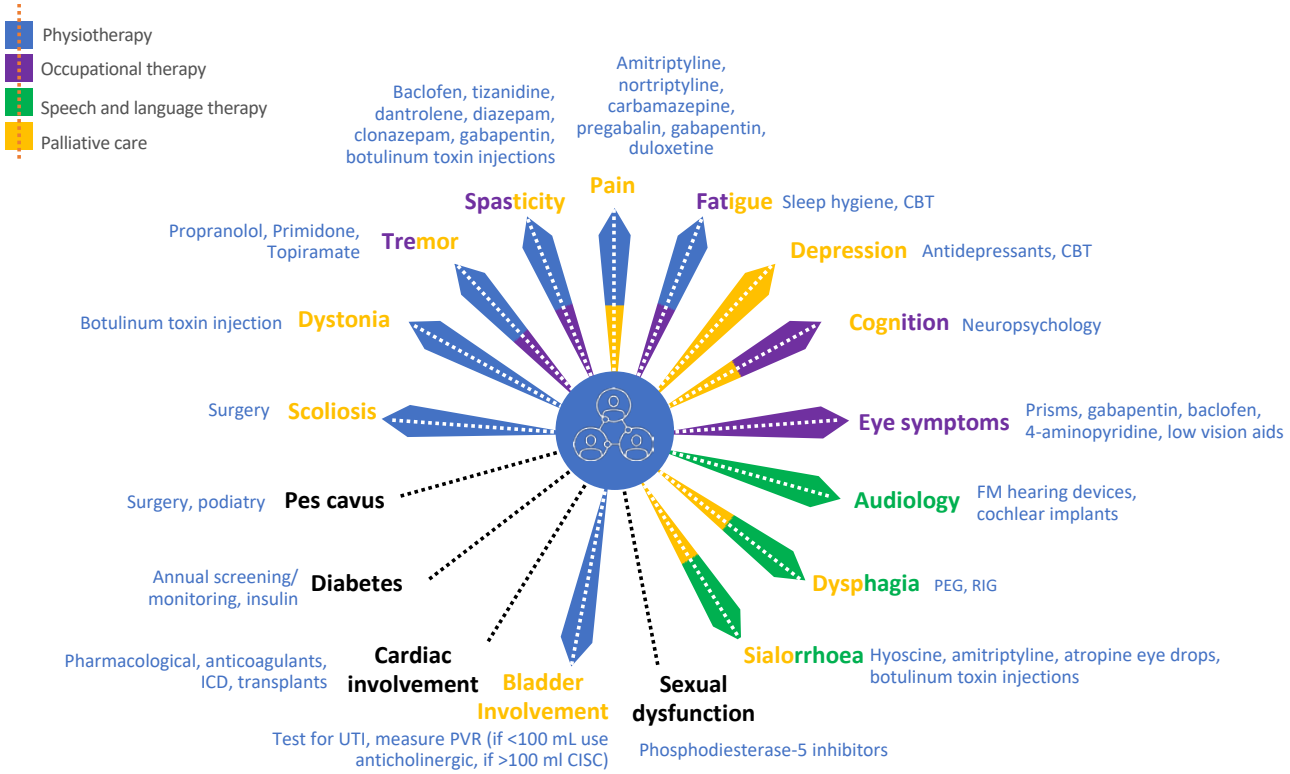
FA is a complex and multisystemic condition for which no treatment is currently available in Europe,[9] and Giunti explained that the management of FA requires a holistic approach within multidisciplinary clinics.[9]

In Giunti's experience, specialist ataxia centres provide adapted treatment and care for patients with FA.[9] These centres co-ordinate patient care, involving neuro-ophthalmologists; neuro-ear, nose, and throat specialists; cardiologists; orthopaedic surgeons; physiotherapists; speech and language therapists; occupational therapists; neuropsychiatrists; and geneticists.[9] Giunti highlighted that such clinics should also begin to deliver overall palliative care. Specialist centres can provide a holistic approach to disease management, with symptomatic treatments and patient education (Figure 1), and these sites can also be hubs for ataxia research and clinical trials.[9]

Guidelines for the best practice treatment of ataxias can be found on the Ataxia UK website,[6] and recommendations specifically for the diagnosis and management of the progressive ataxias have also been published.[26,28] Additional guidelines have been produced that focus specifically on FA.[27] Giunti highly recommended that clinicians refer to these publications.

Giunti explained that the clinical trial landscape for FA has changed considerably over the past decade, with many more trials now being conducted, mainly in Phase I or Phase II. Two trials of novel therapies in FA have recently

Figure 1: Symptom management with multidisciplinary team input.[26,27]



Adapted from de Silva et al.[26]

CBT: cognitive behavioural therapy; CISC: clean intermittent self-catheterisation; FM: frequency modulated; ICD: implantable cardioverter defibrillator; PEG: percutaneous endoscopic gastrostomy; PVR: post-void residual; RIG: radiologically inserted gastrostomy; UTI: urinary tract infection.

been completed, assessing vatiquinone and omaveloxolone, and the omaveloxolone trial has resulted in approval for marketing in the USA.[29-31] Some drugs being trialled in FA target upstream mechanisms, addressing the reduced frataxin levels through replacement or upregulation of expression, while other approaches focus on downstream mechanisms such as the effects on mitochondria.[32]

The modified Friedreich Ataxia Rating Scale (mFARS) is commonly used as a study endpoint in clinical trials. This validated tool assesses neurological function, with a higher score indicating worsened function. It measures upper and lower limb co-ordination, upright stability, and bulbar function (including strength and volume of coughing and clarity of speech).[7,33]

Vatiquinone

Giunti explained that vatiquinone (previously known as EPI-743) is an oral, selective inhibitor of 15-lipoxygenase, an enzyme that regulates energetic and oxidative stress pathways.[34,35] Vatiquinone is also thought to target NAD(P)H quinone dehydrogenase 1.[36] In addition, vatiquinone has demonstrated nuclear factor-erythroid factor 2-related factor 2-mediated neuroprotective effects in frataxin-silenced motor neurons and in neural stem cells isolated from FA mouse models, and has been shown to prevent *in vitro* ferroptosis through the inhibition of 15-lipoxygenase.[37] While vatiquinone does not target FA-specific pathways directly, it helps to improve the regulation of energy metabolism.[36]

A recent randomised, double-blind, placebo-controlled study of vatiquinone in patients with FA (MOVE-FA) was designed to assess the change in total mFARS score from baseline to Week 72 (n=123).[30,38] Secondary endpoints included the change from baseline in Friedreich Ataxia Rating Scale Activities of Daily Living (FARS-ADL), mFARS sub-scores, and the Modified Fatigue Impact Scale (MFIS).[38] The primary analysis was conducted in patients between the ages of 7–21 years, and the study design included a 24-week open label extension phase.[30]

Results from MOVE-FA demonstrated a meaningful slowing of disease symptom progression with vatiquinone versus placebo, including a difference of -0.18 in the mFARS bulbar subscore (p=0.044) and a difference of -1.26 in the mFARS upright stability subscore (p=0.021).[38] However, the study did not reach its primary endpoint, with a non-significant difference in total mFARS change from baseline of -1.61 (p=0.14). In a sensitivity analysis that excluded patients who discontinued treatment during the study (n=26), vatiquinone had a significant effect on MFIS, with difference in change from baseline of -4.73 (p=0.042). Treatment-related adverse events were generally mild to moderate in severity, and gastrointestinal symptoms were the most common. The safety profile was similar between vatiquinone and placebo groups, and also similar to other vatiquinone paediatric studies.

Omaveloxolone

Giunti reiterated that frataxin is fundamental for the activity of the mitochondrial respiratory chain, particularly Complex I, and that reduced levels of frataxin inhibit these complexes, resulting in an increase in reactive O_2 species, increased lipid peroxidation, and deregulation of mitochondrial membrane potentials in fibroblasts from FA mouse models.[39] Omaveloxolone (previously known as RTA 408) is a nuclear factor-erythroid factor 2-related factor 2 activator that prevents Complex I inhibition in FA neurons in mouse models and in fibroblasts from patients with FA, evidenced by a normalisation of NADPH levels and NADPH redox state.[39,40]

The safety and efficacy of omaveloxolone in patients 16–40 years of age with genetically confirmed FA was assessed in the MOXIe study.[29] The study was divided into three main parts:

- Part 1: a randomised, placebo-controlled, double-blind, dose-ranging, multicentre trial to determine the optimal dose of omaveloxolone and evaluate safety over 12 weeks.[40]
- Part 2: a randomised, placebo-controlled, double-blind, parallel-group study to evaluate the safety and efficacy of omaveloxolone at the 150 mg dose identified in Part 1 over 48 weeks.[7]
- Open-label extension: designed to assess the long-term safety and tolerability of

omaveloxolone following completion of Part 1 and Part 2 of the MOXIe study.[41]

In Part 1, patients with FA were randomised 3:1 to omaveloxolone or placebo and treated for 12 weeks (N=69). Patients were randomised to omaveloxolone at doses of 2.5–300.0 mg/day (n=52) or placebo (n=17).[40] The primary endpoint was the change from baseline in peak work (watts/kg) attained during exercise testing at Week 12, along with safety and tolerability, and the secondary endpoint was the change in mFARS score at Week 12. Other measures included the Timed 25-Foot Walk Test (T25-FW), 9-Hole Peg Test (9HPT), low-contrast vision, and health-related quality of life.[29,40]

Despite no significant change in peak work in exercise testing compared with placebo (p=0.77), omaveloxolone significantly improved mFARS scores from baseline in a dose-dependent manner (p<0.001) and, when compared with the placebo-corrected change at 160 mg/day, mFARS improvements approached statistical significance (p=0.06). Omaveloxolone was well tolerated, and adverse events were generally mild. The optimal dose was determined to be 160 mg/day, so a 150 mg/day dose was examined in MOXIe Part 2 as this would reduce the number and complexity of capsules that patients would need to take while still providing similar systemic exposure (Reata Pharmaceuticals, data on file).[40]

Part 2 included patients 16–40 years of age with genetically confirmed FA; baseline mFARS scores between 20–80; and the ability to complete maximal exercise testing on a recumbent stationary bicycle (N=103). Patients were randomised 1:1 to receive 150 mg/day omaveloxolone or placebo daily for 48 weeks, followed by a 4-week follow-up. The primary endpoint was the change from baseline in mFARS at Week 48 (excluding patients with severe pes cavus, as defined in the protocol; n=82), and secondary endpoints included the change in baseline at Week 48 in Patient Global Impression of Change (PGIC), Clinician Global Impression of Change (CGIC), 9-HPT, T25-FW, frequency of falls, peak work during maximal testing, and activities of daily living.[7,29]

In MOXIe Part 2, changes from baseline in mFARS scores in omaveloxolone and placebo patients showed a difference between treatment groups of -2.4 (p=0.014), indicating a neurological function benefit.[7] Improvements were consistent across individual components of mFARS, subgroups, including age, sex, GAA1 repeat length, and ambulatory status. Omaveloxolone was generally well tolerated with few serious adverse events or discontinuations; adverse events were generally mild to moderate in severity. The most common adverse events occurring more frequently in the omaveloxolone arm were headache, increased alanine aminotransferase, nausea, excoriation, fatigue, increased aspartate aminotransferase, abdominal pain, and diarrhoea. Four patients (8%) who received omaveloxolone discontinued treatment due to an adverse event, compared with two patients (4%) in the placebo group.[7]

Data from the open label extension part of MOXIe were analysed to determine the effects of a delayed start to omaveloxolone in the study population.[41] To achieve this, mFARS scores at the end of the 48-week placebo-controlled period (MOXIe Part 2) were compared with those at 72 weeks in the MOXIe open-label extension (up to 144 weeks) for patients initially randomised to omaveloxolone compared with those initially randomised to placebo in MOXIe Part 2. A non-inferiority test was performed to compare the difference between treatment groups (placebo to omaveloxolone [delayed start group] versus omaveloxolone to omaveloxolone [early start group]) using a mixed model for repeated measures. Slopes of the change in mFARS scores were compared between both groups in the open-label extension. The primary endpoint was the difference in the initial placebo and initial omaveloxolone groups in the 'delayed start period' (extension Week 72 change from baseline mFARS values) compared with the initial omaveloxolone-placebo difference in the 'placebo-controlled period' (MOXIe Part 2 Week 48 change from baseline mFARS values).[41]

Results showed that the difference in mFARS between omaveloxolone and placebo observed at the end of placebo-controlled MOXIe Part 2 was preserved after 72 weeks in the extension phase. The results support the outcome of MOXIe Part 2 and indicate a persistent treatment benefit with omaveloxolone.[41]

Data from the open-label MOXIe extension were also compared with propensity-matched

natural history data from FA-COMS.[42] Logistic regression was used to estimate propensity scores based on multiple covariates, including sex, baseline age, age of onset, baseline mFARS score, and baseline gait score. Selection of covariates was based on clinical relevance and availability. The primary endpoint was the change from baseline in mFARS at Year 3 for the MOXIe-extension patients compared with the matched FA-COMS patients using an mixed model for repeated measures.[42]

Results indicated that omaveloxolone provides a persistent benefit over 3 years when compared with an untreated, matched cohort from FA-COMS. In the primary pooled population by Year 3, mFARS scores for patients in the FA-COMS matched set progressed 6.6 points, whereas they progressed just three points for patients treated with omaveloxolone (p=0.0001), suggesting a 55% slower progression in mFARS.[42]

Giunti explained that it is important for clinical trials to use measures of disease that best characterise this multisystem condition, and which best represent the burden of disease. An online survey of patients with FA in the USA and UK found that the symptoms they would most like to see addressed by a clinical trial differed by the patient's stage of disease.[43] Ambulatory patients would most like to see balance problems addressed (walking independently and walking with aids), whereas patients who were wheelchair-dependent were most likely to want to see slurred speech addressed. Giunti stressed that clinical trials need to include patients at different stages of their disease, particularly as the overall quality of life and lifespan of patients with FA increase. Giunti also felt that research is needed to develop predictive and prognostic biomarkers, allowing clinical trials to include more targeted populations. Giunti described one recent study that used machine learning in combination with data from a wearable motion capture suit; this approach was more accurate than the Scale for the Assessment and Rating of Ataxia (SARA) scores in predicting *FXN* gene expression levels for each patient, and in predicting individual SARA scores 9 months into the future.[44]

Giunti concluded that due to the complexity of FA, disease management requires a holistic approach with multidisciplinary clinics, to achieve the best quality of life for these patients.[9] Giunti added that there are several pharmacological compounds with a wide range of mechanisms currently under clinical development,[32] and that both vatiquinone and omaveloxolone studies report promising efficacy data and safety.[7,38]

Closing Remarks

Sylvia Boesch

Boesch summarised the key take aways from the symposium, reiterating that the most common mutation in FA is a homozygous triplet repeat in an intron of *FXN*, resulting in reduced levels of the frataxin protein. The mutation is quite common in the Western population, with an estimated carrier frequency of 1:60–1:110.[14] Boesch stressed that after many years of purely symptomatic treatment for FA, disease-modifying drugs are being developed and are expected be available in the near future, offering hope to patients and their clinicians.

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Development of the Clinical Myotonia Rating Scale and a Mexiletine Prescribing and Monitoring Algorithm for Patients with Non-Dystrophic Myotonia

Posters presented at the 9th Congress of the European Academy of Neurology (EAN), Budapest, Hungary, 1st–4th July 2023

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Meeting Summary

The two most common forms of non-dystrophic myotonia (NDM) are myotonia congenita (Thomsen disease or Becker-type) and paramyotonia congenita. Symptoms, including muscle stiffness, cramps, and transient weakness, can affect a person's quality of life. An unmet need for a validated tool to assess myotonia symptom severity and frequency, as well as disability caused by myotonia, led to the development of the Clinical Myotonia Rating Scale (CMRS). At the 9th Congress of the European Academy of Neurology (EAN), Budapest, Hungary, 1st–4th July 2023, a poster was presented regarding validation and reliability testing of the CMRS, the results of which are discussed here. Such a tool is needed when first

assessing myotonia symptoms in a patient with NDM, as well as when assessing their response to myotonia-targeting medication. One such drug is mexiletine, a Class 1B antiarrhythmic agent that is approved for the treatment of myotonia symptoms in adults with NDM. Although a number of studies, including clinical and real-world trials in people with NDM, have not found mexiletine to be associated with impaired cardiac function, but as an antiarrhythmic drug, cardiac assessment is required with mexiletine prescription. Also presented at the 2023 EAN meeting is an algorithm to aid prescribers in understanding patients in whom mexiletine may be contraindicated, tests needed prior to mexiletine prescribing, and cardiac monitoring under treatment in patients with NDM. This algorithm was developed utilising expert opinion, the mexiletine summary of product characteristics, and a literature review of mexiletine safety data in NDM.

Introduction

In the rare neuromuscular disorders classed as NDM, muscle stiffness (myotonia) is the major symptom and is defined by a delayed muscle relaxation after voluntary contraction.[1] In myotonia congenita (Thomsen disease or Becker-type), myotonia occurs due to loss-of-function mutations in the *CLCN1* gene that codes for the chloride channel CLC-1.[1-3] In paramyotonia congenita, myotonia occurs due to gain-of-function mutations in the *SCN4A* gene that codes for the Nav1.4 sodium channel.[1,4] Depending on subtype, individual symptom severity, and exacerbating factors, a patient with NDM may also experience cramps, transient weakness, myalgia, fatigue, muscle hypertrophy, speech, chewing and swallowing difficulties[5,6] In the IMPACT survey, including 181 adults with NDM and 59 carers, respondents reported how NDM symptoms could physically, socially, and psychologically impact their quality of life.[6]

Development of the Clinical Myotonia Rating Scale

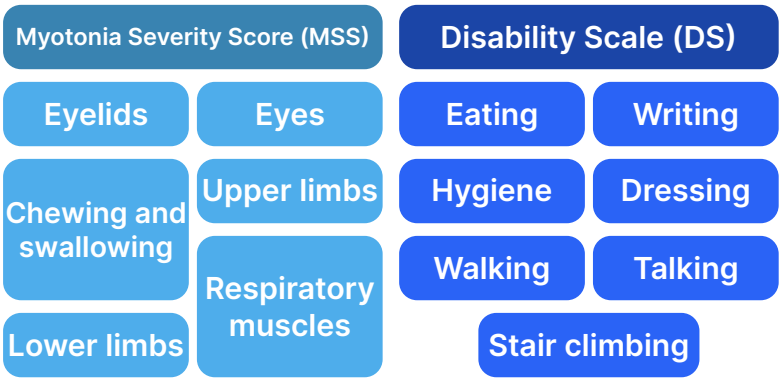
Measures that can help assess myotonia include the modified Myotonia Behaviour Scale (MBS),[7] the Timed Up and Go (TUG) test,[8] and Borg Category-Ratio scale.[9] However, as there are no standardised and validated tools specific to NDM, the CMRS was developed on the model of the Dystonia Movement Scale and Disability Scale[10] to help assess a range of NDM-associated symptoms with regard to severity and disability (Figure 1).[11]

In a poster by Savine Vicart, Muscle Channelopathies Reference Center, Assistance Publique-Hopitaux de Paris (APHP), University Hospital Pitié-Salpêtrière, Paris, France, and colleagues, a tool was discussed that can help objectively in assessing myotonia in routine clinical practice.[12] The CMRS comprises a Myotonia Severity Scale (MSS), which assesses and scores myotonia severity and frequency in six body areas, and a Disability Scale (DS), which scores myotonia severity in seven daily activities (Figure 1). For the MSS, frequency is scored from 0 (none) to 4 (every day). Severity is scored from 0 (none) to 4, according to each area, for example, for eyelids and limbs, a 4 rating is up to 'severe, permanent'; for ocular muscles, it is 'severe, diplopia'; for chewing and swallowing, it is 'unable to chew, choking'; and for respiratory muscles, it is 'permanent dyspnoea.' Total MSS score is calculated based on severity and frequency with a weighting factor for each component, and a total range of 0–104.[11]

For the DS, individualised domain scores go from 0 (normal) to 4 as follows: talking (incomprehensible), writing (unable to handle a pen), hygiene and dressing (requires 100% help), walking (wheelchair), and stair climbing (impossible). Eating is scored up to 3 (dependent on others). The total DS score range is 0–27.[11]

In the poster, validity and reliability of the CMRS was assessed.[11] Study participants were adults with myotonia congenita (n=13) or paramyotonia congenita (n=12) from the randomised, crossover, double-blind mexiletine versus placebo MYOMEX trial.[12] Two investigators used the CMRS to assess baseline scores at six

Figure 1: Components of the Clinical Myotonia Rating Scale (CMRS).[11]



centres in France.[11] Vicart, who presented the poster, discussed during the poster question and answer session how the participants were all assessed in a temperature controlled room (20–25 °C), so that this would not be a variable. Interrater reliability was estimated by weighted κ coefficients (poor: <0.40; fair/good: ≥0.40–<0.75; excellent: ≥0.75).[13] Intraclass correlation coefficients were calculated for global scores.[14] Correlations with the visual analogue scale (VAS) stiffness score (primary efficacy criterion of the Myomex study) and with the Individualized Neuromuscular Quality of Life (INQoL) self-questionnaire[15] were estimated using Spearman rank correlation coefficients.[11]

For the MSS, most κ coefficients for both frequency and severity showed 'fair/good' interrater reliability. Highest interrater agreement was in frequency of 'eyelid blinking' and severity of 'respiratory muscle impairment', which approached the cut-off for 'excellent' interrater reliability. Conversely, three domains were given 'poor' κ ratings for interrater agreement: severity of upper and lower limbs (right and left).[11] For the DS, highest interrater agreement was observed for hygiene (rated as 'excellent'), and dressing. However, eating and writing were in the 'poor' κ range. Overall, the intraclass correlation coefficients indicated moderate interrater reliability in CMRS severity and disability scores.[11]

The CMRS severity global score strongly correlated with both INQoL and VAS stiffness scores, both significantly. While the CMRS disability global score also strongly correlated with VAS, the correlation was not as strong for INQoL, although both were significant. The CMRS severity and disability global scores correlated well with each other, and were significant.[11]

The study investigators concluded that the CMRS demonstrated moderate interrater reliability in this small exploratory analysis, and will continue to undergo validation in study populations with myotonic disorders.[11] In two expert panel discussions, one in response to the IMPACT survey, unmet needs identified for patients with NDM included verified tools for diagnosis, and for monitoring the effectiveness of a drug treatment to manage myotonia symptoms over time.[6,16] As such, the study investigators here concluded that the CMRS was "a promising scale for assessing the severity and impact of myotonia in patients with NDM."[11]

Cardiac Assessment and Monitoring Recommendations for Patients with Non-dystrophic Myotonia Administered Mexiletine

Expression of both Nav1.4 sodium channel, and the CLC-1 chloride channel affected in NDM, is mostly confined to skeletal muscle, with an almost null expression in the heart.[17,18] Accordingly, mutations in the *SCN4A* or *CLCN1* genes in people with NDM would not be expected to affect cardiac function

of patients with NDM, and indeed, cardiac impairment is not a symptom of NDM.[19]

Mexiletine, historically classified as a Class 1B antiarrhythmic, is a non-selective, voltage-gated sodium channel blocker that enhances sodium channel inactivation and repolarisation, and reduces skeletal muscle hyperexitability.[20-22] It has a high affinity for Nav1.4 channels in the open state, and has no effect on potassium channels.[21,22] Mexiletine is less potent, with quicker recovery from sodium channel binding than Class IA or IC sodium channel blockers.[22] However, as mexiletine is also classified as an antiarrhythmic (indicated for treatment of documented, life-threatening ventricular arrhythmias),[23] it is essential that a patient with NDM undergoes cardiac evaluation prior to and during mexiletine administration.[24,25]

Mexiletine has been used off label for myotonias for at least 40 years[26] and, following a double-blind randomised trial (n=59),[27] it is now the only anti-myotonic drug approved for NDM by the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK.[1,25] Another double-blind randomised controlled trial,[12] as well as analysis of Bayesian aggregated placebo-controlled n-of-1 trials of mexiletine,[28] also showed the efficacy and safety of mexiletine in patients with NDM. These trials did not show any serious cardiac adverse events associated with mexiletine use in this patient population.[12,27-29] In the first randomised controlled trial of mexiletine, one incidence of bradycardia was found at the end of Week 4 that resolved on follow-up without stopping treatment.[27] In the second trial, and the n-of-1 trials study, no clinically relevant significant variations were observed in ECG readings at the end of the treatment period.[12,28]

In a long-term retrospective study based on data from a cohort of mexiletine-treated patients with NDM (n=59; treatment duration 1 month–20 years), no patients developed cardiac arrhythmias.[30] In another study (n=63), ECG recordings compared with baseline found no significant changes in PR complex interval; heart rate; QRS duration; or in corrected QT interval when taking mexiletine. A total of 16 patients were referred to a cardiologist due to cardiac concerns prior to or during mexiletine administration but all were medically cleared to start or continue treatment.[29] In a third study, 37 patients with NDM used an anti-myotonic medication, mostly mexiletine or ranolazine, with no reported cardiac adverse events.[31]

Despite these findings, an NDM expert panel discussed challenges around prescribing mexiletine included uncertainties about cardiac problems amongst their concerns.[16] This may be due to mexiletine, and related antiarrhythmic drugs, having a U.S. Food and Drug Administration (FDA) Black Box warning following findings in an encainide or flecainide study, where excess mortality or non-fatal cardiac arrest occurred in patients with recent myocardial infarction.[32] However, mexiletine itself was not tested in this trial, and this warning is not in the mexiletine licensed to treat myotonia in people with NDM summary of product characteristics.[25]

With cardiac concerns in mind, a treatment algorithm was developed to aid prescribers, as described in a poster by Vicart and colleagues, presented by the lead author at the EAN 2023 congress.[33] To help define the treatment algorithm, three workshops brought together three French neurologists and five French cardiologists. They utilised their expertise, alongside the mexiletine summary of product characteristics[25] and a review of the literature regarding mexiletine safety,[12,22,27,28-31] to construct an algorithm to define the screening and surveillance tools needed to help avoid cardiac events in patients treated with mexiletine.[33]

Components of the Algorithm

Stage 1: Assessment

Prior to mexiletine initiation, the patient should be evaluated by a cardiologist, to screen for cardiac contraindications based on medical history, and systematic ECG and echocardiography investigations.[33] According to the summary of product characteristics (mexiletine indicated in adult NDM), medical history that precludes the use of mexiletine includes myocardial infarction; atrial fibrillation or atrial flutter; angina or non-revascularised

coronary artery disease; ventricular tachycardia; complete heart block (i.e., third-degree atrioventricular block) or heart block that may evolve to complete heart block; and cardiac disease-modifying therapy and drugs that may cause torsades de pointes, including ajmaline, amiodarone, disopyramide, dofetilide, dronedarone, encainide, flecainide, ibutilide, moricizine, procainamide, propafenone, quinidine, sotalol, and vernakalant.[25]

Systematic investigations also need to be carried out. For ECG, findings that rule out mexiletine use include bundle branch block; wide QRS complex (≥120 ms); sinus node dysfunction (heart rate <50 beats per min); bifascicular or trifascicular block; high-degree atrioventricular block (Mobitz II or complete block); first-degree atrioventricular block with PR duration of ≥240 ms; and necrosis Q wave and repolarisation abnormalities.[25]

Findings on echocardiography that preclude mexiletine use include segmental wall motion abnormality and a left ventricular ejection fraction below 50%.[25]

Stage 2: Monitoring [33]

Mexiletine can be introduced if the above are ruled out. The maximum effective dose is usually reached 3 weeks after the first dose, when a follow-up ECG should be carried out. A cardiologist's opinion is needed if changes are observed, or if a patient develops any new cardiac symptoms, such as syncope, chest pain, or unusual palpitations.[33]

Once mexiletine is initiated, an ECG should be carried out at least every 2 years, a systematic cardiology consultation should be carried out every 5 years, including screening for coronary artery disease and a cardiovascular risk assessment.[33] For patients with a known cardiac abnormality detected prior to treatment but which not contra-indicated mexiletine use, it is recommended to perform a cardiac evaluation every year, or more frequently if necessary.[25]

During presentation of the poster, Vicart concluded by saying that the authors hope the algorithm will "assist the team caring for patients with NDM, and will enable accurate screening and monitoring to avoid cardiac events during treatment."[33]

Conclusion

Care of patients with NDM requires assessment of myotonia severity and impact and should include symptom monitoring both prior to and during medication prescription, if needed. The CMRS may provide a validated tool by which myotonia can be easily, systematically, and consistently assessed.[11] For patients with NDM treated with mexiletine, an algorithm for cardiac safety monitoring has been developed to assist neurologists and cardiologists managing these patients.[33]

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Abstract Reviews

Presenting key findings from the latest research in the field of neurology from novel abstracts presented at the 9th Annual Congress of the European Academy of Neurology (EAN), and featuring the recipients of the Best Presentation Award at the EAN Tournament Finals.

Multicentre Real-World Case-Control Study of Effectiveness, Tolerability, and Anti-Calcitonin Gene-Related Peptide Response Predictors in the Elderly

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BACKGROUND AND AIMS

Anti-calcitonin gene-related peptide (CGRP) therapies have demonstrated effectiveness and safety in patients with chronic[1-3] and episodic[4-10] migraine in several clinical trials. However, there is limited information regarding clinical characteristics, effectiveness, and safety in the elderly under CGRP therapies, which may prevent clinicians from using these treatments in older patients. Migraine tends to improve with age; however, a substantial proportion of older adults may still suffer from migraine. Besides that, these patients are more likely to have relevant comorbidities and polypharmacy, with potential drug–drug interactions, and are more vulnerable to adverse effects.[11] This cohort could potentially benefit from therapies with a better tolerability profile. In addition, older adults may have tried multiple migraine-preventive drugs over their lives, reducing the therapeutic armamentarium.[11]

MATERIALS AND METHODS

To address this gap, the authors performed a retrospective multicentre study nested in a prospectively collected cohort of cases, in which patients were individuals over 65 years old with migraine, who were receiving anti-CGRP therapies. Sex- and age-matched controls under 55 years old were used. Demographics, effectiveness, and safety variables were collected. Effectiveness, defined by the reduction in the number of headache (HDM) and migraine days per month (MDM); and responder rate, defined as 30%, 50%, and 75% reduction in the number of HDM and MDM at 3-, 6-, and 12 months, were collected. Adverse events (AE) were also evaluated at each time point.

RESULTS

In this study, a total of 228 patients were included: 114 cases and 114 controls. Among these, 84% were female, mean age was 70.1 years (range: 66–86), and approximately 80% of cases had chronic migraine. The authors found a higher percentage of vascular risk factors among the elderly, such as hypertension and dyslipidaemia, and also migraine with aura; higher age of migraine onset; and higher prior number of prophylactic treatments and medication overuse rates in the elderly. However, there were no major differences regarding effectiveness. The authors found that, in these cases, a 50% response rate was achieved by 59% at 20–24 weeks. A lower reduction in HDM was observed in the elderly regarding number of headaches at 3 months, and MDM at 6- and 12 months. The percentage of AEs was similar in the two groups, without serious AEs. The most common AE was constipation, without differences between groups. In this series, independent characteristics associated with the elderly were age of migraine onset and number of prior preventive treatments.

CONCLUSION

This case-control study provides real-world evidence of effectiveness and safety of anti-CGRP therapies for patients with migraine over 65 years old compared with younger patients. These results highlight that anti-CGRP therapies are not only effective as in the elderly, but also have a good tolerability profile in this special population. ●

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Best Presentation Awardee

Sleep Features and Long-Term Incident Neurodegenerative Diseases: A Polysomnographic Study

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BACKGROUND AND AIMS

The most prevalent neurodegenerative diseases (NDD) are Alzheimer's disease and Parkinson's disease, affecting 43.3 and 6.1 million individuals globally, respectively.[1,2] Altered sleep is present early in NDDs, and may contribute to neurodegeneration. However, much of the evidence on the association between sleep changes and incident NDDs comes from self-reports and actigraphy data, which lack objective measures of sleep structure. Long-term, large sample size studies assessing the association between NDDs and objective polysomnography-based sleep features are scant. The aim of this study was to investigate whether objective sleep features are associated with long-term incidence of NDDs.

MATERIALS AND METHODS

This retrospective cohort study included polysomnographic data of patients referred to the Sleep Disorders Unit, Department of Neurology, Medical University Innsbruck, Austria, from January 2004–December 2007. All patients ≥18 years undergoing polysomnography and without NDDs at baseline or within 5 years were included. Main outcome was a diagnosis of NDDs at least 5 years after polysomnography, assessed until December 2021.

RESULTS

Of the 1,454 patients assessed for eligibility, 999 (68.7%) met inclusion criteria (683 [68.3%] male; median age 54.9 years [interquartile range: 33.9–62.7]). In total, 75 patients (7.5%) developed NDDs and 924 (92.5%) remained disease-free after a median follow-up of 12.8 years (interquartile range: 9.9–14.6). After adjusting for several demographic, sleep, and clinical covariates, 1% decrease in sleep efficiency, N3 sleep, or rapid eye movement (REM) sleep was associated with 1.9%, 6.5%, or 5.2% increased risk of incident neurodegeneration, respectively (hazard ratio [HR]: 1.019; 95% confidence interval [CI]: 1.002–1.035; HR: 1.065; 95% CI:

1.007–1.118; HR: 1.052; 95% CI: 1.012–1.085, respectively). Further, 1.0% decrease in wake within sleep period time (SPT) represented a 2.2% reduced risk of incident NDDs (HR: 0.978; CI: 0.958-0.997). Patients with the highest quartile of wake in SPT (>18.6%), or the lowest quartile of REM sleep (<13.0%) or N3 sleep (0%), had the shortest overall mean disease-free survival time (14.9; CI: 14.6–15.3 years).

CONCLUSION

In this cohort, an altered sleep architecture at baseline with reduced sleep efficiency, REM sleep, or N3 sleep, or increased wake in SPT, was associated with incident neurodegeneration after 5 or more years. These findings support the hypothesis that sleep changes may contribute to NDDs' pathogenesis, and point to sleep as an early marker of neurodegeneration and a potential target of neuroprotective strategies. To put it into perspective, consider the analogy of a balanced diet.

We understand that it is not just about the total amount of calories we consume, but the balance and diversity of nutrients, such as proteins, carbohydrates, fats, vitamins, and minerals. Similarly, it is not just the total number of hours that we sleep that matters, but the specific stages and quality of sleep we experience.

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Abstract Highlights

The following highlights have been selected from the European Academy of Neurology (EAN) Tournament Finals, a special session format featuring 6-minute presentations by participants. The abstract topics include novel approaches to communication in brain injury, predicting atrial fibrillation in cardioembolic stroke, and genetic testing for early onset Parkinson's disease.

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Novel Bedside-Approach to Communication in Brain Injury: Tongue-Based Motor Imagery

"Functional near-infrared spectroscopy (fNIRS) offers a non-invasive approach by measuring variations in cortical blood oxygenation levels."

PATIENTS with severe brain injuries face significant challenges in verbal and motor communication, as emphasised by Pardis Zarifkar, Department of Neurology, Copenhagen University Hospital, Denmark, during the 9th Congress of the European Academy of Neurology (EAN). In turn, these challenges present obstacles in conducting cognitive assessments.

In the context of evaluating motor cortex activation in the absence of physical movement, functional near-infrared spectroscopy (fNIRS) offers a non-invasive approach by measuring variations in cortical blood oxygenation levels. The proof-of-concept study by Zarifkar and colleagues investigates the feasibility of utilising tongue-based commands as a novel method of motor imagery communication using fNIRS.

The study included a cohort of 20 healthy staff volunteers from the Copenhagen University Hospital. They underwent fNIRS measurements targeting the frontoparietal and primary motor cortices, while performing tasks related to tongue motor and tongue motor imagery. To distinguish between tongue motor imagery and a relaxed state, the researchers employed a support vector machine classifier to classify the brain activation patterns.

The results revealed that all participants successfully elicited activation in the tongue motor homunculus through tongue motor imagery, showing similar activation responses to those observed during actual physical tongue movement. The activation was specifically localised to the left hemisphere in both the tongue motor and tongue motor imagery tasks. Furthermore, tongue motor imagery specifically activated the frontoparietal regions that are associated with cognitive processing. The classifier achieved a high accuracy of 92% in successfully distinguishing motor imagery from the relaxed state.

Zarifkar underscored the significance of their study as a proof-of-concept for the application of a novel tongue motor imagery paradigm in healthy individuals. This highlights the potential of fNIRS to facilitate cognitive assessments, and enable meaningful interactions in patients with severe brain injury. ●

Pathogenetic Mechanism Underlying Concomitant Continuous Pain in Trigeminal Neuralgia

TRIGEMINAL neuralgia is characterised by the presence of continuous, burning pain, in addition to the characteristic electric shock-like paroxysmal pain. Typically, this pain responds less effectively to available treatments, so it is thought to be caused by a different pathogenetic mechanism. Gianfranco De Stefano, Sapienza University of Rome, Italy, therefore sought to investigate the pathogenetic mechanism underlying trigeminal neuralgia in patients with a definite diagnosis.

Presented during the 9th Annual Congress of the European Academy of Neurology (EAN), participants were subclassified according to the presence or absence of concomitant continuous pain. Both groups then underwent high resolution 3T MRI with a volumetric study of the trigeminal nerve, laser-evoked potentials, and quantitative sensory testing, according to the Network of Neuropathic Pain (DFNS) protocol.

"A total of 73 patients with a definite diagnosis of trigeminal neuralgia were enrolled in the study."

A total of 73 patients with a definite diagnosis of trigeminal neuralgia were enrolled in the study, with 28 reporting concomitant continuous pain (38%). Analysis of MRI data suggested patients with concomitant continuous pain showed a more severe trigeminal root atrophy ($p<0.05$).

Overall, De Stefano concluded that the multimodal findings converged in showing that concomitant continuous pain is associated with axonal loss and the impairment of small trigeminal fibres. Furthermore, it is hypothesised that the axonal loss may trigger hyperexcitability in the second order neurone, as indicated by the correlation between the volume of the affected nerve with the wind-up ratio. This abnormal activity could underlie the development of concomitant continuous pain in trigeminal neuralgia. ●

Multiple Acute Ischaemic Lesions in Secondary Prevention with Dual Antiplatelet Treatment

FINDINGS from an ongoing, prospective, nationwide, multicentre, observational study show evaluating the efficacy of dual antiplatelet treatment (DAPT) for secondary prevention of transient ischaemic attack (TIA) or minor non-cardioembolic ischaemic stroke were presented at the 9th Congress of the European Academy of Neurology (EAN).

Some patients with a diagnosis of non-cardioembolic ischaemic stroke or high-risk TIA experience recurrent ischaemic events, despite receiving optimal treatment and secondary prevention with DAPT. Research by Eleonora De Matteis, Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, Italy, and colleagues sought to evaluate the effectiveness of secondary prevention with short-term DAPT in this patient cohort.

"These lesions occurred in different vascular territories in 20.3%."

The team enrolled patients from 62 different centres with non-cardioembolic ischaemic stroke or high-risk TIA receiving secondary preventive DAPT since February 2021. Whilst the recruitment and 90-day follow-up is ongoing, as of 8th January 2023, a total of 1,578 patients had been included in the study. Of these patients, 1,153 (73.1%) had undergone an MRI scan.

Upon evaluation of these scans to look for evidence of multiple acute ischaemic lesions, an indicator of occult cardioembolism, the team found that 251 patients (21.8%) displayed no acute ischaemic lesions, 558 patients (48.4%) displayed a single acute ischaemic lesion, and 344 patients (29.8%) displayed multiple acute ischaemic lesions. Cardiac monitoring for >24 hours was performed in 79.0% of patients who displayed multiple acute lesions.

Further analysis of those with multiple acute ischaemic lesions on MRI revealed that these lesions occurred in different vascular territories in 20.3%. Further to this, the researchers found that 106 out of 344 (30.8%) were caused by large vessel occlusion, 35 out of 344 (10.2%) were due to other defined causes, and the cause was undetermined in 203 out of 344 patients (59.0%).

The authors concluded that in their real-life prospective study, approximately one-third of patients receiving secondary prevention with short-term DAPT for minor non-cardioembolic ischaemic stroke or high-risk TIA displayed multiple acute ischaemic lesions on MRI, which is a radiological hallmark of cardioembolism. They found that these were mainly caused by arterial stenosis, or an undetermined cause. The ongoing results of this study could help to determine the real-life efficacy of short-term DAPT in secondary prevention of minor non-cardioembolic ischaemic stroke and high-risk TIA.

Novel Findings in Bi-allelic *PRKN* Gene Associated with Parkinson's Disease

MUTATIONS in the *PRKN* gene, coding for the protein parkin, are the most common cause of early-onset Parkinson's disease. New research, presented in the form of an abstract at the 9th Congress of the European Academy of Neurology (EAN), has provided the first proof that missense variants and variants located in the N-terminal of the protein are associated with a more benign progression of Parkinson's.

A total of 644 patients were included in the analysis reported, with age at onset 31.40±11.38 years, and a disease duration 18.00±12.50 years. These patients all had bi-allelic pathogenic mutations in *PRKN*, and no pathogenic mutations in other genes known to result in monogenic Parkinson's disease. Over 140 different mutations spanning the entire gene can be attributed to autosomal recessive inherited Parkinson's diseases; therefore, these research findings are all the more impressive. The type of mutation was analysed for an association with the age at onset and motor severity, considering disease duration as a covariant.

"Missense variants and variants of the N-terminal are associated with a less sinister progression of the disease."

Mean unified Parkinson's disease rating scale (UPDRS) score at the time of disease onset was 12.60±1.40, increasing by 3.85±0.60 every 10 years (n=310; p=3.6e-09). Average initial L-dopa equivalent daily dose among those participants who had never received deep brain stimulation was 320±71 mg, and this increased by 118±30 mg every 10 years (n=94; p=0.0013). Patients with two missense variants had a later age of onset (36.4±12.3 years) compared with those that had two structural variants (31.2±10.8 years; p=0.004). Variants located at the N-terminus of the protein, more specifically exons 1–3, were associated with an earlier age at onset of Parkinson's disease (30.9±10.3 years) when compared with variants located at the C-terminus, exons 7–12 (34.9±12.5; p=0.05).

Demonstrating for the first time that missense variants and variants of the N-terminal are associated with a less sinister progression of the disease, the researchers were proud to present their findings at EAN 2023. The conclusions from this study will certainly provide a springboard for honing the specifics of future study, delving deeper into the complexities of mutations that cause Parkinson's disease, and also opening the door for potential early lifestyle changes, and/or treatment via genetic screening of patients. ●

Plasma Biomarkers: Predicting Atrial Fibrillation in Cardioembolic Stroke

BIOMARKERS found in patient plasma display use in predicting atrial fibrillation (AF) and early identification of cardioembolic stroke, according to researchers from the Neurology Department, Centro Hospitalar Entre Douro e Vouga, Santa Maria da Feira, Portugal, presented at the 9th Congress of the European Academy of Neurology (EAN).

Over a 2-year period, between January 2020–January 2022, Barbara Teixeria, Centro Hospitalar Entre-Douro e Vouga, and colleagues consecutively recruited a total of 717 patients admitted to the Stroke Unit with an ischaemic stroke diagnosis, with the aim of evaluating the accuracy of three plasma biomarkers: brain natriuretic peptide (BNP), N-terminal-proBNP (NT-proBNP), and troponin I, in predicting AF. Medical records were retrospectively reviewed to ascertain plasma BNP, NT-proBNP, and troponin I levels in the acute phase, and ≥48-hour ECG monitoring was also reviewed. Of the 717 enrolled patients, 583 had no previous AF diagnosis.

The results showed for patients without a previous diagnosis of AF, 120 out of 507 (23.7%) patients had a high troponin I on admission, 164 out of 432 (38.0%) had a high BNP, and 24 out of 68 (35.5%) had a high NT-proBNP.

Further analysis showed that of the 120 patients with a high admission level of troponin I, 35.8% had AF (risk ratio [RR]: 2.2, 95% confidence interval [CI]: 1.6–3.0). The AF detection sensitivity and specificity were 40.1% and 81.0%, respectively, with an area under the receiver operating characteristic curve (AUC) of 0.69.

AF was identified in 41.5% of patients with an elevated BNP (RR: 4.8; 95% CI: 3.1–7.4). The sensitivity and specificity for AF detection were 74.7% and 71.8%, respectively, and AUC was 0.73. Similarly, in patients with a high NT-proBNP, 47.5% had AF (RR: 4.5; 95% CI: 1.6–12.8), with a detection sensitivity of 71.8%, specificity of 73.6%, and AUC of 0.72.

The authors concluded that BNP, NT-proBNP, and troponin I can be helpful for early identification of cardioembolic stroke. The study highlighted that of these plasma biomarkers, troponin I displayed greater specificity but lower sensitivity in detection of AF than BNP and NT-proBNP, whereas BNP and NT-proBNP exhibited higher sensitivity but lower specificity in AF detection than troponin I. ●

"Medical records were retrospectively reviewed to ascertain plasma BNP, NT-proBNP, and troponin I levels in the acute phase."

Harmonising Genetic Testing for Early Onset Parkinson's Disease

NOVEL results from the PARKNET multicentre study have highlighted the importance of correctly interpreting genetic testing from multiple different laboratories, for patients with early-onset Parkinson's disease (EOPD). Patients with EOPD often submit to diagnostic genetic testing based on next-generation sequencing (NGS). However, frequently, the subsequent interpretation of the NGS results can be challenging in a diagnostic setting, with an additional lack of research/ literature currently addressing this challenge.

This study, presented at the 9th Congress of the European Academy of Neurology (EAN), retrospectively collected the data of 648 patients with EOPD (age of onset: >55 years), who had undergone NGS of a minimal panel of 15 PD-related genes, as well as a PD Multiplex Ligation-dependent Probe Amplification's (MLPA) from eight Italian genetic diagnostic laboratories. The patients were additionally analysed to look at the very-EOPD subgroup of patients with an age of onset of >40 years. All variants were classified according to the latest American College of Medical Genetics (ACMG) criteria, and the diagnostic outcomes pre- and post-harmonisation were compared.

The researchers found that in 186 of the 648 patients with EOPD (29%), and in 71 of the 167 patients with very-EOPD (45%), the diagnostic report listed at least one single nucleotide variant or copy number variation. In 105 of the patients with EOPD (16%) the testing outcome was considered diagnostic. After harmonisation, the genetic diagnosis changed in 20 out of 186 patients with EOPD, with six reporting shifts from non-diagnostic to diagnostic, and 14 diagnostic reports being reclassified as inconclusive. A definite diagnosis was reached in 97 patients with EOPD (15%), and 39 patients with very-EOPD (25%), the majority of whom carried either GBA variants or bi-allelic *PRKN* single nucleotide variants or copy number variations (17 EOPD [3%]; 12 very-EOPD [8%]). In 89 EOPD (14%) cases and 32 very-EOPD cases (20%), the genetic report was inconclusive.

The study represents a successful attempt to harmonise diagnostic reporting of PD genetic testing across several different laboratories, underlining the current challenges in the interpretation of genetic variants emerging from NGS multigene panels, and highlighting the relevant implications in terms of counselling.

"Patients with EOPD often submit to diagnostic genetic testing based on next-generation sequencing."

Congress Interviews

Erich Schmutzhard, László Csiba, Ambra Stefani, and László Oláh spoke with EMJ, sharing their perspectives on how the European Academy of Neurology (EAN) advances neurology and patient care, as well as highlighting EAN's commitment to education, research collaboration, and the dissemination of best clinical practices.

Featuring: Erich Schmutzhard, László Csiba, Ambra Stefani, and László Oláh

Erich Schmutzhard

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Q1 Was there a particular event or person that encouraged you to pursue a career in tropical neurology and critical care neurology?

With respect to tropical neurology, no. I started medical school with the intention to do a postgraduate diploma/master's course in Tropical Medicine, and to work in a rural Sub-Saharan-African hospital as a tropical medicine specialist. After basic postgraduate training in infectious diseases and general medicine, I completed the course in tropical medicine and hygiene in Liverpool, UK, as I had planned since my early university days. Since it took very long to get my Tanzanian work permit, I accepted the opportunity to work as a resident in neurology at the Department of Neurology, University of Innsbruck, Austria. Here, the head of the department, Franz Gerstenbrand, was very interested in emergency and intensive care neurology, and he completely enticed me into this field of neurology. Nevertheless, after all the bureaucratic processes with my residence and work permit for Tanzania were solved, I quit the residency in Innsbruck and went to Mnero Hospital, Nachingwea District, a rural hospital in Southern Tanzania, where I worked for 4 years as a tropical medicine expert (and beyond, when necessary). After these 4 years, Gerstenbrand encouraged me to join his team again and to continue the residency/training in neurology. In 1986, I interrupted training in Innsbruck and accepted a 4-month scholarship in the Department of Neurology, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. After re-joining the Innsbruck neurology department, I eventually became a specialist in neurology, psychiatry, and a few years a later in intensive care medicine. In the early 1990s, I was given the responsibility to initiate a neuro-critical care unit within the Department of Neurology, University of Innsbruck.

Q2 Do you think there are any misconceptions about your speciality, and with respect to tropical neurology?

Firstly, neurocritical care medicine requires an in-depth understanding of neurology, neuroanatomy, and neurophysiology. Therefore, neurocritical care medicine (or intensive care neurology) must be based upon a full training of neurology with secondary specialisation in intensive care procedures and intensive care medicine. Secondly, tropical neurology is much more than infectious disease neurology in tropical countries or so-called low- and middle-income countries (LAMIC). Besides infections of the nervous system (viruses, bacteria, fungi, protozoa, and helminths), it includes all kinds of malnutrition (vitamin deficiencies, protein-calorie-malnutrition, etc.), air pollution as a risk factors for stroke (including particulate matter and ultra-fine particular matter; indoor and outdoor), heat-related diseases, specific malignancies, neurogenetic disorders, haemoglobinopathies as a stroke risk factor (e.g., sickle cell disease), toxins, and envenomation (snakes, scorpions, fish, jellyfish, etc.), to list a few. We should not forget the severity of traumatic brain injuries in LAMICs.

Q3 Your personal education and professional experience have involved you travelling to numerous destinations such as England, Thailand, and Tanzania. Where do you believe you gained the most experience and do you believe travelling was integral for you to make it to where you are today?

Yes, travelling was essential for my training, both in tropical neurology (UK, Tanzania, and Thailand) and intensive care neurology (several times to the USA: Houston, Baltimore, and Cleveland).

Q4 You currently have more than 370 publications to your name for your research in tropical neurology, neuro-infections, and critical care neurology. What do you believe to be the current gaps in literature and what topics require greater attention?

Critical care neurology in LAMICs is a wide gap in the literature, as is emergency neurology. We attempt to fill these gaps by organising regional teaching courses (sponsored by the European Academy of Neurology [EAN], World Federation of Neurology [WFN], American Academy of Neurology [AAN], International Brain Research Organisation [IBRO], World Stroke Organisation [WSO], International Parkinson and Movement Disorder Society [MDS], and ASEAN European Academic University Network [ASEA-UNINET]), in various Sub-Saharan African countries, including Mozambique, Burkina Faso, Madagascar, Ghana, Uganda, Cameroon, Malaysia, and Pakistan in the last 7 years. Overall, medicine, particularly neurology, intensive care medicine, and infectious diseases medicine must be prepared (i.e., every medical doctor) for all the new challenges caused by migration, globalisation, climate change, air pollution, and pollution (toxic chemicals, microplastics) in food and water, to list a few examples.

Q5 What are the most significant changes you have seen in the field of tropical neurology, neuro-infections, and critical care neurology during your time working within the field?

Regarding tropical neurology, malaria-retinopathy has become an early diagnostic method in cerebral malaria, and fundoscopy can now be done everywhere. Furthermore, hearing impairment has been identified as an important long-term effect of severe *P. falciparum* or malaria, contributing to severe language development problems; and intravenous artesunate is now used for cerebral and severe malaria. Further developments include the development of the tetravalent meningococcal vaccine; the use of neuroimaging in 'classical' tropical diseases (e.g., cerebral malaria); and early vaccination against tetanus, measles, pertussis, etc.

In terms of neuro-infections there are now rapid diagnostic methods such as PCR and multiplex PCR in the cerebrospinal fluid, and we can now recognise central nervous system complications early (e.g., vasculitis related ischaemia, hydro- , and pyocephalus). We are seeing a pandemic of antibiotic resistance, but we are also more prepared for new pandemics. With regard to neurocritical care, there have been advances in artificial ventilation and airway management by neuro-intensivists, as well as continuous

electroencephalogram monitoring multimodal (invasive) neuromonitoring, beyond increased intracranial pressure and cerebral perfusion pressure such as brain temperature, brain tissue O_2, brain tissue CO_2, and brain tissue lactate. We have also identified new risk factors for stroke, with air pollution being the number two in risk factors for ischaemic stroke mortality, particularly in LAMICs, and we are now using temperature management as a therapeutic (neuroprotective) measure.

> "There have been advances in artificial ventilation and airway management."

Q6 You have been the head of the EAN Task Force, and you are on the teaching course sub-committee. How much of an impact do you believe the EAN congress has, both directly on neurologists and indirectly on patients?

It has been a first, yet extremely important step, and as you know, in order to move forward the first step is crucial. By 2022, approximately 1,000 residents from Sub-Saharan African countries had attended these teaching courses and some of them have become professors/teachers of neurology, thereby spreading the knowledge in neurology and the service for neurologically ill patients. The EAN congress certainly is a crucial medium to spread the knowledge of these activities.

Q7 What changes have you brought into effect whilst serving as the head of the EAN Task Force: 'Neurology in Sub-Sahara-Africa'?

A major achievement has been, and is, the close cooperation of the EAN with the African Academy of Neurology (AFAN), the Pan Arab Union of Neurological Societies (PAUNS), the WFN, the AAN, the IBRO, the WSO, the MDS, and all the local universities.

> "A major achievement has been, and is, the close cooperation of the EAN."

Q8 What is one of the biggest challenges for the EAN in their goal to be the 'Home of Neurology', advance high-quality patient care, and reduce the burden of neurological diseases?

The biggest challenges include overcoming economic inequalities such as insufficient neuro-manpower. There are currently 10 African countries without a single neurologist. Additionally, it is very difficult, even impossible, to have access to diagnostic, therapeutic, and preventive resources. It is important to ensure the best possible transfer of knowledge in both directions.

Q9 Since your appointment as Austria's delegate to the WFN and Coordinator for the Innsbruck Medical University to ASEA-UNINET and Eurasia-Pacific University networks, what has been your proudest achievement?

I am proud to have been given the chance and opportunity to meet so many highly engaged medical doctors, in particular neurologists and neuroscientists from all over the world, as well as to appreciate that so many African, Asian, American, and European colleagues are similarly eager to spread knowledge in neurology, both in research and patient care, to many parts of the world. ●

László Csiba

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Q1 What led you to follow a career in neurology?

After graduation, I was going to be a neurosurgeon, but my mentor, Molnár, suggested I change my mind, so I became a neurologist instead. Molnár also supported me in the next period of my life, managing grants for me.

Q2 Your personal education and professional experience have involved travelling to numerous destinations such as Germany, Japan, and France. Where do you believe you gained the most experience and do you believe travelling was important for you to achieve what you have today?

At the Max-Planck Institute, Cologne, Germany, I performed animal experiments and elaborated a new imaging method of focal cerebral ischaemia, which was published. I also developed a new focal brain ischaemia model on rats. In Cologne, I became friends with a Japanese neurosurgeon, who invited me to Kure City, near Hiroshima, Japan, where I stayed for approximately 1 year to demonstrate the experimental methods I developed in Germany. On the other hand, I knew a new non-invasive, neurosonological diagnostic device: the transcranial doppler ultrasound (TCD). After Japan, I spent 6 months in Toulouse, France, and performed haemodynamic studies on patients with stroke-risk using single photon emission CT. Returning to Debrecen, Hungary, I invested a lot of energy to establish the first neurosonological laboratory in Hungary and founded the Hungarian Neurosonological Society. My enthusiastic team started not only the diagnostic but also the research work using ultrasound methods and clinicopathological observations.

Q3 How does your involvement as a serving member on numerous editorial boards contribute to increased awareness of cerebral circulation disorders and neurosonology?

My research team in Debrecen was so successful that I was elected to the Executive Committee of the European Society of Neurosonology and Cerebral Hemodynamics (ESNCH) and 10 years later to president of the society. Hungary is located between East and West, therefore I consciously elaborated scientific and clinical collaborations with German (Münster, Giessen), Israeli (Tel-Aviv), Romanian, Serbian, Croatian, and Ukrainian colleagues. We hosted numerous Japanese, Dutch, Israeli, and German colleagues (e.g., Ritter, Schulte-Altedorneburg, Toyota, Nishi, etc.) who spent months in Debrecen performing clinicopathological observations, experimental investigations, and neurosonological studies. My department was also very active in postgraduate teaching, both by the European Federation of Neurological Societies (EFNS), now European Academy of Neurology (EAN), and in the European Stroke Organisation (ESO). I was the Chair of the European Cooperating Committee of the EFNS for years. The relatively underpaid young neurologists in the Eastern and Middle-European countries could not participate in expensive western conferences; therefore, we invented the system of regional teaching courses in Odessa, Bucharest, Targu Mures, Belgrade, Ushgorod, Lviv, etc. The students did not come to the teachers but the teachers travelled to them. In practice, professors of western neurological departments, including Hacke, Diener, Bornstein, Kalvach, Brainin, and Ringelstein, travelled to the Eastern and Middle European countries to teach the young neurologists on postgraduate courses, with the financial support of the EFNS.

My mentor, Molnár, recognised the outstanding importance of stroke in Eastern European countries due to many vascular risk factors, insufficient healthcare, and unhealthy healthy lifestyle, and established the second Cerebrovascular Stroke Unit in Europe in 1969. As I took over the directorship of the Department of Neurology in Debrecen (1992, aged 40 years), I continued his pioneer efforts collected during my scholarship in Japan, France, and Germany. A modern stroke care system has been built up in Debrecen with a catchment area of 0.5 mi. The patients are transferred directly from their home to the CT after prenotification of the CT-lab. CT angiography, perfusion CT, and MRI help the correct diagnosis. A board-specified neurologist is present in the department 24/7, in person, and they investigate the stroke patients in the CT lab, analyse the results of imaging and lab results, and decide about intravenous or mechanical thrombectomy. The intensive care unit is a part of the Neurology and Cardiology department, which are located in the same building. The close cooperation with cardiologists, the availability of a high quality laboratory, and the CT, MRI, and PET improve our diagnostic accuracy. In 2022 we performed 184 intravenous lyses and 120 mechanical thrombectomies. I think the Széchenyi award, donated me by the President of the Republic, is the acknowledgement of the self-sacrificing work of my team. Our complex activity, which includes education, clinical work, and research, is never a 'one man show', but the effort of a good team.

Q4 You were awarded the Széchenyi Prize in 2020. Can you highlight the breakthrough moments in your academic and research career that led to this outstanding award?

The efficient graduate and postgraduate education of the neurological disorders is of critical importance. The university years provide only a short and superficial insight into neurological disorders; therefore, my coworkers (Kovács and Bencs) and I produced two types of multimedia presentations and films (in English) for young neurology residents.

The first type involved typical or unusual neurological cases, with their history, laboratory findings, imaging, differential diagnosis, outcome, and sometimes autopsy. We have dozens of them. The second type was a multimedia presentation of common acute neurological diseases such as headache and vertigo through video demonstration of a true patient (with informed consent) from admission until discharge, including case history, neurological status, and instrumental investigations. Then, the epidemiology, differential diagnosis, and evidence-based therapeutic options of the disease are discussed and the outcome is shown. Last but not least, we summarise the tasks of the family physician, including follow-up and secondary prevention, and suggest literature for further information and guidelines. This second type of material focuses on the detailed introduction of a disease, rather than a single case, and is therefore useful for medical students or residents who do not have much experience. Recently, I offered the numerous Type 1 and Type 2 teaching materials to EAN for use by its young members.

Q5 Where are the current literature gaps within the field of cerebral circulation disorders and neurosonology?

Neurosonology is important for stroke care from two different points of view. Diagnosis of carotid stenosis, including severity, structure of the plaque, and risk of embolisation during endarterectomy or stenting is an important non-invasive screening method in stroke prevention. On the other hand, some neurological methods, such as TCD, can detect spontaneous or intervention-provoked microembolisation from heart surgery, carotid desobliteration, etc. TCD is useful in neurologic intensive care (e.g., follow-up of vasospasm after subarachnoid haemorrhage) and it is the only simple, non-invasive technique that can monitor the cerebral blood velocity changes continuously. I am very proud of our colleague Garami, who graduated from our university, learned the ultrasound in my lab, and continued his activity at the National Aeronautics and Space Administration (NASA), Houston, USA, instructing astronauts on how to use TCD in the space. I think neurosonology will remain an important discipline for the prevention, diagnosis, and research of stroke.

Q6 You have recently been appointed as Chair for the Local Organising Committee for EAN 2023. Could you please explain what this position involves and how it contributes to the success of the EAN?

I am the chair of the Local Organizing Committee of the EAN congress 2023 in Budapest. Conference venue, programmes, department visits, patient demonstrations, and hands-on courses all need to be managed. Budapest is an optimal location for EAN, because the city is not far from the western countries and near the eastern ones. Neurologists living in Eastern and Middle European countries (Poland, Slovakia, Ukraine, Russia, Bulgaria, Romania, etc.) can easily come to Budapest because the plane, train, and highway connections are excellent, and the city is not only beautiful, but safe and relatively cheap. There are many hotels and museums and I strongly suggest to visit the extraordinary House of Music, which was planned by a Japanese architect and the Museum of Fine Arts.

Q7 Can you talk about the ways in which EAN aims to be the 'Home of Neurology', advance high-quality patient care, and reduce the burden of neurological diseases?

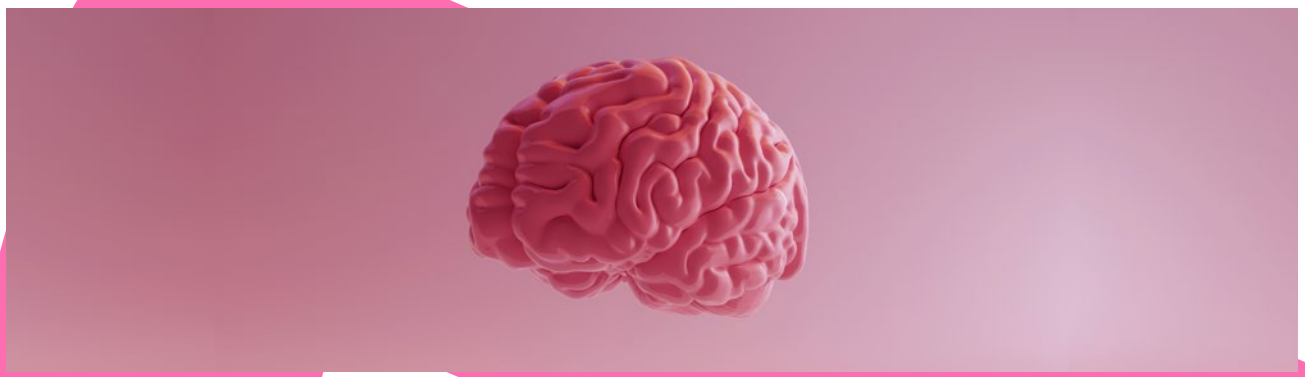
We all know that the western societies are ageing. The older a society is, the more neurological diseases can be found, such as vascular disorders, dementias, and Parkinson's disease. In my opinion, EAN has three important tasks in the future: in person and online postgraduate education, a common platform to find cooperating partners in research, and acting as catalysator to promote the evidence based diagnosis and therapy.

Q8 What are the most exciting changes that have been made to the scientific programme for EAN 2023 compared to EAN 2022?

The use of digital technology for the early diagnosis of dementia, Parkinson's disease, and vascular disorders. Artificial intelligence and robotic technology will increase the efficacy of the neurological diagnosis and therapy in the future. I think that the management of 'big data' and the use of artificial intelligence and robotic technology are the most important new features of the EAN congress 2023, as well as the new observations of neurological complications in patients post-COVID-19.

Q9 Are there any innovations on the horizon in the field of neurosonology that you think are particularly important?

In the future we will have more reliable data about the instability of carotid plaques after analysing the ultrasound characteristics. This information has clinical importance because it helps our decision-making for endarterectomy, stenting, or conservative therapy. TCD has been a useful device for monitoring cerebral microemboli and vasospasm, as well as diagnosis of Parkinson's disease for years, but the therapeutic application of ultrasound (e.g., focused ultrasound in tremor therapy) opens a new avenue in neurosonology. The transcranial ultrasound can monitor the cerebral blood velocity/flow and its changes continuously (second-to second) after pharmacotherapy or interventions such as endarterectomy and stenting, while the MRI, CT, and PET only provide information about the status. So, this unique ability of TCD provides a bright future for the use of neurosonology in central nervous system research.



Ambra Stefani

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Q1 What initially sparked your interest in neurology, leading you to a research career focusing on sleep and neurodegeneration, and what has motivated you to continue researching?

Neurology is a fascinating field, as the nervous system is complex, and most brain functions are still not fully understood. So, for researchers in neurology and in neuroscience, there are still many important questions to be answered, making this area of research very stimulating, challenging, and fascinating. Among the complex brain functions to be disentangled, sleep is particularly captivating. We spend one-third of our life sleeping, and we are only starting to disentangle sleep functions more and more. The link between sleep and neurodegeneration is strong in particular for what concerns isolated rapid eye movement (REM) sleep behaviour disorder as prodromal synucleinopathy, and for what concerns the role of sleep in maintaining brain health, partly through the glymphatic system. The possibility to be able in the future to detect and treat neurodegeneration in the prodromal or even preclinical phase using sleep as a window into the future of the brain, and to help prevent or modulate neurodegeneration through sleep improvement, is a powerful motivation for me to continue research in this field.

Q2 Do you think there are any misconceptions about your speciality?

I do think there are some misconceptions about neurological sleep medicine. Sometimes sleep problems are regarded as a luxury of wealthy people and not considered as a relevant field in neurology. However, sleep disorders are present as comorbidities in several neurological (and non-neurological) diseases and contribute to worse prognosis and/or worse quality of life in these patients. Moreover, it has become increasingly clear that sleep has a vital function in maintaining brain health, and a healthy sleep is as essential as, e.g., a healthy diet and exercise, for healthy brain aging and prevention of neurological diseases. In particular, a growing amount of data is unravelling more and more about the bidirectional relationship between sleep and neurodegenerative diseases. Healthy sleep is fundamental also when addressing health disparities, as for example indigent people can less frequently get a healthy sleep due to environmental and social factors, among others. Thus, the view that health sleep is a problem of wealthy people or wealthy societies is fundamentally wrong. Hopefully, the current misconception will disappear in the near future.

Q3 What are the most significant breakthroughs you have seen in the field of sleep medicine since starting your career as researcher in 2013?

There have been a few breakthroughs in the sleep medicine field in the past 10 years. For what concerns my main area of research, one is the establishment of isolated REM sleep behaviour disorder as early α-synucleinopathy, based on long-term follow-up data, on the investigation of long-standing non convertors (i.e., those patients with still isolated REM sleep behaviour disorder 10 years or more after diagnosis) and on the demonstration of pathologic α-synuclein aggregates in these patients. Additionally, evidence has started

to disentangle the close relationship between sleep and neurodegeneration, also through the study of the glymphatic system. Another important breakthrough is the improvement in understanding of narcolepsy pathophysiology, with demonstration of the long-hypothesised role of autoimmunity in this condition. Moreover, a completely new class of drugs acting on orexin receptors have been developed or are currently under development: dual orexin-receptor antagonists for the treatment of insomnia, and orexin agonists for the treatment of narcolepsy. Besides these advancements, the technological developments with use of wearables and nearables, as well as the application of artificial intelligence in the sleep medicine field need to be mentioned, as these will likely lead to a revolution in how we assess and manage sleep disorders in the coming years.

Q4 You currently more than 120 publications to your name for your research on sleep. What do you believe to be the current gaps in literature?

This is a relatively recent field of research, so there are still gaps in the literature. First of all, long-term follow-up studies are needed, to prospectively confirm that disturbed sleep increases the risk of neurodegeneration. Moreover, basic science data and translational research further elucidating this bidirectional relationship will be critical and will improve knowledge on how specific changes in sleep are linked to specific neurodegeneration pathways. Further, long-term, prospective, randomised controlled trials with interventions to improve sleep longitudinally assessing biomarkers of neurodegeneration will fill a gap in understanding how to promote brain health and prevent or modulate neurodegeneration through sleep enhancement.

Q5 You have specialised in REM sleep behaviour disorders. What topics do you believe require greater attention?

When focusing on the REM sleep behaviour disorder area, I believe that isolated REM sleep without atonia, i.e., prodromal REM sleep behaviour disorder, requires greater attention as it possibly allows identification of α-synuclein related neurodegeneration more than a decade (maybe two or even more) before manifestations of the classical motor or cognitive symptoms. However, this consideration leads to another topic urgently requiring more attention: qualified communication and counselling when diagnosing a prodromal or preclinical neurodegenerative disease (e.g., REM sleep behaviour disorder or REM sleep without atonia). From a scientific point of view, diagnosing neurodegeneration in a prodromal or even preclinical phase is a great opportunity to study the underlying processes leading to the overt clinical manifestations of disease. But it is fundamental to keep in mind that for people diagnosed with these conditions, the diagnosis is a cause of stress and anxiety without a concrete possibility of acting against this sword of Damocles, at least at the present moment. Therefore, assessing patients' preferences regarding disclosure, shared decision-making, individually tailored communication, and availability to answer all potential questions are essential.

Q6 You are on the teaching course sub-committee for the European Academy of Neurology (EAN) 2023. How is the EAN using its position to educate surgeons, nurses, and trainees about the field of neurology?

The EAN aims to foster and support the development of neurological excellence, leading to better patient care and outcomes, and promotes quality in neurology. To achieve this aim, the EAN educates not only neurologists but also related scientists, thus including interested surgeons and nurses. Trainees are a key target group of EAN's activities, as reflected in the manifold events organised specifically for trainees, such as the Spring and Autumn Schools, the most recently started Science School, fellowship grants, a mentoring programme, and the leadership programme. Accordingly, one of the EAN priorities is education, which is reflected in activities like the European Training Requirements for Neurology, the very comprehensive E-learning platform 'eanCampus', and podcast updates through the 'eanCast: Weekly Neurology'. EAN is going even further and working on a pre-graduate neurology curriculum, which can be used afterwards as a recommendation and guidance paper to many neurological member societies and medical

universities when looking at teaching in neurology and to harmonise neurology education even before the beginning of neurology training.

Q7 What is one of the biggest challenges for the EAN in their goal to advance high-quality patient care and to reduce the burden of neurological diseases?

Being a European Academy, one of the biggest challenges is certainly to overcome differences among countries, avoiding having situations where only basic care is possible, coexisting with excellence centres where high-quality patient care is provided, but instead increasing the level in all Europe to high-quality neurological care. So many factors are involved, from education in different countries to cultural and economic issues, making this a huge challenge. On the other hand, reducing the burden of neurological diseases is key, and it becomes more and more clear that the only way to really lower this burden is a shift towards detection of early stages of neurological diseases (i.e., preclinical and prodromal stages, for diseases like neurodegenerative conditions) and towards prevention, acting on risk factors. This is a huge challenge. Raising awareness on brain health is the obvious starting point, and the EAN is doing a great job on this, as can be seen online.[1]

Q8 Are there any innovations on the horizon in the field of sleep disorders that you think are particularly noteworthy?

I expect several innovations and changes in the sleep medicine field in the upcoming years. In my opinion two innovations are particularly noteworthy. As mentioned before, there is a massively increasing use of wearable devices, nearables, and other digital health technologies, which at least in part use artificial intelligence-based methods to analyse and interpret collected data. I believe that these instruments will revolutionise the way we assess and manage sleep and sleep disorders, although a lot still needs to be done to achieve a common framework for assessment and application of digital health technologies. This is already clearly visible on the horizon, whereas more far away and more blurred on the horizon is the other substantial innovation: sleep becoming a constitutive part of the brain health pillars, and sleep improvement as a strategy to prevent neurodegeneration. More work is certainly needed to further clarify the general role of sleep in brain health, as well as the role of specific sleep changes in different neurological disorders, but I am excited about the idea that in the near future we will have instruments to improve sleep, and use them to reduce the risk of neurodegenerative diseases or even prevent them.

Q9 Since your appointment as researcher at the Innsbruck Medical University, Austria, what has been your proudest achievement?

I started my career as researcher at the Sleep Disorders Clinic, Department of Neurology, of the Medical University Innsbruck, Austria, 10 years ago. This time was not fully dedicated to research, as it included my residency in Neurology, besides my PhD in neuroscience. My achievements have been possible thanks to the constant support of my mentor, Professor Birgit Högl, Head of the Sleep Disorders Clinic. If I have to pick one thing as my proudest achievement, I would select the study I planned and coordinated on analysis of olfactory mucosa for pathologic α-synuclein using real-time quaking-induced conversion in isolated REM sleep behaviour disorder, at the Department of Neurology in Innsbruck, Austria, and in collaboration with Professor Gianluigi Zanusso's group from Verona Medical University, Italy, and with Professor Alex Iranzos group from the Hospital Clinic de Barcelona, Spain. Another important achievement I would like to mention was being awarded the Max Kade Fellowship, which supports my current research on REM sleep behaviour disorder with Professor Aleksandar Videnovic at the Neurological Clinical Research Institute, Massachusetts General Hospital, in Boston, USA.

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Q1 What motivated you to pursue a career in clinical neurology?

I have always been attracted to mathematics and logic, and during my university studies I found neurology to be the most logical subject. I was amazed with how we could get closer to such a complex system as the brain, and how it was possible to draw conclusions about brain dysfunction using simple tests and physical examinations. Moreover, I found the brain to be the most amazing organ. Unlike other organs, each area of the brain has its own function, and damage to each area results in a characteristic dysfunction.

Q2 Do you think there are any misconceptions about your speciality?

Many people, sometimes even the professionals, confuse neurology and psychiatry, and do not understand the differences between neurology, psychiatry, and psychology. One of the reasons for this is that the word 'nervousness' includes the nerve, which is examined by neurologists. The other misconception is that painful diseases are more dangerous than the painless ones. It is interesting to see that patients with low back pain get to the hospital earlier than patients with stroke, just because the stroke is not painful. It is difficult to understand why patients are not frightened by weakness of the extremities.

Q3 The Debrecen Clinic is believed to be one of the top departments for neurological care in Hungary. What do you think other university hospitals could learn from the University of Debrecen Clinic?

I think that university clinics in Hungary are well equipped and provide excellent care for neurological patients. Of course, there are times where one clinic is better than another at treating certain diseases, but in other respects the situation can be reversed. Debrecen has always been at the forefront of stroke management and the study of stroke pathophysiology, which can be rooted in the fact that my predecessors were interested in stroke and cerebral circulation. Debrecen can be proud of stroke management and cerebral haemodynamic research based on the non-invasive transcranial Doppler methos, which offers a real time examination of cerebral blood flow changes.

Q4 What was the key message that you were trying to deliver in a recently published article that you co-authored, entitled 'Elevated Blood Alcohol Concentration Is Associated with Improved Clinical Outcomes of Intravenous Thrombolysis Treatment in Acute Ischemic Stroke Patients'?

It was a very interesting observation: that those patients who had a stroke under the effect of alcohol and were treated with tissue plasminogen activator had a much better clinical outcome than patients who had not consumed alcohol. Alcohol seems to potentiate the effect of intravenous thrombolysis without increasing haemorrhagic complications. Of course, this retrospective study needs to be validated in a prospective,

multicentre study, but it is an interesting thought that many neuroprotective drugs have failed, while there is a common, every-day used 'drug' that could be effective.

Q5 As an educator, what will you focus on in the coming years?

Education must be done at many levels. We must educate patients to recognise their illness and not delay in calling the ambulance. We must teach graduate students to recognise the most important neurological diseases and to know the diagnostic and treatment options. Finally, we have to educate the doctors, individuals who have already graduated and specialised, to keep their knowledge up to date and keep up with the development of science.

> "We must teach graduate students to recognise the most important neurological diseases."

Q6 You are on the local organising committee for the European Academy of Neurology (EAN) 2023 congress. How is the EAN using its position to promote and support the development of neurological excellence in Europe, leading to better patient care and outcomes?

The EAN brings together neurologists and scientists at its annual conferences to share their knowledge and exchange experiences. The EAN offers online educational resources and courses to provide continuous learning. Moreover, the EAN's Clinical Fellowship Programme provides visiting opportunities in a department with excellent expertise in a specialist field. Special scientific panels aim to co-ordinate clinical research, interpret results of clinical studies, and produce clinical guidelines. The EAN guidelines promote the practical use of the latest scientific results and ensures the widespread dissemination of the best clinical practice.

> "The EAN offers online educational resources and courses to provide continuous learning."

Q7 You have recently been appointed as Head of the Debrecen Clinic. What are you hoping to achieve in this role?

Our department has always played a leading role in stroke treatment and research. I would like to preserve these results and further develop and expand recanalisation therapies. I would like to develop other areas of neurology, such as movement disorders, epilepsy, neuromuscular and neuroimmunological diseases. For this, more neurologists, who have gained longer or shorter experiences in other leading European clinics, are needed. However, the biggest challenge right now is building and retaining an excellent team of nurses and assistants. If this can be achieved, we can hope that more and more patients will leave the clinic in good condition at the end of their treatment. Furthermore, I would like the students studying at our department to receive the best education and to leave satisfied when they have finished their education.

Q8 Over the years that you have been practising as a neurologist, what are the most significant changes you have observed?

We are witnessing such a rapid and enormous scientific and instrumental development that is difficult to comprehend. Even in the 1980s, neurologists performed pneumoencephalography, percutaneous carotid angiography, and myelography. When I started working in 1991, we had to think about who to send for CT. Today, magnetic resonance examinations belong to a daily routine, and new special magnetic resonance sequences are developed in every year. The human genome is being sequenced, brain activity can be mapped, surgeons operate with robots, non-invasive methods are used to estimate the penumbra, aneurysms are closed, thrombi are removed by neurointerventionalists with use of catheters, Parkinson's disease is treated with a neuropacemaker, and spinal muscular atrophy is cured with gene therapy, etc.

Q9 Are there any significant advancements on the horizon in the field of neurology?

There are a number of advancements, including gene therapies that may change the course of inherited neuromuscular disorders; immune

checkpoint inhibitors that may improve the oncotherapy; antibodies that are being produced and used against β-amyloid plaques in patients with Alzheimer's disease; penumbra imaging, which allows personalised reperfusion therapies in patients with stroke; thrombi causing large vessel occlusion are removed with use of microcatheters; and a minimally invasive surgery technique combined with local tissue plasminogen activator treatment is used to evacuate intracerebral haematoma. It is unbelievable.

Defining Meaningful Outcomes for Patients with Spinal Muscular Atrophy in the Era of Gene Therapy

This industry sponsored symposium took place as part of the 15th Congress of the European Paediatric Neurology Society (EPNS), held 21st June 2023 in Prague, Czechia

Chairpeople:	Jana Haberlová[1,2]
Speakers:	Jana Haberlová,[1,2] Francesco Muntoni,[3,4] Eugenio Mercuri[5]

1. Charles University, Prague, Czechia
2. Motol University Hospital, Prague, Czechia
3. University College London, UK
4. Great Ormond Street Hospital, London, UK
5. Gemelli University Hospital, Rome, Italy

Disclosure:	All symposium presenters received an honorarium from Novartis Gene Therapies, and disclosed involvement in Novartis Gene Therapies educational events. Haberlová reports being a consultant for Novartis, Roche, and Biogen; and Principal Investigator for spinal muscular atrophy study BP42940 (Roche). Muntoni reports being a Principal Investigator for clinical trials sponsored by Novartis, Biogen, and Roche; receiving compensation for participation in advisory boards and symposia from Biogen, Novartis, and Roche; and institutional funding for an spinal muscular atrophy registry from Biogen and Roche. Mercuri reports being a Principal Investigator for, and receiving advisory board fees from, AveXis /Novartis Gene Therapies, Biogen, PTC Therapeutics, Roche, and Scholar Rock; and receiving an institutional research grant for a disease registry from Biogen.
Acknowledgements:	Medical writing assistance was provided by Eleanor Roberts, Beeline Science Communications, Ltd, London, UK. This is an addendum for EMJ Neurol. 2023;11[1]:72-81. Since the publication of this article, the following disclaimer has been added: The symposium content and views expressed herein are those of the speakers. This content is for healthcare professionals only.
Disclaimer:	The symposium content and views expressed herein are those of the speakers. This content is for healthcare professionals only.
Support:	The publication of this article was supported by Novartis Gene Therapies.
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Meeting Summary

Spinal muscular atrophy (SMA) occurs due to a mutation in the *SMN1* gene. It most typically has an onset in early childhood and presents as impairment in motor, bulbar, and respiratory function. In a symposium at the European Paediatric Neurology Society's (EPNS) 2023 congress, three leading experts in SMA discussed the findings of real-world evidence (RWE) studies of the first gene therapy approved in NMD, in 2019 in the USA, and 2020 in Europe. Onasemnogene abeparvovec combines an adeno-associated virus (AAV9) vector with a functional copy of *SMN* complementary DNA, and is delivered in a single infusion. While clinical trials of onasemnogene abeparvovec show its efficacy and safety in populations with SMA who are symptomatic and pre-symptomatic, RWE studies have expanded the understanding of this therapy to wider SMA patient groups in the real-world clinical practice setting. Combined, such studies show how administration of onasemnogene abeparvovec in patients with symptomatic SMA can lead to motor and respiratory function improvement or stabilisation and achievement of motor milestones in naïve or pre-treated patients, while in patients who are pre-symptomatic, administration may lead to a normal development. The experts also discussed how understanding the benefit/risk profile of this gene therapy can help with decision-making over its use in patients with SMA. They highlighted how onasemnogene abeparvovec efficacy and safety can be affected by clinical status, disease severity, weight, age, and previous treatment at the time of infusion. Recently published RWE points to improvements being best predicted by baseline Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) score and age at treatment initiation, and in regard to safety and tolerability profile, liver enzyme elevation is the most predominant treatment-emergent adverse event (TEAE) with onasemnogene abeparvovec; hence, a prednisolone (or equivalent) dosing regimen is administered prior to, during, and for at least 3 months following infusion. The experts discussed how careful monitoring and adequate multidisciplinary team discussion, including colleagues from other specialities, such as hepatologists and paediatric immunologists, is advised in all cases of SMA receiving an onasemnogene abeparvovec infusion.

Introduction

At the 15th Congress of the EPNS, Jana Haberlová, Charles University, Prague, Czechia, and Motol University Hospital, Prague, Czechia; Francesco Muntoni, University College London, UK, and Great Ormond Street Hospital, London, UK; and Eugenio Mercuri, Gemelli University Hospital, Rome, Italy, all of whom have been involved in a number of studies investigating SMA treatment, reviewed efficacy and safety data from RWE settings of onasemnogene abeparvovec. This is a non-replicating recombinant AAV vector that delivers a fully functional, stable, human SMN transgene to the nuclei of motor neurons via use of an AAV9 capsid that can cross the blood–brain barrier. The *SMN1* gene in transduced cells is expected to be stably expressed by post-mitotic cells for an extended time. The AAV9 virus is not known to cause disease in humans.[1,2] The experts also discussed benefit/cost considerations for this therapy, and managing patient and caregiver expectations in those eligible to receive it.

SMA occurs at a global incidence of approximately 1 out of 10,000 live births, though this can differ by region.[3] The muscular weakness and atrophy indicative of SMA is due to motor neuron loss, as a result of reduced expression of SMN protein. This occurs because of a mutation in the *SMN1* gene at chromosome 5q11.1–13.3.[4] More recently, progression of, and survival with SMA has been improved by disease-modifying therapies that work by allowing SMN expression, to the extent that if SMA is detected early, some

treatments may enable some patients who are pre-symptomatic to achieve age-appropriate motor milestones.[5-7] These therapies include onasemnogene abeparvovec;[1,2] nusinersen, a splice-switching antisense oligonucleotide;[8] and risdiplam, which binds to *SMN2* pre-messenger RNA.[9] Onasemnogene abeparvovec is a gene therapy approved for SMA treatment,[10] with the European indication being for patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene, and either a clinical diagnosis of SMA Type 1, or up to three copies of the *SMN2* gene.[1]

Across clinical trials, managed access programmes and commercial settings, currently over 3,000 children with SMA have been treated with onasemnogene abeparvovec.[11] Completed trials include START,[12,13] STR1VE-US,[14] STR1VE-EU,[15] and STR1VE-AP[16,17] in patients who are symptomatic, and SPR1NT[6,7] in patients who are pre-symptomatic. There are ongoing or recruiting trials including long-term follow-up studies LT-001 and LT-002[18] in patients who are symptomatic;[13] and OFELIA,[19] and SMART[20] in symptomatic and previously treated patients. LT-002 also follows up patients who are pre-symptomatic, treated in the core SPRINT trial.[18] RESTORE is a sponsored SMA registry of patients treated in RWE in co-operation with the main Academic SMA Registries.[21]

Real-World Evidence of Onasemnogene Abeparvovec Efficacy in Spinal Muscular Atrophy Gene Therapy

Jana Haberlová

The first objective of the symposium was to discuss how RWE data have expanded the use and understanding of onasemnogene abeparvovec treatment beyond the cohorts investigated in the clinical trials. Haberlová discussed how, up to May 2023, there have been 27 peer-reviewed, independent, RWE publications of onasemnogene abeparvovec, including treatment-naïve, and those switched from nusinersen or risdiplam. These involved 574 patients with, where data are available, an age range of 2 weeks–6 years, and a weight range of 2.5–17.0 kg (Table 1).[2,22-47]

Table 1: Numbers and types of patient in real-world evidence studies of onasemnogene abeparvovec.[2,22-47]

SMA type	n (%)*	*SMN2* copy number	n (%)*	Other treatment	n (%)†
Pre-symptomatic	59 (10.3)	1 copy	3 (0.5)	Bridge	4 (0.7)
Type 0	1 (0.2)	2 copies	320 (55.7)	Switch	324 (56.4)
Type 1	380 (66.2)	3 copies	146 (25.4)	Add-on/ combination	10 (1.7)
Type 2	73 (12.7)	≥4 copies	17 (3.0)	Naïve	236 (41.4)
Type 3	1 (0.2)	Not reported	88 (15.3)	Not reported	0 (0.0)
Not reported	60 (10.5)	N/A			

*Not all studies report SMA Type or *SMN2* copy number.

†One patient in the combination group received only three of the four loading doses of nusinersen and was excluded from the analysis.

N/A: not applicable.

Overall, these RWE data found that administration of onasemnogene abeparvovec in patients with SMA led to stabilisation or improvement of motor function and achievement of motor milestones, and stabilisation or improvement of respiratory function.[2,22-24,27,29,31,33-36,39-41,43-47] Also shown was that the efficacy and safety of onasemnogene abeparvovec can be affected by several factors, including clinical status, weight, age, previous treatment, and disease severity at the time of infusion.[24,34,41,44,45]

Many of the published data of SMA use the CHOP-INTEND measure to ascertain baseline function and track changes over time. CHOP-INTEND was developed to capture specific targeted motor skills that are clinically significant for the SMA-I population. Each of the 16 motor skills, including neck flexion, rolling, hand grip, and spontaneous movement, is scored from 0–4, from none to full ability, for a total possible score of 64.[48] In regard to the efficacy of onasemnogene abeparvovec, RWE data of patients who are pre-symptomatic appear to attain the highest mean increase in CHOP-INTEND scores compared with patients with SMA Type 1 or 2,[24,41] with motor function outcomes not influenced by *SMN2* copy number or sex in patients who are pre-symptomatic.[41] In patients with SMA Type 1 treated with onasemnogene abeparvovec, while an increase in motor function is observed in all age groups,[2,22,31,33,36,38,41,43,46] the level of improvement is best predicted by baseline CHOP-INTEND score and age at treatment initiation.[24] For patients who have been previously treated with a disease-modifying therapy, onasemnogene abeparvovec infusion can lead to further respiratory function improvement or stabilisation, and/or achievement of new motor milestones.[2,22-24,27,29,31,33-36,38-41,43-47]

From data gathered in the RWE data, Haberlová concluded that, further to clinical trial data, onasemnogene abeparvovec shows efficacy in patients with SMA in terms of symptom stabilisation and improvement.

Adeno-Associated Virus-Based Gene Therapy Benefit/Risk Profile

Francesco Muntoni

Although the benefits of viral vector therapy include how targeted it can be to the cause of a disease (in this case, onasemnogene abeparvovec replaces the missing *SMN1* gene and boosts SMN production),[1] there are potential treatment-associated, but manageable, adverse events. An immune response to the vector can arise as, while the virus itself is not pathogenic, a high viral load is needed for AAV-based gene therapies.[49] Due to such potential adverse events, close monitoring is required for a number of weeks pre- and post-onasemnogene abeparvovec infusion.[25,30,50,51] With this in mind, Muntoni discussed how knowing and understanding the overall benefit/risk profile of onasemnogene abeparvovec can help healthcare professionals when making treatment decisions for patients with SMA. Muntoni also stressed the necessity prior to and during an onasemnogene abeparvovec infusion of having a network of colleagues that have been educated with regard to gene therapy, and pre-warned prior to the infusion. “It is critical,” Muntoni said, “that other colleagues, such as physicians and nurses, are aware of what you are doing, because not everyone necessarily has expertise in this field.” Muntoni highlighted the need to “prepare the hospital team, even if 99% of the time they are not involved.”

To aid in identifying typical events following onasemnogene abeparvovec infusion, Muntoni highlighted how, in the first week, events indicative of activation of innate or adaptive immunity includes flu-like symptoms, such as malaise, loss of appetite, and fever, along with vomiting and troponin increase.[30] In the first 2 weeks, an early humoral response and/or an innate immune response against the viral capsid proteins is observed in some patients. This can cause complement activation consistent with thrombotic microangiopathy (TMA), low platelets, troponin release from cardiac muscle and platelets, and kidney and liver injury. Cardiogenic shock has been reported with other AAV therapies;[25,50,51] however, Muntoni reported that they had not personally seen this with onasemnogene abeparvovec. In the first month, liver toxicity and inflammation may be indicative

of a T cell-mediated immune response against the viral capsid.[51] In the following months, heart muscle inflammation, which can be indicative of a humoral and T cell-mediated immune response against the transgene protein, has been reported with other AAV therapies, but has not been observed with onasemnogene abeparvovec.[51]

Where safety and tolerability was assessed in onasemnogene abeparvovec RWE settings, TEAEs were reported fairly frequently, but with different degrees of severity.[2,22,23,28,30,31,36,40-43,46,47] The most common risk associated with AAV-based gene therapies is hepatotoxicity,[52] as evidenced by liver enzyme elevation.[2,22,23,28,30,31,36,40-42,46,47] This may be due to the AAV9 vector in onasemnogene abeparvovec having tissue tropism to the liver, as well as to skeletal muscle, the heart, and the brain.[53] It may also be due to an immune system primed by prior exposure to wild-type AAV, which can result in T cell and humoral immunity against the vector in the liver.[49,53] With onasemnogene abeparvovec, there appears to be a lower risk of liver transaminase elevation in patients who are younger and/or have a lower body weight, and a higher risk in older, previously treated patients.[2,23,24,40,41,44,45] According to Muntoni: "More severe liver involvement than usual may be observed in some patients who experience quite significant elevation of transaminases. Although liver failure is exceptional, it can potentially occur."[28]

Corticosteroids are used prior to and following onasemnogene abeparvovec infusion, as they can block the T cell response to capsid-derived peptides presented by transduced hepatocytes, and have a role in protecting hepatocytes against apoptosis and preventing cytolysis of ballooned hepatocytes.[54,55] According to Muntoni: "Corticosteroids appear to be effective in removing the most significant peaks of transaminitis." Indeed, studies show that elevations in liver enzymes resolve in most cases following such treatment,[2,23,36,37,40,41,44] and that most patients do not require corticosteroid treatment long term.[24,30,40,41,44]

Scheduling of corticosteroid administration is detailed in onasemnogene abeparvovec prescribing guidelines.[1] This includes starting oral prednisolone (or equivalent) at 1 mg/kg/day 24 hours prior to infusion, then continuing this dose for 30 days, followed by 28 days' tapering if liver enzyme values are below two-times the upper limit of normal.[1,56] Where liver-related AEs have occurred, short-term treatment with high-dose corticosteroids is advised in the prescribing information of a number of gene therapies, including onasemnogene abeparvovec.[1,49,57,58] Muntoni confirmed that, "if the patient is having bigger liver problems than you expect, there are protocols for using high doses of steroids, including intravenous administration." During the panel discussion, when asked if the initial dose should be 2 mg/kg/day prednisolone (or equivalent), Muntoni noted how, in their centre's experience, this higher starting dose did not make a difference, although it can be used if liver enzymes increase. Mercuri commented how the higher dose may also lead to liver complications; hence, not being suitable for every patient.

Other TEAEs reported following onasemnogene abeparvovec infusion are transient, mild increases in troponin I levels with no aberrant cardiac assessment report;[2,23,36,41] pyrexia;[2,23,28,30,36,41,42,47] vomiting; loss of appetite; and diarrhoea.[2,23,28,30,41-43,47] RWE evidences showed transient thrombocytopenia (where this was assessed) in 16–100% of patients, which generally normalised without intervention.[2,23,36,37,40,41,44] Also observed, though rare, is TMA.[42,43] "This is the adverse event that is most important in terms of morbidity," said Muntoni, "but only exceptionally is it very significant, and it is not difficult to monitor for." During the panel discussion, Muntoni explained how TMA usually occurs in the first 2 weeks after infusion, but stressed that a patient needs to be monitored very carefully for a potential TMA in the first 3 months.

Due to potential TEAE, patients should be followed-up every 6 months to a year following the initial infusion and have liver function tests as, said Muntoni: "We have an obligation to follow these patients clinically." Muntoni discussed how vital it is that the family of the patient understand the immediate post-infusion time. "When you describe and discuss [the treatment], managing expectations with the family is important, so they do not receive an AAV gene therapy then disappear for 6 months." Haberlová confirmed that, in their practice, even cases identified via newborn screening, so treated while pre-symptomatic, are followed up for at least 10 years.

Understanding and Discussing Long-Term Outcomes with Onasemnogene Abeparvovec Across Different Spinal Muscular Atrophy Patient Populations

Eugenio Mercuri

The final objective of this symposium was to explore treatment expectations ,and which outcomes are most meaningful for patients and their families. Mercuri discussed how improving understanding of gene therapy predictors and outcomes can aid treatment decisions, and help with expectation management.[13,24] Mercuri utilised the results of the recent RWE publication from the Italian experience in treating patients with SMA with onasemnogene abeparvovec in a clinical setting, which they had been involved in Italy to discuss.

In this paper, predictors of the efficacy and safety of onasemnogene abeparvovec were investigated in both treatment-naïve patients (n=19) and those switched from nusinersen (n=46) or risdiplam (n=2). All 67 patients had at least 6 months' follow-up and an available safety profile, with 46 followed up for 12 months. Patients varied with respect to age (22 days–58 months, with one child of 72 months), weight (3.2–13.5 kg, with the older child being 17.0 kg), and disease severity.[24] Mercuri highlighted how these ranges, especially at the higher end, were much broader than those in clinical trials.[12-21,59] Most (63 out of 67) patients were symptomatic with SMA Type 1 (94.0%), and four were identified through neonatal screening and were pre-symptomatic. Just over two-thirds (68.7%) of the patients had a CHOP-INTEND assessment at the time of treatment, and at 12 months from first infusion.[24]

As can be seen from Table 2, independent sitting after onasemnogene abeparvovec infusion was achieved by all patients who were pre-symptomatic, and most of those who were symptomatic but had received another treatment prior to onasemnogene abeparvovec, even if they had not achieved this functional milestone with such treatment. Of the four patients who achieved standing, two were pre-symptomatic and also acquired independent walking at 16 and 17 months; one was symptomatic and treatment-naïve and stood independently at 12 months; while the other was symptomatic and pre-treated, and achieved this motor milestone at 34 months.[24]

For many patients, their CHOP-INTEND scores did not fall from baseline over the follow-up period, and for some there was an increase from baseline at 12 months. For example, most patients with a baseline CHOP-INTEND score <40 achieved a 12-month score ≥40, with some achieving a score ≥60. The best predictor of change in CHOP-INTEND scores was patient age, with the greatest change in those aged <6 months and the least change in those aged >24 months.[24]

"It is very important when we counsel families to try to keep their expectations under control," said Mercuri. In regard to these findings and treatment expectations, Mercuri discussed how "it is important to look at the variability of responses because, while a number of patients did achieve sitting at the time they were taking onasemnogene abeparvovec, some, though very few, never achieved sitting, even if they had been on both [onasemnogene abeparvovec and another] therapies." Conversely, Muntoni commented in the panel discussion that while the baseline CHOP-INTEND score is useful, these results show that "you could have a low CHOP-INTEND score in a [young] child with a very short disease duration, and significant improvement is still possible."

Safety findings in this RWE publication reflected those shown in clinical trials[12-21,59] with TEAEs within 7 days of onasemnogene abeparvovec infusion, including pyrexia (22.4%), vomiting (20.9%), a two-fold increase in aspartate transferase (AST; 39%), and a two-fold increase in alanine transaminase (ALT; 29.9%). The risk of elevated liver enzymes increased with age and weight, with a 5.76x greater risk of abnormal AST and a 11.08x greater risk of abnormal ALT in patients aged >24 months compared to those aged <6 months (where 'abnormal' is defined as two-times the upper limit of normal). No major serious TEAEs were observed.[24] Mercuri stressed how the age stratification regarding tolerability and safety results "does not mean we should not treat patients if they are aged over 24 months, but we should be extra careful."

While shorter term clinical trial and RWE results are promising for onasemnogene abeparvovec, Mercuri commented that "one concern is whether

Table 2: Achievement of motor milestones following onasemnogene abeparvovec infusion according to patient subgroup (n=66*).[24]

	Independent sitting†	Independent standing	Independent walking
Subgroup	**% (n/N)**		
Pre-symptomatic	100.00% (4/4)	75.00% (3/4)	50.00% (2/4)
Symptomatic, treatment naïve	37.50% (6/16)	6.25% (1/16)	N/A
Symptomatic, pre-treated*	82.60% (38/46)	2.17% (1/46)	N/A
Before onasemnogene abeparvovec	36.80% (14/38)	N/A	N/A
After onasemnogene abeparvovec	63.20% (24/38)	N/A	N/A

*One patient is not included due to non-treatment related fatality.

†Ability to sit without support and without a brace for at least 3 seconds.

N/A: not applicable.

these children are going to lose what they have acquired in the first year." LT-001[59] and LT-002[18] are two long-term follow-up studies of patients treated with onasemnogene abeparvovec across five clinical trials. LT-001 includes 13 patients with SMA Type 1 enrolled in the START clinical trial, which was carried out between May 2014–December 2017.[12,13] Participants are planned to be followed up for 15 years with annual visits for 5 years, then annual phone contact for 10 years. The current data cut-off is up to 7.5 years post-dosing.[60] LT-002 includes 25 patients with pre-symptomatic SMA with two or three copies of *SMN2* (from the SPR1NT trial),[59] and 38 patients with symptomatic SMA Type 1 (from the STR1VE-US, n=12;[14] STR1VE-EU, n=24;[15] and STR1VE-AP, n=2,[16,17] trials, run up to February 2020), with the 15-year follow-up consisting of biannual visits (years 0–2), then annual visits (years 3–5), then annual phone contact for up to 10 years. The current data cut-off is up to 4.3 years post-dosing.[18]

Interim data from these studies show the efficacy of onasemnogene abeparvovec up to 7.5 years post-treatment.[18,60] In LT-001, all included patients who received a therapeutic dose of this drug (n=10), achieved or maintained head control and independent sitting (sitting up straight with their head erect for ≥10 seconds without using arms or hands for balance or support), and two out of 10 (20%) maintained independent walking.[60] In LT-002, 32 out of 36 (89%) patients with SMA Type 1 and two *SMN2* copies achieved or maintained unsupported sitting. All four patients who did not achieve the motor milestone of independent walking in the parent study achieved this at follow-up.[18]

"When we have long-term follow-up, it is also possible to see whether there are additional [safety] concerns which were not addressed in the clinical trial," said Mercuri. "During the 90 days is when we really focus on adverse events," they continued, "but past this time frame, there was no evidence of any new safety signals, even up to 7.5 years post-dosing." In LT-002, two TEAEs

(bronchiolitis and pneumonia) occurring in one patient were deemed potentially treatment-related, but in both studies there were no serious TEAEs that led to study discontinuation, and there were no adverse events of special interest.[18,60]

In conclusion, Mercuri discussed how RWE[24] and long-term follow-up[18,60] data may help clinicians to work with caregivers to set appropriate expectations around gene therapy outcomes in children of different ages. "These data are important," Mercuri said, "as we all face families who want to switch therapy and the expectations are generally based on the clinical trials, so RWE and long-term evidence help us, as clinicians, to communicate and set up best expectations." Muntoni also, during the panel discussion, stressed that when counselling parents with a child who has noticeable motor dysfunction, including a low CHOP-INTEND score, bulbar involvement, and respiratory dysfunction, it is important to explain that while they may improve, it may not be to the same extent as a child without this baseline. However, they said, "any outcome is meaningful when it's different from progression and death, so it's just a matter of having the right expectations."

Conclusion

RWE data of onasemnogene abeparvovec[2,22-47] support the clinical trial data[6,7,12-17] and suggest that a wide range of patients with SMA can gain motor and respiratory function stabilisation or improvement following a single infusion. While TEAEs appear to be mostly transient, careful monitoring and long-term follow-up are needed.[2,22-47] These findings may help healthcare professionals with the treatment decision-making process for patients with SMA.

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Mitochondrial DNA Maintenance Disorders: Impact of Impaired Deoxynucleoside Triphosphates Metabolism

Presentation took place on 14th May 2023, as part of Euromit 2023 in Bologna, Italy

Presenter:	Ramon Martí[1,2] 1. Research Group on Neuromuscular and Mitochondrial Diseases, Vall d'Hebron Institut de Recerca, Barcelona, Spain 2. CIBERER, Madrid, Spain

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Meeting Summary

The maintenance of mitochondrial DNA (mtDNA) is dependent upon several nuclear gene-encoded proteins including enzymes forming the replisome needed to synthesise mtDNA. These enzymes need to be present in balanced quantities to function properly. In addition, mtDNA synthesis requires a balanced supply of nucleotides that is achieved by nucleoside recycling inside the mitochondria, and nucleotide import from the cytosol. Mitochondrial DNA maintenance defects are a group of diseases caused by pathogenic variants in the nuclear genes involved in mtDNA maintenance, and result from impaired mtDNA replication. Pathogenic nuclear gene variants identified to date include genes that encode enzymes of mtDNA replication machinery (such as *POLG*), genes that encode proteins that help to maintain a balanced mitochondrial nucleotide pool (such as *TK2*), and genes that encode proteins involved in mitochondrial fusion. Here, the presentation provided by Ramon Martí, Research Group on Neuromuscular and Mitochondrial Diseases, Vall d'Hebron Institut de Recerca, Barcelona, Spain, and CIBERER, Madrid, Spain, is

summarised. A leading expert on mitochondrial pathology, Martí presented at the Euromit 2023 International Conference on Mitochondrial Disease, which took place in Bologna, Italy, in May 2023.

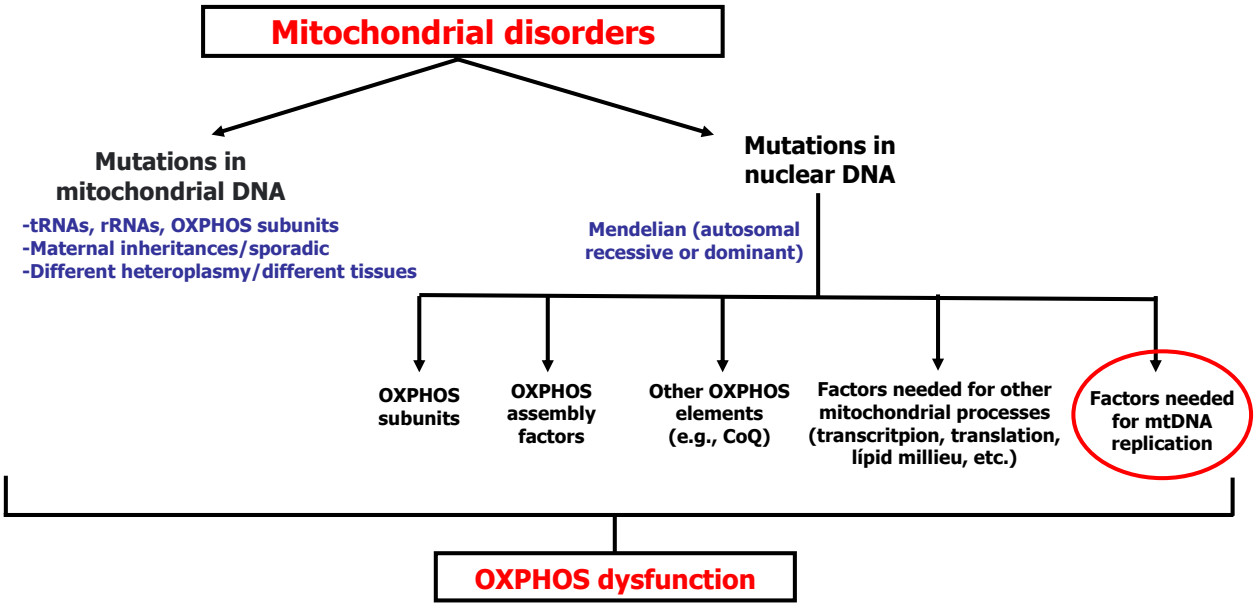
Introduction

Mitochondria are organelles present in almost all eukaryotic cells. Responsible for orchestrating cellular energy production, they are central to the maintenance of life and the gatekeepers of cell death. Many mitochondrial diseases originate from pathogenic mtDNA mutations (Figure 1)[1] that lead to defects in various mitochondrial proteins, disrupting the electron transport chain and oxidative phosphorylation (OXPHOS). With these dysfunctions, mitochondria are unable to produce sufficient energy in different tissues, especially in the highly adenosine triphosphate-demanding tissues, such as skeletal muscle, cardiac muscle, liver, and the renal and central nervous systems.[2,3] An increasing number of mutations in nuclear genes involved in deoxyribonucleotide homeostasis have been identified in causing disorders associated with somatic mtDNA abnormalities. Dysfunction of the products of these genes causes limited availability of substrates for mtDNA replication, which leads to multiple deletions, point mutations, or mtDNA depletion. The latter is the molecular feature linked to greatest clinical severity.[3,4] At the Euromit 2023 International Conference, Martí presented recent results demonstrating that enhancement of the salvage pathways by increasing the availability of deoxyribonucleosides improves the mtDNA copy number. Martí further discussed the administration of selected deoxyribonucleosides as a potential pharmacological strategy to treat mtDNA depletion/deletions syndromes (MDDS).[1]

Mitochondrial Diseases

Martí opened their talk by explaining that mtDNA contains genes necessary for mitochondrial

Figure 1: Causes of mitochondrial disorders.[1]



CoQ: co-enzyme Q10; mtDNA: mitochondrial DNA; OXPHOS: oxidative phosphorylation; rRNA: ribosomal RNA; tRNA: transfer RNA.

OXPHOS function. The mitochondrial OXPHOS system is the final biochemical pathway, whereby cells use carbon fuels and O_2 to produce adenosine triphosphate.[5,6] In addition, many nuclear encoding proteins are needed for the function of the OXPHOS system. Human mtDNA is a double-stranded, circular molecule of 16.6 kb, and contains 37 genes, which encode for two ribosomal RNAs, 22 mitochondrial transfer RNAs, and 13 polypeptides involved in OXPHOS.[6,7] Many mitochondrial diseases are caused by mutations in mtDNA, but also by mutations in nuclear DNA encoding different factors, including those needed for mtDNA replication (Figure 1).[1]

When mtDNA replication is dysfunctional due to gene defects, there can be a reduction in the quality of the mtDNA due to multiple deletions and point mutations, or reduction in quantity of mtDNA (depletion) in affected tissues.[8,9] Disorders of mtDNA maintenance are clinically heterogeneous and severe due to mtDNA depletion and multiple deletions.[8] Mitochondrial DNA is replicated and repaired by nuclear-encoded mtDNA *POLG* and several other associated proteins, which compose the mtDNA replication machinery.[10] To achieve correct replication of mtDNA, Martí explained that functional machinery is needed, but also a correct supply of deoxynucleoside triphosphates (dNTP), the building blocks of new DNA strands made during DNA replication.[9,11] A central enzyme for generating dNTPs is ribonucleotide reductase.[9] Martí then reviewed the genes identified so far to be associated with mtDNA maintenance disorders, including a group of genes (Figure 2) that encode not only mitochondrial proteins but also cytosolic proteins that participate in dNTP homeostasis.[9]

Currently, five key nuclear genes encoding proteins that participate in dNTP homeostasis have been identified to be associated with MDDS. These genes are *TYMP*, *TK2*, *DGUOK*, and *RRM1* and *RRM2B* (encoding subunits of the ribonucleotide reductase).[9,12] Mutations in any of these nuclear genes can lead to imbalanced dNTPs and impaired mtDNA replication.[4,13,14]

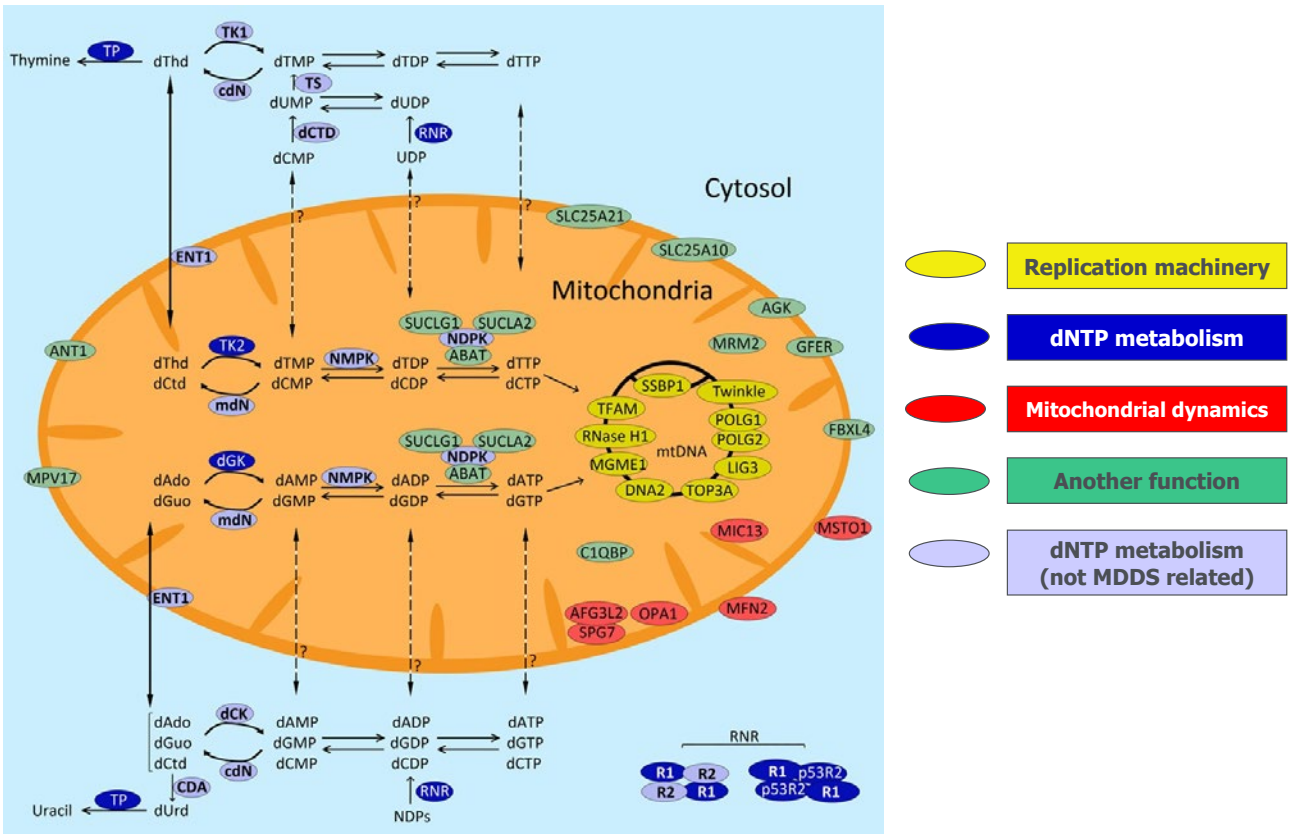
Mitochondrial DNA Replication

Martí studied the replication of mtDNA in isolated mitochondria using an experimental murine liver model, and showed that an excess of deoxythymidine triphosphate (dTTP) decreased mtDNA synthesis, but this effect was due to secondary deoxycytidine triphosphate (dCTP) depletion rather than the excess dTTP.[15] The group found that the addition of dCTP restored mtDNA replication in the presence of thymidine overload, thus confirming that thymidine excess in itself does not slow down mtDNA replication. Their group showed that by supplementing dTTP excess with an excess of dCTP caused the recovery of mtDNA levels, indicating that the availability of dNTP is the key factor that leads to mtDNA depletion.[15] This was confirmed in human cultured cells. Martí discussed that the delay of mtDNA replication rate observed when dTTP is in excess produces a *TK2*-mediated secondary dCTP depletion that actually delays mtDNA replication. Therefore, the common factor accounting for mtDNA depletion in these disorders is the limited availability of one or more nucleotides.[15] Martí concluded that, as far as we know, all the mtDNA replication disorders directly related to disturbed dNTP homeostasis are, in fact, caused by limited availability of one or more dNTPs.[1] This study indicated that strategies to provide nucleotides to patients' mitochondria should be explored as a possible treatment for these fatal disorders.[15]

TK2 Deficiency

Martí went on to discuss TK2, a nuclear-encoded mitochondrial enzyme that catalyses the conversion of deoxythymidine and deoxycytidine nucleosides to their nucleoside monophosphates that, in turn, are further phosphorylated to generate dTTP and dCTP, which are incorporated into replicating mtDNA.[9,16] TK2 deficiency can present as various phenotypes; the predominant one is moderate-to-severe myopathy.[9] Patients with infantile onset are most severely affected, presenting with severe myopathy and only ~25% survival 2 years post-diagnosis.[16]

Figure 2: Genes (proteins) associated with mitochondrial DNA maintenance disorders.[9]



Proteins whose mutations have been linked to MDDS are depicted in yellow (mtDNA replication/ maintenance machinery), dark blue (dNTP metabolism), red (mitochondrial dynamics), and green (unknown role in mtDNA replication). Light blue colour represents proteins participating in dNTP metabolism but not associated with MDDS.

Modified from Ramón et al.[9]

ABAT: 4-aminobutyrate aminotransferase; AFG3L2: AFG3-like protein 2; AGK: acylglycerol kinase; ANT1: adenine nucleotide translocator 1; CDA: cytidine deaminase; cdN: cytosolic deoxyribonucleotidase; C1QBP: complement component 1 Q subcomponent-binding protein; dAdo: deoxyadenosine; dCK: deoxycytidine kinase; dCtd: deoxycytidine; dCTD: deoxycytidylate deaminase; dGK: deoxyguanosine kinase; dGuo: deoxyguanosine; DNA2: helicase/nuclease DNA2; dNTP: deoxynucleotide triphosphate; dThd: deoxythymidine; dUrd: deoxyuridine; ENT1: equilibrative nucleoside transporter 1; FBXL4: F-box/LRR-repeat protein 4; GFER: growth factor, augmenter of liver regeneration; LIG3: ligase III; MDDS: mitochondrial DNA depletion/ deletions syndromes; mdN: mitochondrial deoxyribonucleotidase; MFN2: mitofusin 2; MGME1: mitochondrial genome maintenance exonuclease 1; MICOS13: MICOS complex subunit MIC13; MPV17: protein MPV17; MRM2: rRNA methyltransferase 2; MSTO1: protein misato homolog 1; mtDNA: mitochondrial DNA; NDPK: nucleoside diphosphate kinase; NMPK: nucleoside monophosphate kinase; OPA1: dynamin-like 120 kDa protein; POLG1: catalytic subunit of polymerase gamma; POLG2: ancillary subunit of polymerase gamma; p53R2: p53-inducible small subunit of the ribonucleotide reductase; R2: small subunit of the ribonucleotide reductase; RNASEH1: ribonuclease H1; RNR: ribonucleotide reductase; SLC25A10: mitochondrial dicarboxylate carrier; SLC25A21: mitochondrial 2-oxodicarboxylate carrier; SPG7: paraplegin; SSBP1: mitochondrial single strand binding protein; SUCLA2: subunit of the succinate-co-enzyme A ligase; SUCLG1: subunit of the succinate-co-enzyme A ligase; TFAM: mitochondrial transcription factor 1; TK1: thymidine kinase 1; TK2: thymidine kinase 2; TOP3A: DNA topoisomerase 3-alpha; TP: thymidine phosphorylase; TS: thymidylate synthase; Twinkle: mitochondrial helicase.

Treatment Option for TK2 Deficiency

Martí then explained that the first biochemical strategy to treat TK2 deficiency was the administration of thymidine and deoxycytidine monophosphates (nucleotides) to patients to correct this mitochondrial defect.[1] Martí reviewed that the efficacy of this approach was actually demonstrated in 2014 by Garone et al.,[17] in which they orally supplemented a *TK2* deficient animal model (a *TK2* knock-in mouse) with deoxycytidine and deoxythymidine monophosphates. The group found that untreated animals lived for approximately 13 days; however, if they received monophosphates, they lived longer, in a dose-dependent manner with a response to treatment with these compounds. In these mutant animals, the addition of monophosphate compounds raised dTTP concentrations, increased levels of mtDNA, ameliorated defects of mitochondrial respiratory chain enzymes, and significantly prolonged their lifespan (34 days with treatment versus 13 days untreated).[17] Martí explained that this was the first demonstration that this supplementation could be a potential therapy for this disorder.

This raised some questions because the monophosphates are charged compounds that cannot pass across plasma membranes, so they cannot be absorbed as monophosphates through the intestinal epithelium, and even if you inject it into the blood, they will not enter the cells. However, these nucleotides are rapidly degraded by extracellular ectonucleotidases and phosphatases to the nucleoside, which is uncharged, and to the phosphate. Martí resolved that this enables the nucleoside to enter, because there are specific transporters that allow them entrance not only here but also to the mitochondria. So, at this point, their group thought that probably the effect was not by the monophosphates but by the nucleosides.[1]

Martí then raised the questions: "Why administer nucleosides if you still have this step blocked? Why would you need to do this?" Martí answered these by explaining that you are giving something that is before the blocking. They clarified that their group thought that these nucleosides are using their corresponding or their equivalent cytosolic enzymes that catalyse the same reactions but in the cytosol. The excess of substrate provides an extra amount of nucleosides to push the reaction towards the anabolic direction due to two complementary effects: saturation of the cytosolic salvage enzymes (or even some residual mitochondrial *TK2* activity, if present) with excess of substrate increasing their catalytic rate, and the excess of substrates, in itself, displaces the reaction towards the reaction products (the nucleotides), due to the thermodynamic balance of the reaction.[4,18] This enables nucleotides to enter mitochondria and restore normal mtDNA replication rate.

Martí discussed that Lopez-Gomez et al.[19] and Blázquez-Bermejo et al.[20] tested the nucleosides. Lopez-Gomez et al.[19] tested the administration of deoxythymidine plus deoxycytidine, and the co-administration of the deaminase inhibitor, tetrahydrouridine, with thymidine monophosphate plus deoxycytidine monophosphate in *TK2*-deficient mice, and found that deoxycytidine plus deoxythymidine delayed disease onset, prolonged lifespan, and restored mtDNA copy number, as well as respiratory chain enzyme activities and levels. Blázquez-Bermejo et al.[20] tested daily deoxythymidine plus deoxycytidylate deaminase (dCtd), thymidine monophosphate plus deoxycytidine monophosphate, deoxythymidine alone, or deoxycytidylate deaminase alone to *TK2* knockout mice, and found that deoxythymidine plus deoxycytidylate deaminase treatment extended the average lifespan of *TK2* knock out mice from 16 to 34 days, attenuated growth retardation, and rescued mtDNA depletion in skeletal muscle and other target tissues. These works indicated that the effect is produced by the nucleosides and not the monophosphates.[19,20]

POLG

POLG is the polymerase that replicates mtDNA.[14] Mutations in *POLG* can cause early childhood mtDNA depletion syndromes, or later-onset syndromes arising from mtDNA deletions.[9] *POLG* mutations are the most common cause of MDDS, producing a wide range of clinical presentations, some of which are severe, including Alpers–Huttenlocher syndrome, ataxia neuropathy spectrum, and progressive external ophthalmoplegia.[9]

Treatment Option for *POLG*-related Disorders

There are many known mutations in the *POLG* nuclear gene.[21] Consequently, Martí's group hypothesised that for those mutations that affect the affinity of the polymerase for the dNTPs, treatment with the nucleosides could also be effective. Martí explained that if there is a reduction of the affinity because of the mutation, and if you provide more dNTPs through the precursors that have the nucleosides, you could also counteract the problem. As there were no appropriate animal models, Martí's group assessed their theory in quiescent fibroblasts isolated from patients harbouring mutations in different domains of *POLG*, and measured mtDNA copy number recovery rates following ethidium bromide-forced depletion. They found that when the ethidium bromide was withdrawn, the fibroblast controls recovered the amount of mtDNA. However, fibroblasts with mutations in *POLG* were not able to repopulate mtDNA copy number after ethidium bromide was withdrawn. Martí further showed that supplementation of the cells with nucleosides counteracts and prevents this mtDNA replication defect, regardless of the specific *POLG* mutation.[14] Their group has repeatedly observed that nucleoside supplementation promotes mtDNA repopulation following this design, for all *POLG* pathogenic mutations tested.[4,14] Martí emphasised that the important thing is that they had a positive effect for the whole range of *POLG* mutations, indicating that maybe, for some reason, this is not only working in mutations that affect their affinity of the polymerase for the dNTP, but may be useful for all mutations.

Martí continued that their group then hypothesised that the mechanism would be a different one. For enzymes following Michaelis–Menten kinetics, such as *POLG*, the reaction rate (velocity of the reaction catalysed by the enzyme) increases as the substrate concentration augments, following a known mathematical model (Michaelis–Menten equation). When you have saturating substrate concentrations, you reach the maximum velocity; however, if you have a low substrate concentration the rate of the reaction responds to increases of the concentration of the substrate. So, Martí's group's hypothesis was that if in normal conditions, you have a normal rate of replication, if you increase or you do an expansion of the entities by supplying nucleosides, you would accelerate polymerase, and then in this way you would counteract whatever defect the mitochondrial replication is having because you are forcing or pushing the mtDNA replication. So, you are probably incrementing or enhancing the synthetic pathway. But in order for this to be a possible sub-mechanism, there are two conditions that should be accomplished. One of them is that, in normal conditions, ie., in the conditions in which you do not treat the cells or the patients, the mitochondrial substrate (dNTP) concentration is not excessively above the Km (i.e., the enzyme is not saturated), so the reaction rate can respond to substrate concentration increases. Martí cited that the concentration of the substrate is similar to or around the Km (also known as the Michaelis constant), the substrate concentration at which the reaction rate is 50% of the Vmax or the maximum rate of the reaction. Km is a measure of the affinity an enzyme has for its substrate, as the lower the value of Km, the more efficient the enzyme is at carrying out its function at a lower substrate concentration) because if, in normal conditions for the tissue that you want to treat, you are at levels that are already saturated, you would not obtain a response. Martí emphasised that one condition is that in the normal or baseline situation that we want to correct, the concentration of the substrates of the dNTPs is low. The second condition is that when we treat the patient or the animals with deoxynucleosides, this significantly increases the concentration of the dNTPs because otherwise there would not be any effect.[1,22]

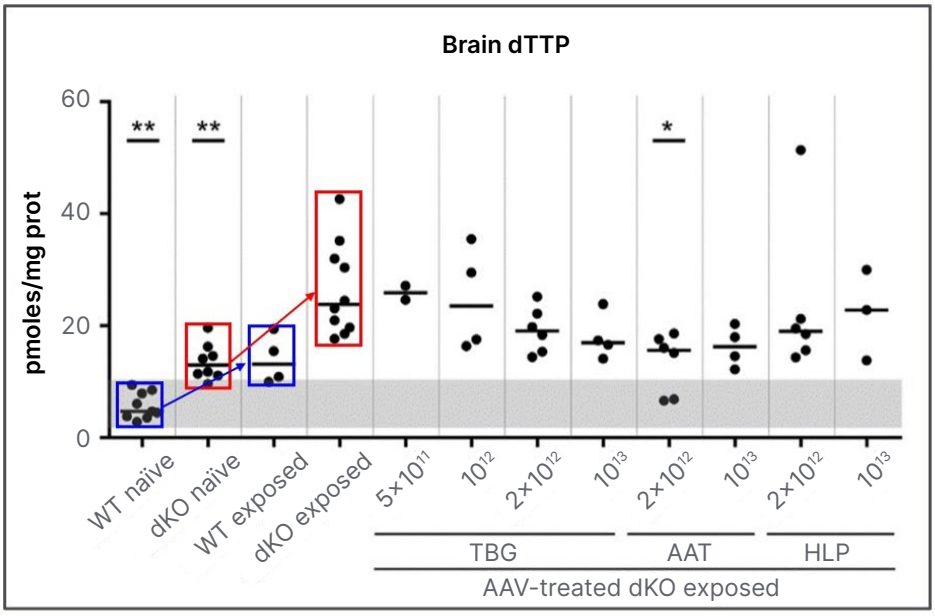
Martí explained that there is wide variability in experimental estimations of the Km for *POLG* for different nucleotides.[23-31] Martí reviewed these estimations to select a Km of approximately 1 µM for their hypothesis. A higher Km would be easier to prove; therefore, this lower estimation would really challenge the hypotheses. Values for the dNTPs were provided by Vila-Julià et al.[32] This study examined the mitochondrial brain dNTP in wild-type and mutant (knockout for *TYMP* and *UPP1*) mice, and the authors found that exposure of the animals to a continual dose of the nucleosides deoxythymidine and deoxyuridine in their drinking water resulted in a two-fold increase in mitochondrial dNTP levels.[32] The exposed mice had more or less double the level of brain dTTP compared with the non-exposed

ones. For the mutants, who at baseline already had double the level of dNTP, levels were further doubled after oral nucleoside administration. Martí emphasised that there is variability; however, their group was able to double the concentration of the dNTP in these conditions.[32]

For values in cells and tissues, Martí used a range between 1 and 10 µmol per mg mitochondrial protein. With this combination, Martí then estimated the dNTP concentration range between 1.3 and 13 µM. The experimental results are shown in Figure 3, along with a table obtained from Wendelsdorf et al.[33] that shows different Km values depending on the status of the tissue. Martí stated that, "of course, these are probably levels of dNTPs of replicating cells that need more dNTPs." However, these values are consistent. Combining the estimate of Km

Figure 3: *POLG* enzyme kinetics data and deoxynucleoside triphosphate levels support the notion that deoxynucleoside -induced deoxynucleoside triphosphate expansion enhances mitochondrial DNA replication[32,33]

A



Exposed mice: 16.6 g/L dThd in drinking water (ad libitum)

B

Mitochondrial dNTP concentrations Km values

dNTP Level	dATP (µM)	dCTP (µM)	dGTP (µM)	dTTP (µM)
High	22.5	28	19.5	26
Medium	1.675	1.644	0.47	0.76
Low	0.1675	0.1644	0.047	0.076
Km with polymerase-γ	0.8	0.9	0.8	0.6

→ $[S] \sim K_M$

A) modified from Vila-Julià et al.;[32] and **B)** modified from Wendelsdorf et al.[33]

AAT: α_1-antitrypsin; AAV: adeno-associated virus; dATP: deoxyadenosine triphosphate; dCTP: deoxycytidine triphosphate; dGTP: deoxyguanosine triphosphate; dKO: double knockout; dNTP: deoxynucleoside triphosphates; dTTP: deoxythymidine-triphosphate; HLP: hybrid liver-specific promoter; TBG: thyroxine-binding globulin; WT: wild type.

with the estimate of the concentration that was calculated, Martí was able to achieve the deoxynucleoside-induced dNTP expansion of mtDNA replication by saturating *POLG*.[32,33]

Martí then explained that using the Michaelis–Menten equation, they were able to show that the sustained concentration of the dNTPs in the quiescent situation is more or less similar to Km, which means that the rate of the reaction is 50% of the maximum velocity. However, if the substrate concentration is doubled to 2 Km, then Martí was able to increase the velocity of reaction to 67% of the maximum. This 33% increase indicates an ability to significantly increase the rate of the semantic fate of the polymerase gamma in this condition.[1]

Martí concluded that the hypothesis demonstrated that this strategy of administering nucleosides can produce dNTP in an anabolic way, either mediated by the functional cytosolic enzymes or via the mitochondrial pathway. Martí stressed that in cases of mutations of *POLG*, there is also the mitochondrial pathway. This increase that is produced is stimulating the activity of *POLG*, increasing the rate of mtDNA replication. Martí's group has also seen positive effects for this strategy in other diseases. Further investigation is needed to validate these results.[1]

Conclusion

MDDS constitute a group of genetic diseases defined by dysfunctional mtDNA replication and maintenance. Currently, the options for the treatment of these disorders are limited. Administration of selected deoxyribonucleosides may offer an expanded treatment armamentarium for patients with some forms of MDDS, such as *TK2* deficiency and *POLG*-related disorders.

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Interview

EMJ had the privilege of interviewing Hugh Selsick, who provided valuable insights into the complex interplay between sleep and psychiatric disorders, while also spotlighting innovative approaches for diagnosing and treating these conditions.

Hugh Selsick

Consultant in Sleep Medicine and Psychiatry at University College London Hospitals (UCLH); and Lead Clinician at the Royal London Hospital for Integrated Medicine and UCLH's Insomnia Clinic, Bloomsbury, UK

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Q1 You have obtained a BSc in physiology, a BSc Honours in experimental physiology, and an MBBCh degree. How has your educational background shaped your career and passion for sleep medicine and psychiatry?

My science degrees were pivotal in fuelling my passions and setting out my career path. During my undergraduate physiology degree, I also did 1 year of archaeology, 1 year of zoology, and 2 years of psychology. These courses expanded my view of the world in a way that the very focused medical degree could not. But my science degrees also determined my trajectory in a more direct way: our physiology department had a sleep laboratory, and I signed up to be a subject in an experiment they were running. Whilst I was being wired up, the head of the laboratory told me about the different stages of sleep, and some of the sleep disorders. From that moment, I was absolutely hooked. I took a year out of medical school to do a postgraduate degree in physiology, where I was able to work in the sleep laboratory, and the rest of my training was always geared towards a career in sleep.

The higher training for psychiatry in the UK helped immeasurably, as we were given time each week to attend special interest clinics, which allowed me to work in sleep clinics and build my experience.

Q2 As the Chair of the Sleep Group, a special interest group in the Section Neuropsychiatry at the Royal College of Psychiatrists (RCPsych), can you detail the objectives and activities of this group?

I started the group after attending the American Psychiatric Association (APA) Conference in Toronto, Canada, in 2006, where there were numerous sessions on sleep, and they were all completely packed. Yet, when we ran a single sleep session at the RCPsych Conference in London, UK, only 15 people attended. I realised that there needed to be more awareness of sleep issues amongst psychiatrists, so I set up the sleep special interest group with the aim of raising awareness of sleep and sleep disorders amongst psychiatrists. We do this through webinars, contributing to college Continuing

Professional Development programmes, running sessions at congresses, and linking people together. Whether through our efforts, or a general increase in interest in sleep in our society, we have seen many more psychiatrists getting involved. The next time we ran a sleep session at the RCPsych conference, the hall was so full they had to turn people away, and we had to run the session a second time!

Q3 You are the lead clinician at the Royal London Hospital for Integrated Medicine, and the University College London Hospital's (UCLH) Insomnia Clinic, UK. Can you outline the clinic's approach to treating insomnia? Are there any innovative techniques or treatments used to combat this common sleep disorder?

All the patients who come to the clinic get a full sleep history taken. This is vital, as many patients who present with a complaint of insomnia turn out to have a different sleep disorder, such as restless legs, obstructive sleep apnoea (OSA), or a circadian rhythm disorder. Most patients with insomnia will go on to have group cognitive behavioural therapy (CBT) for insomnia, online or in person. For those patients who do not make sufficient progress with CBT, we may use medication or other psychological and behavioural interventions. For example, we are just starting to use intensive sleep retraining, and are also trialling a technique called heart rate variability coherence training, which has a small evidence base for use in insomnia but is very quick to deliver. We also do imagery rehearsal therapy for nightmares, and CBT for sleep paralysis.

Q4 You also used to practice in the Sleep Disorders Centre at Guy's Hospital, London, UK. What was your role at this centre, and how does it differ from your role at the aforementioned clinics?

At the Sleep Disorders Centre at Guy's Hospital, I saw a wider range of sleep disorders, with many more patients there suffering from narcolepsy, parasomnias, etc. But the most common condition I saw and treated was OSA. I often joke that I may have looked in more throats than any other psychiatrist in Britain! But treating OSA can be very rewarding, as the improvement in symptoms can be almost instantaneous.

> "I realised that there needed to be more awareness of sleep issues amongst psychiatrists."

Q5 Having specialised in insomnia and the relationship between sleep and psychiatric disorders, have there been any recent breakthroughs in these areas? Could you highlight any emerging research findings that show promise in improving patient outcomes?

There is a growing body of research demonstrating the bidirectional relationship between sleep disorders and psychiatric

disorders. What has become clear is that we should not view sleep disorders, and insomnia in particular, as a symptom of psychiatric disorders, but as a treatable risk factor for psychiatric illness. Also, there is evidence that where there are comorbid sleep and psychiatric disorders, treating the sleep disorder leads to improvements in the psychiatric condition as well.

"Sleep medicine is one of the last genuinely multidisciplinary fields."

Q6 Sleep disorders can have a significant impact on an individual's mental health and overall wellbeing. Based on your experience, can you spotlight any approaches that have proven to be most beneficial for your patients?

Ultimately, it depends very much on the sleep disorder. There is no question that CBT for insomnia markedly improves people's sleep and mental health. It is also critical to treat nightmares where they occur as, of all the sleep disorders, nightmares carry the highest suicide risk. Imagery rehearsal therapy and medications with α1 blocking properties are also very effective. I think it is important for prescribers to understand the role of centrally acting neurotransmitters in sleep-wake regulation, and the pharmacology of the drugs they are prescribing. This is to ensure that they select and time medications in a way that improves, rather than harms, a patient's sleep. For example, when treating a patient with insomnia and depression, one can choose an antidepressant that will treat both conditions, reducing the number of medications the patient requires.

Q7 Could you highlight the key challenges you have faced when diagnosing sleep disorders, particularly insomnia? How have you overcome these challenges?

The biggest challenges are lack of time and diagnostic resources. Teasing out whether a person has insomnia or a circadian rhythm disorder, for example, can take some time, a resource in short supply in the National Health Service (NHS). Technology has made it easier for us to get some patients to fill in questionnaires and sleep diaries before their appointments, which helps. Technology is also helping to tackle the problem of limited inpatient diagnostic resources, as we are now able to do more home studies, particularly when screening for OSA. Finally, better education on sleep medicine amongst referrers would be useful, so they can refer patients to the most appropriate service for their particular condition.

Q8 What are some points of emphasis you would recommend to healthcare professionals to be successful in specialising in sleep medicine and psychiatry?

I think to be a psychiatrist you have to be comfortable with uncertainty. We do not have any specific diagnostic tests for the conditions we treat, and we can never truly be confident about our risk assessments, even though this is a significant element of modern psychiatric practice. In sleep medicine, the best advice I can give is that there is no substitute for sitting in on as many clinics, with as many colleagues as possible. Sleep medicine is one of the last genuinely multidisciplinary fields of medicine. Observing how patients with sleep disorders are managed by neurologists, psychiatrists, respiratory physicians, otorhinolaryngologists, etc., will give you a whole range of different perspectives that will extend your knowledge beyond your own speciality.

Diagnostic Odyssey of Myotonic Disorders

The publication of this infographic was supported by **Lupin Neurosciences, a Specialty Pharma Division of Lupin Atlantis Holdings SA**

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Insights from a patient and caregiver survey, treating physicians and scientific literature.

Patient/caregiver surveys:

38 Participants with Myotonic Disorders

- 19 NDM with chloride channelopathies
- 10 DM1
- 7 NDM with sodium channelopathies
- 2 DM2

KOL roundtable to leverage insights from survey participants with experience in clinical practice:

- 7 paediatric neurologists
- 2 adult neurologists

Experts from : United Kingdom, Spain, Italy, Germany, France

Key

Symptoms · Treatment · Diagnosis · Barriers

NDM paediatric patient journey

DM paediatric patient journey

Birth

- Cl⁻ channelopathy: Symptoms may be present from birth.
- SNEL: Symptoms may present during infancy.
- No curative treatment for SNEL. Mexiletine (off-label) and flecainide.
- Present from birth with main symptoms being severe generalised weakness, hypotonia and respiratory compromise. Myotonia is usually absent in infancy, and muscle strength can improve with time if the infant survives.

1 Year

- Cl⁻ channelopathy: Myotonic symptoms may become apparent when children start to walk.
- Congenital DM1 diagnosed.

2 Year

- Na⁺ channelopathy: Age of onset can range from 2–30 years. Myotonia is usually mild, often involving eyelids, hands and tongue.

3 Year

- TMC myotonia: Onset within the first decade of life.
- Congenital DM1 myotonia: Myotonic symptoms can start to become apparent.

4 Year

- Parents may assume children will 'grow out' of symptoms as they develop.

5 Year

- Na⁺ channelopathy: Myotonic symptoms may become apparent when children begin to participate in sports.

6 Year

- Parents may be unable to describe symptoms of myotonia and focus on other DM symptoms.
- Myotonia is not reported by patients.
- Cl⁻ channelopathy: Symptoms usually present in the first decade of life with stiffness in legs more than arms, hands and face.

7 Year

- Childhood-onset DM1: Myotonia starts to become apparent from 7 years of age; increased impact at 13–18 years.
- PMC myotonia: Onset within the first decade of life.

8 Year

- Myotonia in DM is considered a secondary symptom, and is under-appreciated by HCPs.
- Diagnosis delayed due to patients developing coping strategies and lack of specialist diagnostic knowledge.

9 Year

- BMC myotonia: Onset from 4–12 years of age.
- HyperPP myotonia: Onset from 2–30 years of age.
- Clinical assessment is complicated by lack of myotonia during clinic visits and and difficulties to test for myotonia in clinic.
- Access to treatment can be hindered by lack of awareness of severity and impact of myotonia.

10 Year

- Diagnostic delays can range from 4 months from onset of symptoms to 20 years.
- Age of diagnosis is hugely varied from infancy to adulthood.
- Patients and caregivers may refuse treatment due to: bad taste, hesitancy, safety concerns.

11 Year

- Patients may be reluctant to worry their parents
- Myotonia treatment age ≥10 years. No curative treatment, off-label symptomatic treatment include acetazolamide, carbamazepine, flecainide, mexiletine
- Treatment age ≥10 years. No curative treatment, off-label symptomatic treatment include carbamazepine, flecainide, mexiletine.
- Parents may not actively pursue a diagnosis.
- Diagnosis difficult in patients with no family history.

12 Year

- Diagnosis can be delayed up to 18 years.
- Age of diagnosis is variable, but often in early adolescence.

13 Year

- Embarrassment may prevent children seeking advice about their symptoms.

16 Year

- DM2: Myotonic symptoms can present from 8 years, but are more commonly seen from late adolescence.

17 Year

18 Year

- Diagnosis of DM2 typically occurs in adulthood.
- Cardiac arrhythmias or other cardiac conditions may occur as patients enter adulthood.
- Access to treatment can be hindered by lack of awareness of severity and impact of myotonia.

NDM Ch- Channelopathy: 13-18 Years of Age

Combined prevalence = ~1:100,000 (higher in Scandinavia (7-10:100,000)

- BMC = ~1:25,0004
- TMC = ~1:400,0004

Predominant symptoms

- Limb stiffness (lower limbs more often)
- Grip myotonia
- Pain with stiffness
- Cold trigger
- Warm-up phenomenon

NDM Na+ Channelopathy: 13-18 Years of Age

Combined prevalence = ~1:100,0001

- PMC = ~1:250,0002
- HyperPP = ~1:200,0003

Predominant symptoms

- Pain with stiffness
- Episodic weakness
- Grip myotonia
- Cold trigger
- Eye closing myotonia
- Limb stiffness
- Facial stiffness
- SNEL: hypertonia and laryngospasm

DM: 13-18 Years of Age

DM1: Estimated prevalence of 3–15:100,000 (higher prevalence (≥20X) in Sweden, Basque of Spain and Quebec)

Childhood-onset DM1: no published data

Congenital DM1: exact global prevalence is unknown; however, congenital DM1 likely represents 10–30% of overall DM1 population

Estimates of incidence: 2–28:100,000 live births

DM2: prevalence unknown

BMC:Becker's myotonia congenita; Cl-: chloride; DM: myotonic dystrophy; DM1: myotonic dystrophy Type 1; DM2: myotonic dystrophy Type 2; HyperPP: hyperkalemic periodic paralysis; KOL: key opinion leader; Na+: sodium; NDM: non-dystrophic myotonia; PMC:paramyotonia congenita; SNEL:severe neonatal episodic laryngospasm.

EU-DMS-2306-00001

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NfL as a Potential Biomarker in ATTRv Amyloidosis

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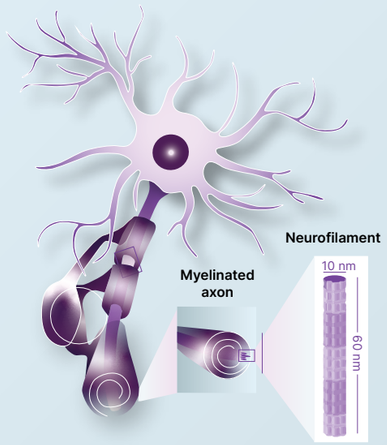
An overview of ATTRv amyloidosis and NfL

ATTRv amyloidosis is a rare, underdiagnosed, progressive and debilitating disease caused by variants in the TTR gene, which leads to the accumulation of dissociated, misfolded TTR as amyloid deposits in organs and tissues.[1-4]

NfL is a well-studied biomarker for neuroaxonal injury across multiple PNS/CNS diseases, that has been suggested to reflect active/continuing neuronal damage in patients with ATTRv amyloidosis.[3,5,6]

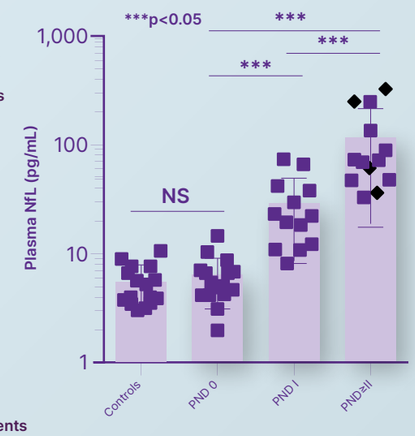


NfL levels are found to be significantly elevated in patients with ATTRv amyloidosis with PN versus healthy controls, and to correlate with disease severity.

60 patients with ATTRv amyloidosis or V30M variant carriers

16 healthy controls

Plasma NfL levels in patients with ATTRv amyloidosis, individuals who are V30M variant carriers, and healthy controls.[7]



Full diamonds represent patients with a PND score of III.

All data are represented as group means ±SD.

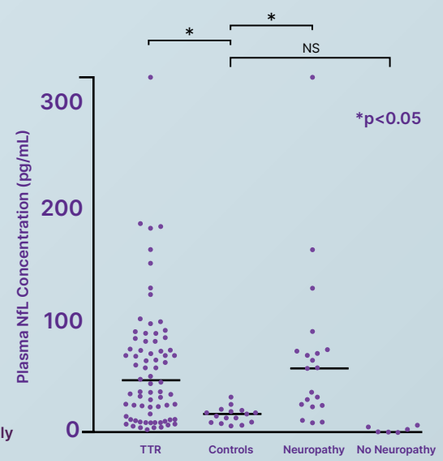
NfL was elevated in patients with ATTRv amyloidosis as a function of disease severity.

NfL differentiated asymptomatic carriers (PND 0) from early symptomatic patients (PND I).

73 patients with pathogenic TTR variants

16 healthy controls

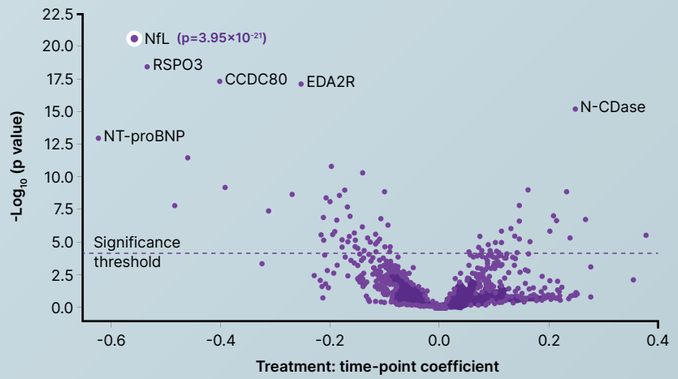
Plasma NfL levels in all patients with ATTRv amyloidosis (TTR), healthy controls, and ATTRv patients with or without neuropathy.[8]



NfL levels were significantly higher in patients with ATTRv amyloidosis with PN versus controls (p<0.001).

NfL levels correlated with disease severity (NIS).

In a post-hoc proteomic analysis from the APOLLO study,[1] NfL was found to be the most significantly changed protein between patisiran-treated and untreated patients with ATTRv amyloidosis with PN.[3]

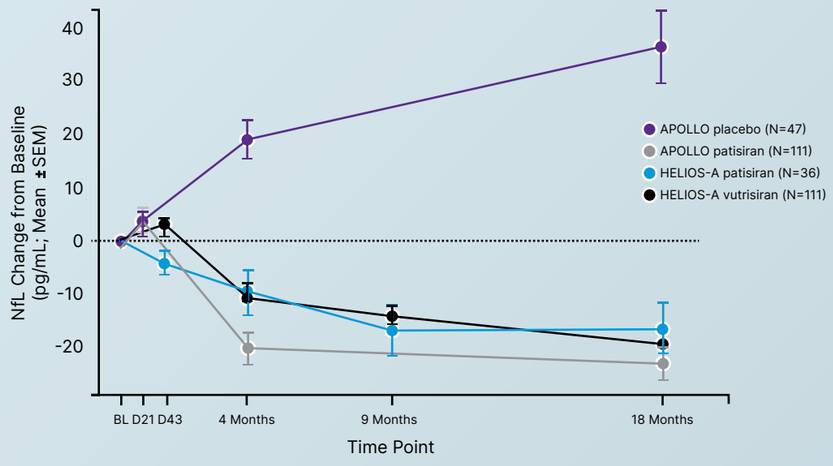


Results from a proteomic analysis conducted to determine the effect of patisiran treatment over time on the plasma level of multiple proteins.

On the volcano plot, each protein is represented with a dot. The y-axis demonstrates the strength of the association ($-\log_{10}$ [p value]) and the x-axis demonstrates the effect size.

Treatment with RNAi therapeutics led to a significant decrease in NfL levels, which was seen as early as 4 months with a sustained response over time.[9]

Change in NfL levels from baseline in APOLLO[1] and HELIOS-A[2] studies



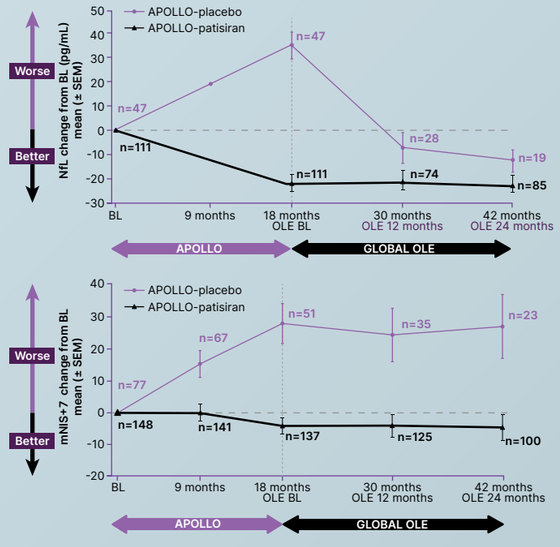
In post-hoc analyses of APOLLO and HELIOS-A studies, NfL levels decreased significantly in patisiran and vutrisiran groups as early as 4 months (p<0.05), and these decreases were maintained to 18 months after treatment initiation (p<0.01).[9]

A positive correlation (R=0.32) was observed between change in NfL levels and change in mNIS+7 in APOLLO and HELIOS-A at 18 months.[9]

A significant decrease in NfL levels with patisiran in the APOLLO study was sustained during the open-label extension period.[4,10]

NfL level significantly decreased after patients receiving placebo began active treatment in the Global OLE (p<0.001).[10]

NfL has been suggested to reflect active or continuing neuronal damage at a specific point in time, whereas mNIS+7 measures the overall clinical burden of neurologic impairment.[3]



Measuring NfL levels may have value in monitoring treatment response in patients with ATTRv amyloidosis.[11]

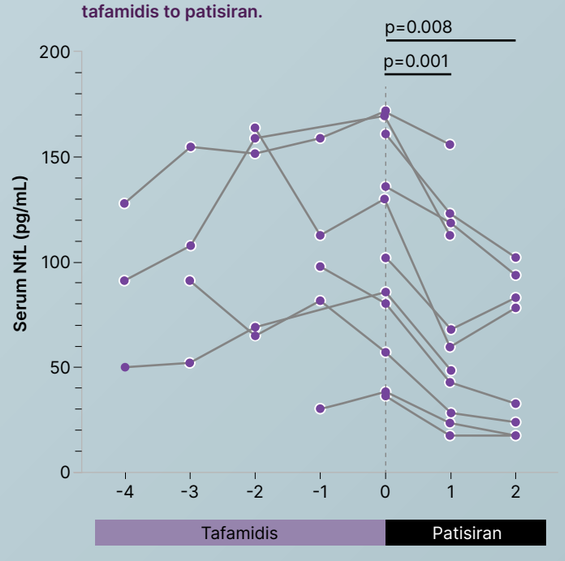
11 patients with ATTRv amyloidosis with PN who switched from tafamidis (20 mg) to patisiran.

Significant decrease in NfL levels was observed at 1 and 2 years following switch

NIS values did not change significantly following switch.

The limitations of this study included the small number of patients and absence of a control group. Further, longer-term studies are necessary to validate the findings.

Serum NfL levels before and after switch from tafamidis to patisiran.



Pre-switch NfL levels are depicted according to the calendar year in which the measurement was made.

Abbreviations

ATTRv amyloidosis: hereditary amyloid transthyretin amyloidosis; BL: baseline; CCDC80: coiled-coil domain-containing protein 80; CNS: central nervous system; EDA2R: ectodysplasin A2 receptor; mNIS: Modified Neuropathy Impairment Score; N-CDase: neutral ceramidase; NIS: Neuropathy Impairment Score; NfL: neurofilament light chain; NS: not significant; OLE: open-label extension; PN: peripheral neuropathy; PND: polyneuropathy disability; PNS: peripheral nervous system; RNAi: RNA interference; RSPO3: R-spondin-3; SEM: standard error of the mean; TTR: transthyretin.

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Orthostatic Hypotension and Concomitant Paraneoplastic Syndromes: A Case Report

Editor's Pick

My Editor's Pick delves into the intriguing encounter with an elderly male patient. This case report unravels the presence of paraneoplastic autonomic neuropathy, despite a negative work-up for the aetiology of orthostatic hypotension, underscoring the importance of accurate identification. Orthostatic hypotension, prevalent among the elderly, and linked to falls and trauma, necessitates further investigation when traditional treatments prove ineffective. The article emphasises that patients with new-onset orthostatic hypotension, a history of malignancy, and symptoms consistent with ongoing malignancy, should be evaluated for paraneoplastic autonomic neuropathy. Despite the strong association between paraneoplastic syndromes and malignancies, research remains limited, highlighting the need for future studies to offer potential insights into symptomatic management and disease progression, to ultimately enhance quality of life.

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Abstract

This case study discusses the incidence of a paraneoplastic autonomic neuropathy in an elderly male who had an otherwise negative work-up for their aetiology of orthostatic hypotension. This case illustrates the importance of trying to correctly identify the aetiology of orthostatic hypotension, which is often overlooked, and frequently diagnosed as idiopathic. Orthostatic hypotension is most prevalent in elderly populations and can be debilitating, leading to a higher incidence of falls and trauma. Thus, it is important to obtain further work-up when traditional treatments are ineffective. In patients with new and insidious onset of orthostatic hypotension, previous history of malignancy, and possible symptoms consistent with ongoing malignancy, it is imperative to consider paraneoplastic autonomic neuropathy as a potential cause of orthostatic hypotension.

Key Points

1. In addition to the common causes of orthostatic hypotension, paraneoplastic autonomic neuropathy should still be considered in the differential diagnosis when assessing patients who present with acute, yet persistent, orthostatic hypotension.

2. It is imperative to obtain a comprehensive paraneoplastic antibody titre panel in patients with a history of malignancy who show no improvement with the typical orthostatic hypotension treatment, such as midodrine and fludrocortisone.

3. There is limited research on paraneoplastic syndromes, despite their strong association to malignancies. Further studies can provide insight into symptomatic treatment and slowing down disease progression to improve quality of life.

INTRODUCTION

Paraneoplastic autonomic neuropathy is a syndrome with an unclear aetiology and wide array of symptoms. Some studies have identified a strong autoimmune component in the development of paraneoplastic autonomic neuropathy, though some aetiologies are non-immune in nature.[1-3] The symptoms present in a progressive autonomic fashion and include orthostatic hypotension, dry mouth, new onset urinary retention, and constipation.[2] The diagnosis is difficult to arrive at, as it is a diagnosis of exclusion when other causes of autonomic dysfunction have not been confirmed.[4,5] A proper diagnosis is imperative in populations with new onset of these symptoms, and can help direct symptomatic treatment for patients suffering from these symptoms. In addition, it can help identify potential malignancy in patients who otherwise have not been diagnosed. In this case of paraneoplastic autonomic neuropathy, the patient had new onset urinary retention and orthostatic hypotension. This article reviews clinical presentation, diagnostic steps, and management of paraneoplastic autonomic neuropathy to raise awareness of an uncommon condition.

CASE DESCRIPTION

The case presented in this article is of a 78-year-old White male, with a past medical history of hypertension, hyperlipidaemia, coronary heart disease, advanced emphysema, gastro-oesophageal reflux disease (GORD), previous myocardial infarction, previous pneumothorax, and bladder cancer with multiple trans-urethral resection of bladder tumour procedures, who presented to the hospital with a chief complaint of dizziness. The patient also presented with complaints of significant weight loss and poor appetite for the past 2 weeks. The patient denied any recent falls or loss of consciousness. They reported that their dizziness had been going on for a couple of months and that their primary care physician recommended discontinuing their unknown dose of metroprolol tartrate to prevent any episodes of falls. In addition, there was no pertinent family history, but the patient reported a 20-year smoking history that was discontinued after their bladder cancer diagnosis.

Upon admission to the emergency department, the patient's vitals revealed a temperature of 97.6 °F, a blood pressure of 155/75, a heart rate of 133 beats per minute, a respiratory rate of 22 breaths per minute, and an oxygen saturation of 97% on room air. Physical examination revealed an elderly patient with cachetic symptoms who appeared to be in slight respiratory distress. The patient had a normal physical examination except for decreased breath sounds bilaterally in both lung bases. In addition, the patient was noticeably coughing and producing a greenish-white sputum. Upon admission, the patient's initial basic metabolic panel was within normal limits. However, the complete blood count panel upon admission revealed leukocytosis of 10,800, anaemia with a haemoglobin/haematocrit ratio of 9.3/29.6, and thrombocytosis with a platelet count of 417,000. The patient's initial basic metabolic panel was within normal limits. Urinalysis was drawn and was positive for 10–25 wbc/hpf, nitrites, and leukocyte esterase, which

was consistent with a urinary tract infection (UTI). The patient was admitted due to fulfilling sepsis criteria due to UTI and community-acquired pneumonia (CAP).

Imaging was also done for further diagnostic work-up. Their chest X-ray showed bilateral opacification in their lungs with no evidence of pneumothorax. CT scans showed acute left upper lobe and right lower lobe pneumonia superimposed on severe emphysema and chronic interstitial lung disease, fluid in the right upper lobe bullae, right hilar adenopathy, chronic prostatitis, calcifications layering the urinary bladder, bilateral renal cysts, and cholelithiasis. In addition, the patient's urine culture came back positive for coagulase negative *Staphylococcus aureus*.

The patient's CAP and UTI were treated with azithromycin and cefuroxime. Although the patient was being treated acutely for the CAP and UTI, their recent weight loss needed to be addressed. They had reported a significant loss of appetite, early satiety, dyspepsia, dysphagia, and unintentional weight loss of 30 lb. Metastases to the patient's gastrointestinal tract were suspected due to a previous history of bladder cancer and smoking history, and thus an upper gastrointestinal series was obtained, which showed mild to moderate sliding hiatal hernia. The patient reported that they did not want to pursue any surgical intervention for their sliding hiatal hernia. The patient's GORD was medically treated with a gastrointestinal cocktail consisting of sucralfate, a proton pump inhibitor, and lidocaine.

However, while the patient's CAP, UTI, and GORD were treated, their dizziness persisted. During the beginning of their hospital course, orthostatic measurements were taken. During the first few days at the hospital, the patient reported dizziness after a few minutes of standing during orthostatic measurements and walking to the restroom. This eventually progressed to dizziness even when sitting upright. The orthostatic measurements were initially seen as benign and secondary to the patient's presenting symptoms, health conditions, and deconditioning. However, as the patient's other acute conditions were being treated, their routine blood pressure readings continued to drop. During the physical exam, the patient appeared more ill than on admission, and reported a new and increased frequency of dry mouth, which was believed to be due to discontinuation of intravenous normal saline fluids, and several instances of night sweats. In addition, there were many overnight event chart notes that reported standing hypotension severe enough to require stat intravenous normal saline boluses.

The patient would report feelings of persistent fatigue while standing, which eventually became fatigue with sitting and lying down towards the end of their treatment. Towards the latter half of their hospital stay, physical therapy examined the patient's mobility. The patient walked from their bed to the hospital room door, only to report severe dizziness and a feeling of presyncope. An Aspergillosis test, a Fungitell® (Associates of Cape Cod, Intl, Inc., Liverpool, UK) test, a QuantiFERON (Qiagen, Venlo, the Netherlands) test, and a thyroid panel were all obtained and were all negative. The patient's cancer antigen was elevated, and they were started on 5 mg of midodrine three times a day while continuing their other treatments. As a work-up for orthostatic hypotension, two A.M. cortisol levels and a 24-hour urine cortisol were found to be elevated, and Endocrinology was consulted as a result. Initially, the elevated cortisol levels were attributed to hospital stressors as the patient did not fit the clinical picture for Cushing's syndrome, including symptoms of weight gain and hypertension. However, two dexamethasone tests were still conducted, which did not fully suppress the patient's cortisol. After 9 days of escalating doses of midodrine, there was no clinical improvement of the patient's orthostatic hypotension, and they were switched to 0.1 mg of fludrocortisone. ACE™ wrap (3M, Maplewood, Minnesota, USA) placement was attempted, but they were removed at the request of the patient. The serum adrenocorticotropic hormone levels that were collected reflected low levels of the hormone, though this was collected while the patient was on fludrocortisone. A repeated chest CT showed no significant changes apart from some increased fluid in their right upper lobe bullae. Paraneoplastic antibody panels, including Hu antibodies, were thus sent in to evaluate the possibility of undetected malignancies, such as small cell lung cancer, causing the orthostatic hypotension. The patient requested and was discharged on home hospice services following a discussion with palliative care.

Several weeks after discharge, the patient's paraneoplastic antibody panel came back positive. The report showed a P/Q type calcium channel antibody, consistent with an autoimmune neurological diagnosis of paraneoplastic autonomic neuropathy. No further work-up was done as per the patient's wishes.

DISCUSSION

Orthostatic hypotension is defined as a drop in at least 20 mmHg systolic blood pressure or at least 10 mmHg diastolic blood pressure within 3–5 minutes of standing up.[6,7] This type of hypotension is most commonly seen in the elderly who are 65 years of age and older.[8,9] In fact, up to 10–30% of the elderly population present with orthostatic symptoms, with idiopathic orthostatic hypotension being the most common aetiology.[8] Symptoms such as lightheadedness and fatigue are commonly seen when the patient is sitting upright or standing during blood pressure readings.[2] The causes can vary case by case and are split into two categories: non-neurogenic, such as medication-induced and volume depletion, and neurogenic, such as autonomic nervous system failures or baroreflex dysfunction.[10,11] One study found that 35% of patients with orthostatic hypotension had autonomic failure due to diabetic neuropathy or paraneoplastic syndromes, 38% had no evidence of general autonomic dysfunction, and 27% had underlying neurodegenerative disorders.[12] Another study found that most medication-induced orthostatic hypotension is caused by hypertensive medications, such as vasodilators.[9] This explains why the patient's primary care physician had initially discontinued their metoprolol tartrate.[9] Treatment for orthostatic hypotension can include the following: removal of the inciting medication, providing intravenous fluids for hypovolaemia; compression stockings to reduce venous pooling; or pharmacological treatment, which includes midodrine or fludrocortisone.[9] In this case study, the patient was not responsive to non-pharmacological and pharmacological forms of treatment. In addition, the patient's orthostatic work-up was negative for endocrinological causes, such as Cushing's syndrome. Only after extensive lab work up, including an abnormal paraneoplastic antibody panel, was a potential cause of the patient's orthostatic hypotension determined.

As previously mentioned, the patient's orthostatic hypotension persisted with medical management, which included midodrine, fludrocortisone, fluid boluses, and ACE™ wraps. Aside from repeat CT scans and endocrinological work-up, Hu and paraneoplastic antibody panels were sent in. The patient's Hu antibody panel came back normal, whereas the paraneoplastic antibody panel came back abnormal: 0.05 nmol/L of the P/Q type voltage gated calcium channel antibody was detected. While a low titre of the antibody was found, it is likely that the patient's persistent orthostatic hypotension was secondary to autonomic paraneoplastic syndrome.

To begin with, paraneoplastic syndromes are immune-mediated syndromes that impact central, peripheral, or autonomic nervous systems.[13] Some paraneoplastic syndromes include paraneoplastic cerebellar degeneration, Lambert–Eaton myasthenic syndrome, limbic encephalitis, and paraneoplastic opsoclonus-myoclonus.[14] Symptoms typically include difficulty ambulating, loss of muscle tone and co-ordination, difficulty swallowing, dry eyes and mouth, sweating, urinary incontinence, and abnormal gastrointestinal motility.[14] Paraneoplastic syndromes are usually categorised as endocrinological or autonomic/neurological in origin and are associated with malignancies, most commonly small cell lung cancer, and less commonly breast cancer and haematological cancers.[4,13,15] These syndromes encompass disorders that occur due to tumour secretion of peptides (endocrine), or by autoimmune cross reactivity between normal and malignant tissues (autonomic/neurological).[4] The autoantibodies that are seen in autonomic/neurological paraneoplastic syndromes target intracellular neuronal proteins, including Hu protein, or against neuronal cell surface or synaptic proteins, including P/Q- and N-type calcium channels.[5,16]

The P/Q type calcium channel binding antibody is one of many autoantibodies tested in the paraneoplastic antibody panel. The P/Q type calcium channel is a voltage-gated calcium channel that mediates the amount of calcium influx for neurotransmitter release.[17,18] They are predominantly found in the synaptic terminals of neurons in the cerebellum, cortex, and hippocampus.[17-19] Antibodies against these

channels are most commonly found in Lambert–Eaton myasthenic syndrome, and antibodies against the P/Q and N-type channels are associated with small and non-small cell lung cancer.[20]

The positive predictive value of the paraneoplastic antibody panel test for an autoimmune neurological paraneoplastic syndrome is 19%, and a cancer diagnosis is 21%, with 18% of the 21% being a historical cancer diagnosis.[21] In one study, it was determined that this antibody "has a diverse neurological presentation in cancer types, including squamous cell carcinomas, adenocarcinomas, and small cell carcinomas."[21] In addition, another study showed that low titres of the P/Q type calcium channel antibody were specifically found in a little more than half of patients with paraneoplastic encephalomyeloneuropathy complications of the lung, ovary, or breast carcinomas.[3] Many of the cases that presented with a P/Q type calcium channel binding antibody frequently also presented with Lambert–Eaton syndrome, with occurrence in only 1% of patients with small cell lung cancer.[1] Though the P/Q type calcium channel binding antibody is most commonly seen in Lambert–Eaton syndrome, the patient's laboratory and clinical symptoms were interpreted as paraneoplastic autonomic neuropathy secondary to an unidentified developing lung cancer due to an extensive smoking history.[21,22]

Early detection of paraneoplastic syndromes can aid in the diagnosis of a developing cancer.[23] It is imperative to measure serum and cerebrospinal fluid Hu and paraneoplastic antibody levels during the work-up of a patient whose history is positive for malignancies, and shows no improvement in orthostatic hypotension with typical treatment of midodrine or fludrocortisone.[23] While a niche subject, current research shows that there are few peptide molecules available, such as ω-agatoxins IVA and IVB, that selectively target and block P/Q type calcium channels.[18] If the patient's paraneoplastic antibody levels were discovered earlier, then administration of these medications could have been provided for symptomatic relief. In addition to the limited research on the P/Q type calcium channel autoantibodies and their implications on paraneoplastic syndromes, another limitation to the study included the patient's desire to go home on hospice care after a long hospital course.[18] Given the acute nature of the orthostatic hypotension in relation to the patient's admitting conditions, as well as the patient's desire to go home, further work-up, such as brain MRI, electromyography, and PET scans, was not done. If the autoantibody tests were performed earlier during the patient's hospital stay, this may have changed the course of laboratory and imaging work-up to fit a more paraneoplastic syndrome and cancer picture. However, despite all of this, a strength of this case was that the patient was readily willing to repeat clinical measurements, as well as undergoing numerous medication changes and diagnostic testing in hopes of treating their symptoms. This case overall provides perspective on the array of symptoms often overlooked in autonomic dysfunction that could have an insidious aetiology.

It is important to consider patient history as well as a holistic viewpoint when reflecting on a patient's symptoms. In this report, the authors treated the patient symptomatically, and were able to deduce the underlying aetiology only after extensive inpatient hospitalisation and work-up. The authors add the perspective that it is important to cast a wide differential diagnosis, and with strong clinical suspicion, to consider malignancy as a potential cause of novel autonomic dysfunction in the elderly population.

PATIENT PERSPECTIVE

While the patient was unable to share their written perspective of their diagnosis and hospital treatments, they repeatedly shared their thoughts with the medical team throughout the duration of their hospital stay. The patient always explained that they were willing to undergo testing in order to find out a cause and solution to their orthostatic hypotension. However, the patient inevitably decided to go home on hospice, as they believed that there was no proper treatment that the hospital could provide for their condition.

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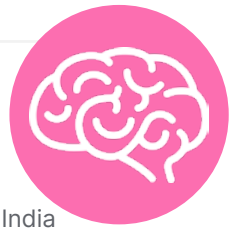
Isolated Sacral Tuberculosis: A Case Report and Review of Literature of this Rare Sacral Pathology



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Abstract

Introduction: Tuberculosis (TB) of the spine is one of the rare secondary manifestations of the disease, while isolated TB of the sacrum is an even rarer finding of the disease.

Case: The authors present the case of a male patient in their late 20s who was suffering from lower back pain radiating to the leg, on and off fever for 5 months, and stiffness of the lower back. X-ray and MRI showed a sacral mass-like lesion, which led to the suspicion of spinal TB. This diagnosis was later confirmed through adequate microbiological testing.

Methods and Materials: A review of literature by a thorough search of the PubMed and Google Scholar databases was carried out, and a total of 42 patients with isolated TB of the sacrum were studied.

Results and Conclusions: Sacrum in isolation is a rare location for spinal TB, often overlooked by primary physicians. A prompt diagnosis and early treatment of the disease will mitigate the risk of developing complications.

Key Points

1. Pott's spine (tuberculosis of the spine), a presentation of secondary tuberculosis with huge morbidity in India, rarely presents isolated to the sacral spine.

2. Pott's spine presents variably with a spectrum of symptoms, including high fever, weight loss, radiculopathy, and back pain, and it requires thorough clinical and radiological investigations to reach a definitive diagnosis.

3. The treatment modalities are dependent on the extent of spread of the disease, and include surgical intervention, as well as medical treatment in form of anti-tubercular therapy, with regular follow-up to prevent morbidity.

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by the transmission of *Mycobacterium tuberculosis* bacillary complex, which usually involves multiple systems if not recognised and treated early. TB of the spinal region is categorised as secondary TB, involving the spinal vertebrae and the intervertebral discs.[1] The burden of spinal TB is 5% of total TB cases around the globe; it is higher in developing countries, with the Indian subcontinent housing a majority of its cases. The overall risk of spinal TB increases with co-infection with HIV.[2]

The involvement of the spine in the case of TB generally occurs after the haematogenous spread of the bacteria from a primary region, usually the lungs. The spread occurs through the anterior part of the vertebral bodies, or may involve the central portion of the vertebrae by communicating through the valveless venous plexus or the Batson plexus.[1] Patients usually present with fever, night sweats, pain in the lower region of the back radiating to the legs, and weight loss.[1] X-ray is usually the primary imaging modality, while MRI of the spine is more specific. Biochemical and microbiological analysis of the biopsy or aspirate confirms the diagnosis.[2] It is pharmacologically treated by anti-tubercular therapy, supplemented by surgical management if the spread leads to physical deformities or complications.[1,2]

In the wide spectrum of spinal TB, isolation to the sacrum is a rare presentation. Amongst various sacral pathologies diagnosed on imaging, TB of the sacrum is one of the rare conditions that need adequate clinical, biochemical, and microbiological analysis to be ruled as the disease, which is why the authors believe a thorough review of the same is necessary.

CASE REPORT

A male patient in their late 20s presented to the outpatient department of a tertiary care hospital in Northern India with insidious, progressive pain in the lower back for the past 1.5 years, specifically in the right lower paraspinal region. The pain varied in intensity, radiating to the right lower leg, and was associated with weakness of lower limbs bilaterally. The pain was aggravated by walking and sitting, and relieved by taking analgesics. The patient had no seasonal or diurnal variation of the pain. The patient also had a low-grade fever, on and off for the past 5 months, which they managed with over-the-counter analgesics.

There was no reported previous history of any trauma to the back, or any similar complaints. There was a history of right inguinal hernia 6 years before presentation, treated with hernioplasty, and history of abscess in the scrotum 3 years before presentation, treated with incision and drainage of the abscess. The patient noticed no changes in their sleep pattern, appetite, bowel movements, or urination. The patient was a carpenter by profession, and would frequently lift heavy weights. There was no other relevant past, family, or personal history.

On examination, the patient was calm, conscious, co-operative, and well oriented to time, place, and person. There was no swelling or localised tenderness present in the lower back region. There was restricted bending of the lower back and the straight leg raise test was limited at 60° bilaterally. Normal power, tone, sensations,

and reflexes were observed in both legs with no significant signs. The higher motor, cerebellar, gastrointestinal, respiratory, cardiovascular, and urological examinations were normal.

Routine investigations, such as complete blood count and urine analysis, were within normal limits. Antero-posterior and lateral X-ray of the lower back showed suspicious lesions in the sacral area. Erythrocyte sedimentation rate and C-reactive protein levels were significantly elevated. An MRI of the spine showed a mass-like lesion in the sacral vertebrae, along with osteolytic lesions. A biopsy of the same ruled out any suspicion of malignancy. Ziehl–Neelsen staining of the same yielded acid-fast bacilli and a PCR confirmed the presence of *Mycobacterium* TB in the lesion. Chest X-ray was normal and showed no signs of infection. Human leukocyte antigen B27 was negative.

A diagnosis of isolated TB of the sacrum was reached, and the condition, treatment, and prognosis were explained to the patient. The patient was initiated on anti-tubercular therapy (ATT), consisting of rifampicin, isoniazid, and ethambutol for a period of 9 months, and pyrazinamide, streptomycin, and ofloxacin for a period of 3 months, along with pyridoxine and analgesics. The patient was transferred to the Directly Observed Therapy (DOT) governmental department, which ensured compliance and monitored cure and side effects.

METHODOLOGIES

Informed consent was taken from the patient to publish the case report, and all the personal identifiers were removed from the case report.

The authors carried out a thorough search of the PubMed and Google Scholar databases for cases of isolated sacral TB, using the keywords "sacral tuberculosis," "tuberculosis of the sacrum," and "sacrum tuberculosis." Ultimately, the authors were able to find a total of 26 articles,[3-28] including one retrospective analysis of 15 cases,[5] a case series comprising three cases,[17] and 24 others classified as case reports. Articles without abstracts or available literature were excluded. Articles without isolated sacrum involvement, namely sacrococcygeal, lumbosacral, or multifocal spinal TB were also excluded.

DISCUSSION

The authors' patient presented with pain in the lower back, radiating to the lower limbs bilaterally with weakness and intermittent fever. The involvement of the lumbosacral region was speculated and the differential diagnosis of osteomyelitis, tumour of the local area, and lumbar disc herniation was taken into consideration.[29] An X-ray of the lumbosacral region was taken, which showed suspicious lesions. This was followed by an MRI to understand the extent of these lesions. As the patient had osteolytic lesions in the anterior sacral region, an histopathological investigation was advised to differentiate the infectious causes from neoplastic ones. After adequate biochemical and microbiological investigations, a diagnosis of sacral TB was established.

After a thorough review of the available medical literature, the authors isolated a total of 42 cases mentioned across 26 research articles. This case might be the 43rd case of isolated sacral TB reported across the aforementioned databases. The sample included 18 males and 23 females, and ranged from age 5.00–73.00 years (mean: 30.97 years). In their case report, Meurice et al.[3] chose not to disclose the gender identity of the youngest patient. Patanakar et al.[5] noted a much more severe disease presentation (abscesses and sinuses) in younger patients compared with older ones after reviewing 15 cases. The authors' patient, a male in their late 20s, fitted the typical presentation.

Sacral TB presents with a wide spectrum of symptoms, including fever, night sweats, pain in the lower back and legs, and weight loss, with the intensity ranging from very severe to mild or minimal. Lower back pain was the most common symptom, present in 34 patients, including the authors' case.[4,5,7,9-23,25-28] This also includes the three cases in the case series by Lazrak et al.,[17] and 10 cases in the observational study.[5] Fever due to underlying inflammation[5,16,17,19,21,27,28] and weight loss[13,16-19,22,25,27,28] was reported in 10 cases. Rigidity and stiffness of the lower back were reported in five cases.[4,5,9] Mild swelling of the local region was present in three cases,[15,18,21] of the right buttock in one case,[20] and of the thighs bilaterally in a case reported by Djaja et al.[24]

Night sweats, a common symptom of TB, were reported in four patients.[7,16,17,28] The presence of neurological symptoms is a common feature in sacral TB due to the local involvement of the nerve plexus. Wellons et al.[7] and Sament et al.[16] both reported cases of numbness of the lower limbs with associated weakness in the latter. Patanakar et al.[5] reported a case of paraparesis in their observational study. Lower limb functional loss was reported by both Meurice et al.[3] in the left leg, and Lmejjati et al.[6] in the right leg. Khosla et al.[8] reported a case of a female who reported no symptoms of sacral TB during their pregnancy, but presented with obstructed labour due to a swelling of the sacral region obstructing the vaginal canal.

Sacral TB usually presents with localised symptoms, with very few cases diagnosed prior to presentation in another system of the body. The case reported by Meurice et al.[3] presented as a recurrence post-9 months. Wellons et al.[7] reported a positive purified protein derivative skin test in a patient in their 30s, 3 years prior to presentation. Shah and Kulkarni[12] reported a patient in their 20s who presented with lumbar TB 11 months prior to presentation. A patient in their 50s reported by Djaja et al.[24] had presented with TB of the lymph nodes 25 years prior to presentation. There was no diagnosed prior presentation of TB in the authors' patient.

On laboratory investigations, patients usually have elevated erythrocyte sedimentation rate and C-reactive protein levels due to the underlying infectious pathology,[1] while leukocytosis may or may not be present in the patient, similar to the presentation of the authors' case. Chang et al.[10] reported a case of sacral TB mimicking a neoplasm with elevated levels of carbohydrate antigen 19-9. A mandatory chest X-ray should be done in all cases of sacral TB so as to rule out pulmonary TB. Of the 42 cases available, an abnormal chest X-ray with the presence of pleural effusion and atelectasis of the right side was present just in one case.[28]

An initial diagnosis may be made using a radiograph of the spinal region, but the definitive diagnosis and the extent of the disease are better understood via MRI of the spinal region, as MRI is more sensitive than a spinal radiograph, and more specific than a CT scan of the same region.[1] The most common MRI finding is the presence of osteolytic lesions in the sacrum, followed by a mass-like presentation that could be mistaken for cancerous growth.[3-28] In a few cases, the infection might extend to the piriformis muscles, leading to the formation of abscesses and collections in the same.[16,20,21,24,25] The tissue diagnosis can be confirmed by aspirating tissue and analysing histopathology (showing acid-fast bacilli), Lowenstein Jensen culture, and PCR.[1,14]

Adequate treatment for sacral TB includes primary therapy ATT, consisting of isoniazid, rifampin, pyrazinamide, and ethambutol. The World Health Organization (WHO) recommends ATT for a period of 9 months for patients who have TB in bones and joints,[30] while the American Thoracic Society (ATS) recommends ATT for 12 months for children and 6 months for adults.[31] The duration of ATT can vary depending on the local guidelines, as well as the severity of the disease. The reviewed cases had ATT prescribed varying from 6[7] to a maximum of 18 months.[13,16,19] Surgical intervention was required in a female patient in their 20s with a severe destructive lesion of the S1 body, requiring a lumbopelvic fixation, along with S1 reconstruction using an allograft.[12] Surgical debridement was carried out for a female patient in their 50s who had developed submuscular gluteal abscesses bilaterally as a complication of sacral TB.[24]

In the absence of early diagnosis and adequate treatment, complications may occur, such as structural and postural deformities, permanent neurological complications, and the extension of the disease to the neighbouring structures, leading to the formation of cold abscesses in the gluteal and piriformis muscles.[1,2,21,24] Surgical intervention might be required in patients who develop structural complications, such as bone insufficiency, abscesses, and spinal deformities.[1]

The prevalence of TB is higher in lower-middle income countries, and India suffers from a significant burden of the disease owing to the associated morbidity and mortality.[32] To address this issue, it is crucial to prioritise the primary and secondary prevention of the disease. This involves implementing measures by identifying individuals at high risk, such as immunodeficient individuals, young individuals, and patients suffering from chronic diseases of diabetes, chronic kidney disease, and HIV.[33]

Additionally, early detection and identification of the disease is necessary. Tuberculin skin test and interferon-γ release assays serve as valuable methods for detection of the disease.[34] Timely diagnosis and anti-tubercular therapy administration can potentially reduce the morbidity and complications associated with the disease.[35]

Sacral TB might extend to the other surrounding structures. Lumbosacral TB is common in comparison to isolated sacral TB, and sacrococcygeal TB is rarer.[36,37] Sacrococcygeal TB presents as lower back pain[36] or gluteal and coccygeal pain with anococcygeal fistula and discharge.[37]

CONCLUSION

Sacrum in isolation is a rare location for spinal TB, often overlooked by primary physicians. A prompt diagnosis and early treatment of the disease will mitigate the risk of developing complications. The authors hope that this review helps physicians and surgeons to consider TB of the sacrum as one of the key differential diagnoses in patients exposed to the endemic region presenting with a sacral lesion.

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Cerebrotendinous Xanthomatosis: A Clinical Series Illustrating the Radiological Findings

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Abstract

Cerebrotendinous xanthomatosis is a rare autosomal recessive disorder that occurs due to defective bile acid biosynthesis, causing unusual cholesterol and cholestanol deposition in multiple soft tissues. It is manifested by various neurological and non-neurological symptoms. The characteristic imaging features and clinical symptoms can help to make an early diagnosis and induce timely treatment to prevent neurological sequelae. The authors present two adults with differing clinical symptoms, whose imaging provided pivotal cues in diagnosing cerebrotendinous xanthomatosis.

Key Points

1. There is a correlation between the imaging findings and neuropathologic changes observed in patients with cerebrotendinous xanthomatosis (CTX).

2. Despite the presence of characteristic clinical and imaging findings, it is important to differentiate CTX from similar conditions, as misdiagnosis can occur.

3. Prompt diagnosis and treatment are essential to prevent the neurological complications associated with CTX. Fortunately, CTX is a treatable condition, and with appropriate treatment, there is no progression of imaging abnormalities in affected patients.

INTRODUCTION

Cerebrotendinous xanthomatosis (CTX) is a unique disease with an autosomal recessive inheritance, occurring due to the accumulation of cholestanol and cholesterol, mainly in the brain, spinal cord, peripheral nerves, lungs, liver, kidneys, tendon xanthomas, and bile.[1] It was first made known by Bogaert et al.[2] in 1937. The pathogenesis includes abnormal synthesis of bile acid due to deficient action of liver mitochondrial enzyme sterol 27-hydroxylase.[3] This leads to reduced production of cholic acid and negligible chenodeoxycholic acid, thereby lowering its negative effect on 7α-hydroxylase, which is the most limiting enzyme in bile acid synthesis. This induces an alternate pathway causing excessive accumulation of cholestanol in tissues. Also, bile alcohols are synthesised in these patients through 24- and 25- hydroxylase routes.[4] CTX is diagnosed biochemically by showing definitively increased levels of urinary bile alcohols and serum cholestanol levels.[5]

This increases the deposition of cholesterol and cholestanol in various tissues and organs, especially in the brain and tendons, and unusually in the peripheral nerves, lungs, liver, and kidneys. As a consequence, juvenile cataracts, developmental disability, tendon swelling, and cerebellar ataxia constitute the distinguished clinical presentation of this entity. Other neurological symptoms include diminished intelligence, loss of memory, dystonia, seizures, and psychotic behaviour.[6] Non-neurological features could be diarrhoea, early atherosclerosis, and reduced bone density.[7,8] Early diagnosis and intervention are crucial as treatment with chenodeoxycholic acid (CDCA) is helpful to the patients, and further progress of the disease can be prevented. The authors present the ultrasound (US), CT, and MRI findings of two patients of Indian ethnicity. Both patients gave written informed consent. The purpose is to add to the literature and illustrate the classic radiological findings in patients with CTX, which is commonly erroneously diagnosed, leading to neurological deterioration and delay in treatment induction, and thus affecting the prognosis of these patients. A well-timed and accurate diagnosis is of utter importance as therapy is of extreme help to these patients, and further devastation can be stopped.[9]

CASE REPORT

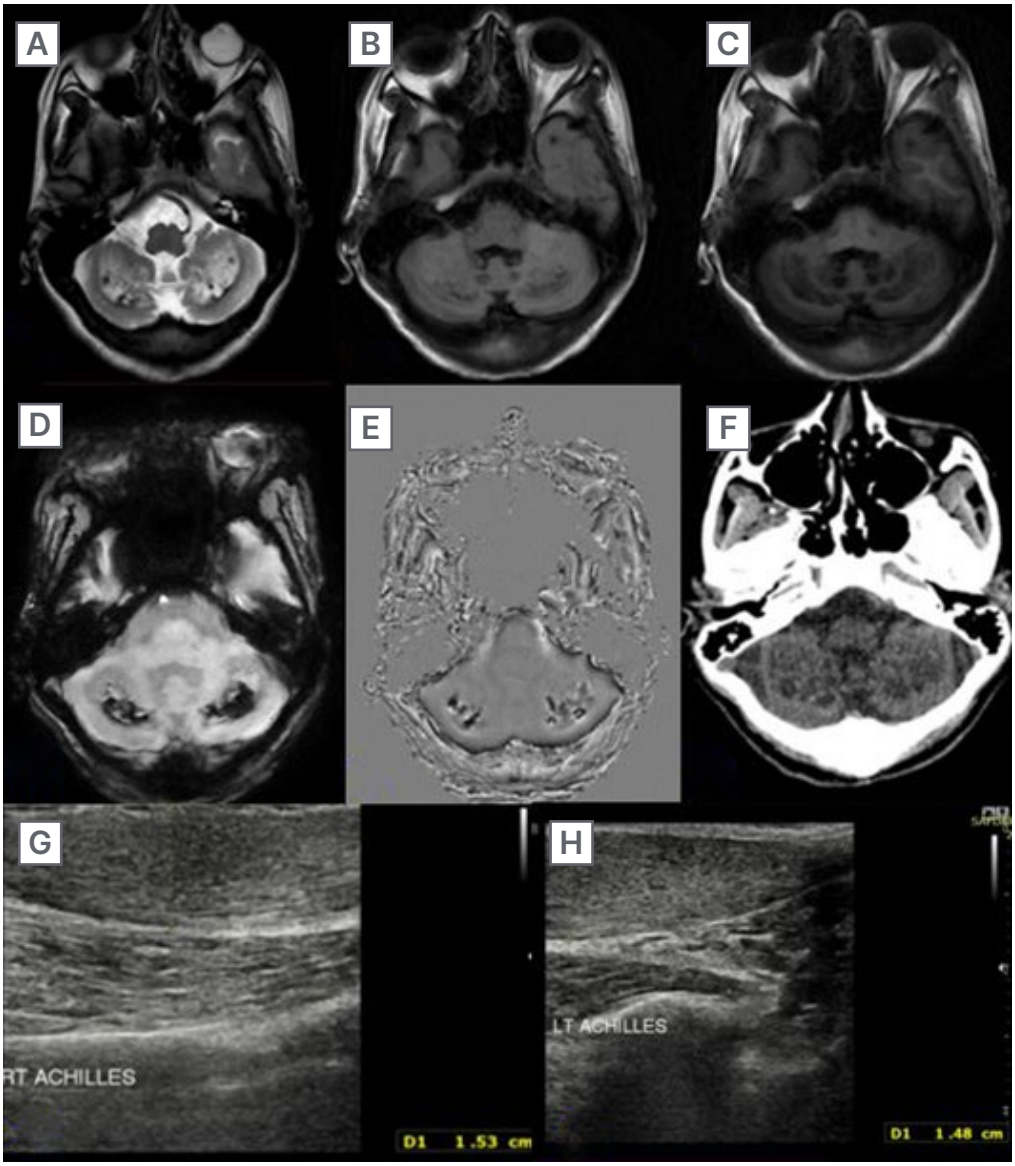
Case I

A 19-year-old female presented with progressive weakness of bilateral lower limbs and multiple episodes of seizures over the last 15 years, with an inability to walk without support for the last 2 months. The patient also had complaints of swelling over the posterior aspect of bilateral ankles for the last 6 months. They suffered from difficulty in reading and writing since childhood, and were not able to continue school after third standard. The patient also gave a history of bilateral cataract surgery a few years ago.

On examination, the patient had cerebellar dysarthria with bilateral upper and lower limb incoordination. Deep tendon reflexes were brisk with decreased plantar reflex. Bilateral pseudophakia was also noted. A nerve conduction study showed axonal sensory-motor polyneuropathy. The patient presented to the department for an MRI of the brain. Brain MRI with cervical spine screening was done on a 3T MRI scanner. The sequences acquired were T1 weighted (W), T2W, fluid attenuated inversion recovery (FLAIR), diffusion-weighted (DWI), susceptibility-weighted (SWI), and post-contrast T1W for MRI brain; and sagittal T2 fast spin-echo, sagittal T1 FLAIR, and axial T2 fast recovery fast spin-echo.

Brain MRI detected diffuse cerebellar atrophy, and bilateral symmetrical T2/FLAIR hyperintensity with intervening hypo-intense areas in dentate nuclei and surrounding cerebellar white matter (Figure 1A and 1B). On T1W imaging, these areas appeared hypointense (Figure 1C). SWI revealed corresponding areas of hypo-intensity, which appeared hyperintense on filtered phase s/o soft calcifications (Figure 1D and 1E). No diffusion restriction on DWI or contrast enhancement was noted. Screening of the cervical spine revealed no evidence of any abnormal signal intensity within the spinal cord. Additionally, the authors conducted a non-contrast CT of the head and US of bilateral ankles. Head non-contrast CT revealed bilaterally symmetrical hypodense areas in deep cerebellar white matter (Figure 1F). On US of ankles, the authors observed fusiform enlargement of bilateral Achilles tendon with increased anteroposterior thickness, loss of

Figure 1: Imaging (MRI and ultrasound) findings of Case 1.



A–C) MRI brain T2/FLAIR images showing bilateral symmetrical hyperintensity and hypointensity on T1 weighted images. **D–F)** Areas of soft calcifications on susceptibility-weighted angiography and non-contrast CT head. **G and H)** Ultrasound sonography of the ankles revealing fusiform enlargement and multiple dark foci in the bilateral Achilles tendons.

FLAIR: fluid attenuated inversion recovery.

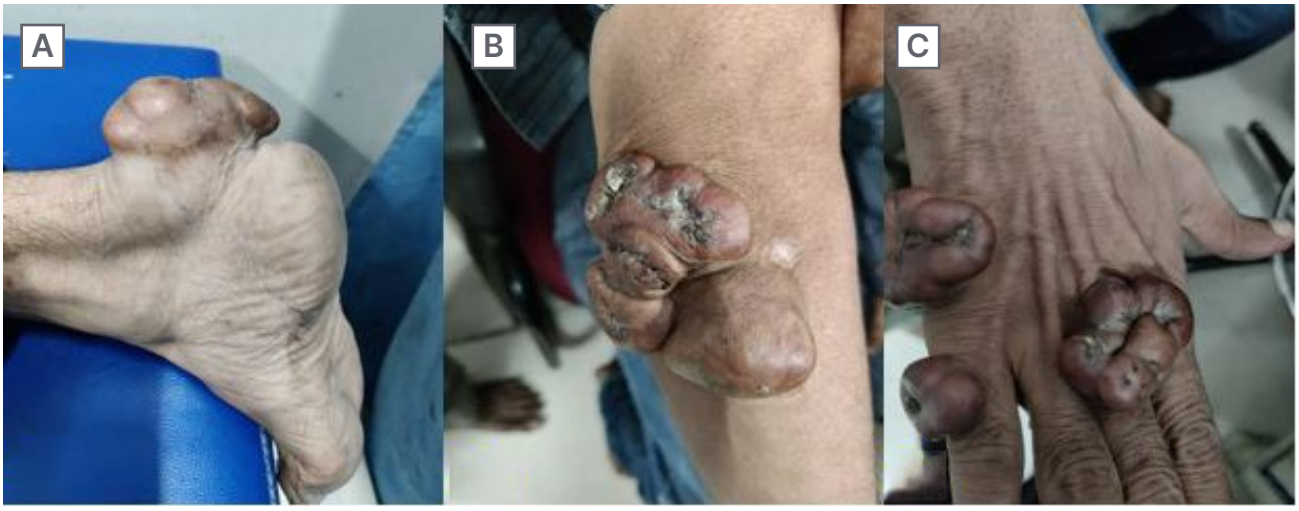
normal fibrillary pattern, and multiple dark foci within the tendons (Figure 1G and 1H).

Case II

A 40-year-old male presented with clinical complaints of multiple soft tissue growth over bilateral ankles, elbow, knee, and dorsum of hands for many years. The patient also had cognitive and language impairment. They gave a history of unilateral cataract surgery with a diminution of vision in the contralateral eye.

On clinical examination, the patient had firm, non-tender lobulated swellings seen over the bilateral Achilles tendon, bilateral infrapatellar region, bilateral elbows, and dorsum of bilateral hands (Figure 2A–C). The biopsy of the swellings

Figure 2: Clinical pictures of Case 2.



A–C) During the clinical examination, showcasing firm and non-tender lobulated swellings were observed over the Achilles tendons bilaterally, as well as in the infrapatellar regions, elbows, and dorsum of the hands bilaterally.

revealed diffuse sheets of foamy histiocytes in the dermis and collections of cholesterol clefts with foreign-body giant cells, suggestive of xanthoma with foreign-body giant cell reaction.

MRI brain with cervical spine screening was done on a 3T MRI scanner. The sequences performed were T1W, T2W, FLAIR, DWI, T2-weighted magnetic resonance angiography, and post-contrast T1 fast spin-echo for the brain MRI. This showed bilateral symmetrical altered signal intensity areas involving dentate nuclei and deep cerebellar white matter, which appeared heterogeneously hypointense on T1W and T2W image, with surrounding T2/FLAIR hyperintensity, which was seen extending to bilateral middle cerebellar peduncle and dorsal pons (Figure 3A–D). SWI revealed corresponding areas of hypo-intensity, which appeared hyperintense on filtered phase, suggestive of the presence of soft calcifications (Figure 3E). No diffusion restriction on DWI or contrast enhancement was noted. No abnormal signal intensity within the spinal cord was appreciated on cervical spine screening done by sagittal T2W sequence.

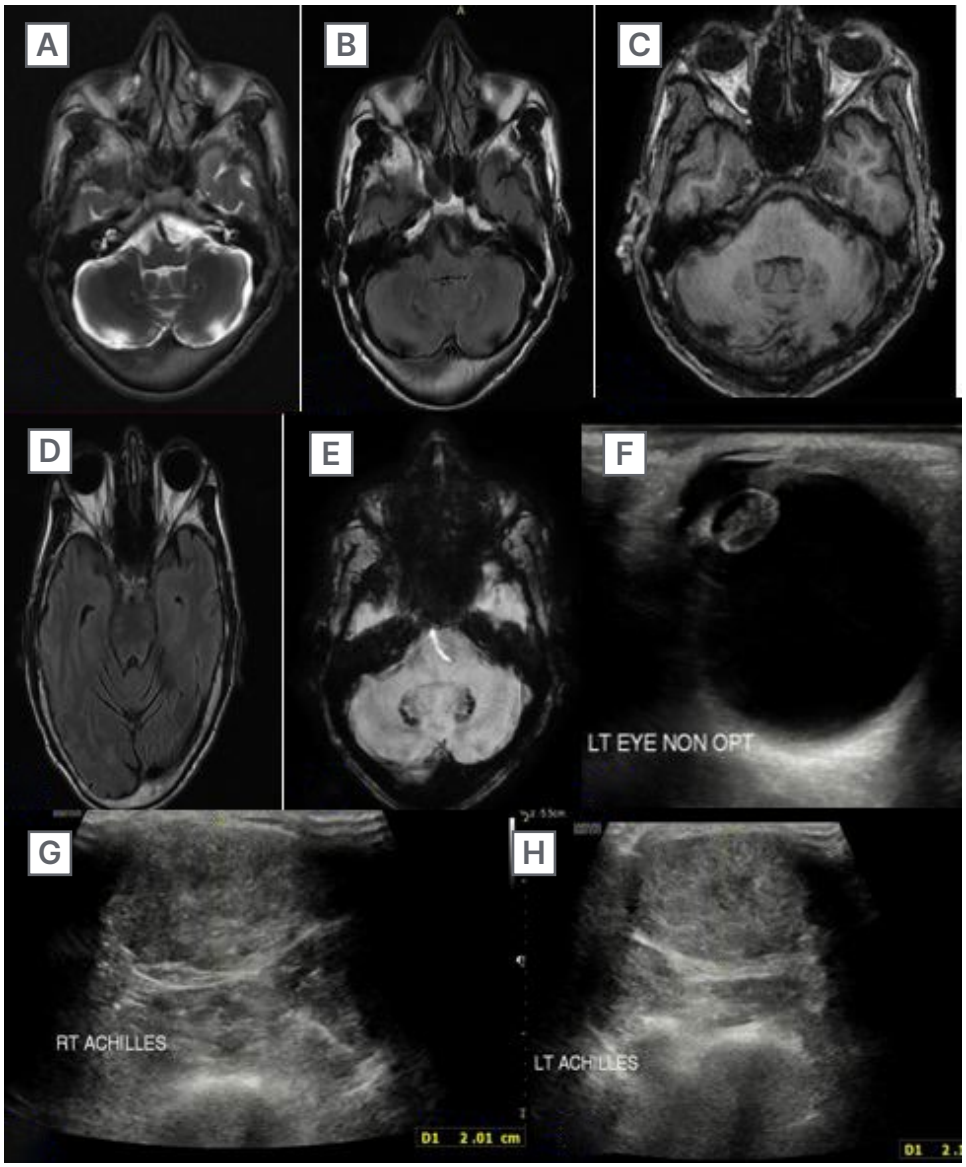
Additionally, the authors conducted US of bilateral ankles and bilateral ocular US. Ocular US revealed right-sided pseudophakia, and the left lens revealed an expanded lens with stippled hyperechoic contents within lens material (Figure 3F). On US of the ankles, the authors observed fusiform enlargement of bilateral Achilles tendon with increased anteroposterior thickness, and loss of normal fibrillary pattern with multiple dark foci within the tendons (Figure 3G–H).

The diagnosis in the authors' patients was based on clinical and radiological findings, and treatment with CDCA was started in both. After 3 months of therapeutic interval, Achilles tendon lesions decreased; however, no significant change in neurological symptoms was noted.

DISCUSSION

CTX is an uncommon autosomal recessive disorder due to mutations in the gene *CYP27A1*, on chromosome 2q33-qter, causing deficiency of an enzyme, mitochondrial sterol 27-hydroxylase, which plays a crucial role in bile acid synthesis.[1] It is a widely stated mitochondrial enzyme, associated with the mitochondrial chrome P450 enzyme family, capable of catalysing multiple hydroxylation reactions in the synthesis and metabolism of cholesterol and bile acid. Its deficiency leads to the absence of negative

Figure 3: Imaging (MRI and ultrasound) findings of Case 2.



A–D) The MRI brain scan revealed bilateral symmetrical hyperintensity on T2/FLAIR sequences in the dentate nuclei and deep cerebellar white matter, affecting the bilateral middle cerebellar peduncle and dorsal pons. **E)** The susceptibility-weighted imaging scan showed the presence of soft calcifications. **F)** The ultrasound scan of the left eye revealed an enlarged lens with stippled hyperechoic contents. **G**–**H**) The ultrasound scan of the ankles revealed fusiform enlargement of the bilateral Achilles tendons.

FLAIR: fluid attenuated inversion recovery.

feedback with excessive production, and build-up of cholestanol in various tissues, chiefly in the brain, lens, and tendons.[10] The blood cholestanol levels are raised; however, serum cholesterol levels can stay within normal range.[6]

CTX shows slow progression and significant variation in age of onset and clinical presentation.[11] These patients usually present at an average age of 35 years, and commonly there is a lag in the diagnosis of 16 years.[12] This disease entity, however, does not interfere with the lifespan of patients. They usually present with various neurological and non-neurological symptoms. Early diagnosis and intervention are important to stop the progression of neurological

deterioration.[13] The usual triad of clinical features consists of over-early bilateral cataracts, tendon xanthomas, and neurological abnormalities.[14] These clinical manifestations occur due to the abnormal accumulation of cholesterol and cholestanol, and include juvenile cataracts, progressive neurologic dysfunction, pyramidal and cerebellar signs, diminished intelligence, peripheral neuropathy, tendon xanthomas, chronic diarrhoea, atherosclerosis, osteoporosis, bone fractures, and respiratory symptoms.[15,16]

Ram et al.[17] reported two cases of CTX, both showing Achilles tendon xanthomas, cataracts, diarrhoea, and mental disability. The most involved tendons are the Achilles tendon and the quadriceps tendon. The triceps, finger extensor tendons, olecranon, tibial tuberosity, and plantar surface of the foot are relatively uncommon to be involved.[17] Hokezu et al.[18] reported only mild cerebral atrophy on imaging, even in the cases of severe mental deterioration in eight patients diagnosed with CTX. The patients in the present study had differing clinical complaints, with one showing prominent cerebellar signs with progressive weakness, while the other patient had multiple subcutaneous swellings with cognitive impairment.

One of the authors' patients had extensive tendon xanthomas involving multiple extensor tendons, as confirmed on histopathology and US, and another patient had bilateral Achilles involvement. Detailed high-resolution US of the Achilles tendon can be used to monitor disease progression. This technology is equally good as MRI, and still the best modality for follow-up because of its easy availability and lack of radiation. These tendon xanthomas appear hypointense on T1 and T2W image MRI, in contrast to the T1W hyperintense appearance of the normal tendon, due to the presence of internal fat. The decrease in anteroposterior diameter is indicative of a better response to the treatment. Histopathology of the tendons shows an aggregation of xanthoma cells with various, distributed lipid crystal rifts.[19]

Classical MRI findings are bilateral symmetrical altered signal intensity in dentate nuclei and surrounding cerebellum, which appear hyperintense on T2W image. There are widespread or localised supratentorial white matter abnormalities due to demyelination, which can also be seen in cerebral peduncles and globus pallidus. A characteristic hypointense rim along these lesions on T2W image has also been described, which is formed due to xanthomas.[20,21] A few hypointense foci likely representing haemorrhage or calcification have also been noted within the hyperintense areas in the dentate nuclei and the cerebellar white matter.[19] Cerebral and cerebellar atrophy is also a common finding. The authors' patient's non-contrast CT and MRI findings were typical and consisted of bilaterally symmetrical hypodensities on CT and hyperintense signal on T2W/FLAIR in deep cerebellar white matter.

The imaging findings, especially symmetrical cerebellar lesions, are typical for CTX; however, few of these findings, such as symmetric deep grey matter and cerebellar involvement, can be observed in other rare diseases, like Erdheim–Chester disease, Langerhans cell histiocytosis,[22-25] and a few peroxisomal disorders, such as Refsum disease and adrenomyeloneuropathy.[26,27] The pathogenesis responsible for central nervous system findings, as suggested by a few authors, is due to demyelination, whereas few suggest mainly a neuroaxonal process, rarefaction with resultant loss of neurons and myelin.[28,29] The dentate nucleus has been reported to be most susceptible to ischaemic, metabolic, infectious, and degenerative nerve diseases.[30] Other findings, like atrophy of the spinal cord, brainstem, and corpus callosum, including spinal lateral and dorsal column lesions, are quite rare.[19] None of the authors' patients revealed such a finding. The involvement of the spinal cord has also been described in a symmetrical pattern predominant involving grey matter with mild contiguous extension in the white matter. In rarer circumstances, isolated involvement of the spinal cord has been described in the form of chronic myelopathy without any cerebral or cerebellar signs.[31] Common differential diagnoses of CTX are tabulated in Table 1.[32-36]

Stelten et al.[37] found that the prognosis is good if therapy is started before 25 years of age, and follow-up time should be prolonged.[37] Another study found that CDCA is effective and safe, with positive results on an average of 9 months after induction of therapy.[38] The mainstay for the therapy of CTX is CDCA, which holds the production of cholestanol and bile alcohols by

Table 1: Differential diagnosis.

Differential Diagnosis	Imaging Features
Lipid storage diseases[17] • Homozygous familial hypercholesterolaemia • Familial dysbetalipoproteinaemia • Sitosterolaemia • Cholestatic liver disease	• Xanthomas are different, consisting of eruptive xanthomas and xanthelasmata.[32] • Typical progressive juvenile immature cataracts and neurologic dysfunction are lacking in these conditions. • Serum cholesterol levels are usually normal in CTX.
Metronidazole toxicity	• Symmetrical non-enhancing lesions involving the dentate nucleus, midbrain, pons, and corpus callosum. • Reversible, and disappear within a few weeks of discontinuation of metronidazole.[33] • Cerebellar or psychiatric symptoms, but never comes with Tendo Achilles xanthoma or cataracts.
MSUD	• Symmetric T2W/FLAIR bright lesions involving the cerebellar white matter, dorsal brain stem, cerebral peduncles, globus pallidum, bilateral thalami, internal capsules, and corticospinal tracts, with marked diffusion restriction.[34]
Marinesco–Sjögren syndrome	• No tendon involvement.
Isolated spinal involvement • Multiple sclerosis • Neuromyelitis optica	• Patchy, peripheral, asymmetrical, and short-segment cord involvement.[35] • Optic neuritis, central, and long segment involvement of the cord.[36]

CTX: cerebrotendinous xanthomatosis; FLAIR: fluid attenuated inversion recovery; MSUD: decompensated maple syrup urine disease; W: weighted.

providing negative feedback for the bile acid biosynthesis pathway.[10] It is not suggested to remove the xanthomas surgically, as they might show rapid growth again.[39] Therefore, it becomes essential that the disease is diagnosed at the earliest and treatment initiated to prevent neurological sequelae and complications.

Among the recent advances, magnetic resonance spectroscopy might help, as an association between N-acetyl aspartate levels and patients' ailment has been established, and its role to evaluate the disease aftereffects needs to be further validated.[20] Magnetic resonance spectroscopy has also shown lipid peaks, elevated choline, and reduced N-acetyl aspartate levels in affected areas, which suggests significant axonal and mitochondrial injury.[40] CTX is a rare genetic entity, with less than 400 cases reported in the literature, and through this case report, the authors intend to emphasise the diverse imaging perspective of this entity.

CONCLUSION

CTX is an uncommon condition with typical clinical and radiological findings. Treatment is successful if initiated at an early stage; therefore, prompt identification of the disease is very important. The radiologist should be aware of the multimodality imaging approach to this entity

so that prompt therapeutic intervention can be done to avoid further progression, neurological sequelae, and complications.

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Study for Assessment of Mental Health in Survivors of COVID-19

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Abstract

Background: The authors aimed to study the levels of anxiety, depression, and stress in survivors of COVID-19, and to correlate their level with severity of COVID-19 infection.

Methodology: This study was conducted on a total of 200 survivors of COVID-19 as an observational cross-sectional study. The cohort reported to the Hamidia Hospital, Bhopal, India, during the study period of 21 months. The Depression Anxiety Stress Scale-21 (DASS21) was used for assessment of mental health.

Results: Overall, depression, anxiety, and stress were observed in 38.5% of cases, 38.5% of cases, and 11.0% of cases, respectively. The authors reported a significant association of worst saturation recorded with depression and severity of depression ($p<0.05$); significant association of depression and severity, and anxiety and its severity; and severity of stress with moderate-to-severe high-resolution CT findings ($p<0.05$). The authors also documented a medium positive and significant correlation of the severity of COVID-19 infection with stress and DASS21 overall score (analysis of variance: $r=>0.40$; $p<0.05$). However, a weak positive but significant correlation of severity with depression and anxiety was noted ($r=0.20–0.40$; $p<0.05$). The authors reported a weak positive correlation of worst saturation with depression and anxiety, as well as overall DASS21 score ($r=0.20–0.40$; $p<0.05$).

Conclusion: COVID-19 has long-term effects, especially in the form of psychological morbidity. Patients have recovered from the physical illness, but psychological distress and mental problems are still persistent among the survivors as the prevalence of depression, anxiety, and stress is reported to be high among them.

Key Points

1. The COVID-19 pandemic had a devastating impact on the lives of individuals worldwide. The impact was not only seen on health, but also day-to-day activities. It significantly changed the normal course of life of an individual.

2. The authors present a cross-sectional observational study for the assessment of the mental health of survivors of COVID-19.

3. All survivors of COVID-19 must be screened for mental problems periodically, as these illnesses may significantly negatively impact their quality of life.

INTRODUCTION

COVID-19 infection was first reported in December 2019 in Wuhan, China, as a pneumonia outbreak presenting with fever, cough, body ache, dyspnoea, etc.[1] The COVID-19 pandemic resulted from a novel coronavirus infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] As of 21st July 2022, a total of 567 million cases and 6.3 million deaths were reported across the world.[3] In India, 43.8 million people were affected, and 528,000 deaths were reported in the same period.[4]

Psychological health was affected during the pandemic, as there is distress and uncertainty regarding one's own health, due to the absence of proper management and availability of beds during the ongoing pandemic. Also, the situation was further worsened by the quarantine of patients away from their families, prolonged hospital stays, panic due to social media posts about the pandemic, and false or unverified information. These may be the factors associated with high levels of psychological and mental stress among individuals.[5,6] The research to date has mainly focused on assessing mental health among medical staff, doctors, and the general population amidst the COVID-19 pandemic.[7,8] However, the mental health status of patients with COVID-19 who suffered from the illness and trauma of isolation in quarantine wards and COVID-19 care centres has not been explored much. Recently, a few researchers highlighted the negative impact of COVID-19 on mental health and quality of life among survivors, which may be an indicator of prognosis in such patients.[9,10]

Previous studies have reported that mental illnesses such as anxiety, depression, and post-traumatic stress disorders (PTSD) are common among survivors of COVID-19.[11-13] The mental health status of survivors of COVID-19 may remain affected even after discharge, and the pandemic may have long-term chronic effects on the mental health status of patients.[14] Addressing the impact of COVID-19 on the mental health status of survivors of COVID-19 is essential for improving their overall health status. With the above background, the present study was conducted at a tertiary care centre in India to study the level of anxiety, depression, and stress in survivors of COVID-19, and to correlate the level of depression, anxiety, and stress in individuals who had recovered from COVID-19 with the severity of infection.

MATERIALS AND METHODS

The Department of Medicine and Psychiatry at Gandhi Medical College and associated Hamidia Hospital, both in Bhopal, India, conducted a cross-sectional observational study from January 2021–September 2022. The study population includes Indian patients who visited the psychiatry and medicine outpatient department; who had tested positive for COVID-19 infection in the past 6 months using a rapid antigen test kit and/or reverse transcription-PCR test; who were admitted for 3 or more days for their illness; and who had subsequently recovered. Patients aged 18 years and above who consented to participate in the study were included. However, the study had certain exclusion criteria. Patients with a past history of psychiatric disorders or any other psychiatric disorder were excluded from the study.

Data Collection Method

After obtaining ethical clearance from Gandhi Medical College and Hamidia Hospital's Ethical Committee, all the patients fulfilling the inclusion criteria and giving written consent for participation were enrolled in the study. Detailed history regarding sociodemographic variables; their current complaints; and comorbid conditions, such as diabetes, hypertension, or any respiratory illness, was obtained and documented. Detailed history regarding previous COVID-19 infection and investigation workup was obtained. Their past records and data regarding the findings of high-resolution CT (HRCT) chest, and worst O_2 saturation (severe illness: saturation of peripheral O_2: <94% on room air) were accessed. A CT severity score was assigned out of 25, based on the percentage area involved in each of the five lobes. The total CT score is measured by the sum of the individual lobar scores, and can range from 0 (no involvement) to 25 (maximum involvement) when all five lobes show more than 75% involvement. CT severity scores of 1–5, 6–14, and 15–25 were categorised as mild, moderate, and severe involvement, respectively.

Psychiatric conditions in such patients were assessed using the Depression Anxiety Stress Scale-21 (DASS21),[14] with 21 items (Figure 1).[15] The scale is based upon the dimensional concept of psychological disorder rather than categorical conception.[15]

Statistical Analysis

Data was compiled using Microsoft Excel (Microsoft, Redmond, Washington, USA), and analysed with the help of IBM® (Armonk, New York, USA) SPSS software version 20. Categorical data was expressed as frequency and proportion, whereas continuous data was expressed as mean and standard deviation. The association of mental disorders with the severity of infection was done using the χ^2 test, and correlation was done using the Pearson correlation coefficient. A p value of less than 0.05 was considered statistically significant.

RESULTS

The study was conducted on a total of 200 survivors of COVID-19, with a mean age of 39.370±12.938 years. Male predominance was observed with a male:female ratio of 1.3:1.0. Approximately 74% of survivors of COVID-19 belonged to middle socioeconomic status. The most common comorbid condition observed among the group was diabetes (19.5%), followed by hypertension (17.0%).

The mean saturation (worst) recorded among survivors of COVID-19 was 91.220±5.385%. Approximately 2.5% of cases had saturation below 80, whereas 40.0% had saturation in the 80.0–90.0% range. HRCT was suggestive of mild severity in 53.0% of cases, whereas CT severity score was moderate and severe in 16.5% and 2.0% of cases, respectively.

Mean depression, anxiety, and stress scores were 11.220±6.490, 6.060±3.513, and 7.950±3.007, respectively. Overall, depression was observed in 38.5% of cases, and the majority of cases had mild (21.0%) and moderate (17.0%) depression. However, anxiety was noted in 38.5% of cases, and the majority of patients had mild anxiety (21.0%), followed by moderate anxiety (17.0%). Stress was present in 11% of cases, and the majority had mild stress.

The authors reported a significant association of worst saturation recorded with depression and severity of depression ($p<0.05$; Table 1). They also documented a significant association between depression and its severity and anxiety and its severity; and severity of stress with moderate-to-severe HRCT findings ($p<0.05$; Table 2)

The authors documented a medium positive and significant correlation between the severity of COVID-19 infection with stress and DASS21 overall score (analysis of variance: r=>0.40; $p<0.05$). However, a weak positive but significant correlation of severity with depression and anxiety was noted (r=0.20–0.40; $p<0.05$). They reported a weak positive correlation of worst saturation with depression and anxiety, as well as overall DASS21 score (r=0.20–0.40; $p<0.05$; Table 3 and Table 4).

Figure 1: Psychiatric conditions were assessed using the Depression Anxiety Stress Scale-21.

DASS21

Name: Date:

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you **over the past week**. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:

0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree or a good part of time
3 Applied to me very much or most of the time

1 (s)	I found it hard to wind down	0	1	2	3
2 (a)	I was aware of dryness of my mouth	0	1	2	3
3 (d)	I couldn't seem to experience any positive feeling at all	0	1	2	3
4 (a)	I experienced breathing difficulty (e.g. excessively rapid breathing, breathlessness in the absence of physical exertion)	0	1	2	3
5 (d)	I found it difficult to work up the initiative to do things	0	1	2	3
6 (s)	I tended to over-react to situations	0	1	2	3
7 (a)	I experienced trembling (e.g. in the hands)	0	1	2	3
8 (s)	I felt that I was using a lot of nervous energy	0	1	2	3
9 (a)	I was worried about situations in which I might panic and make a fool of myself	0	1	2	3
10 (d)	I felt that I had nothing to look forward to	0	1	2	3
11 (s)	I found myself getting agitated	0	1	2	3
12 (s)	I found it difficult to relax	0	1	2	3
13 (d)	I felt down-hearted and blue	0	1	2	3
14 (s)	I was intolerant of anything that kept me from getting on with what I was doing	0	1	2	3
15 (a)	I felt I was close to panic	0	1	2	3
16 (d)	I was unable to become enthusiastic about anything	0	1	2	3
17 (d)	I felt I wasn't worth much as a person	0	1	2	3
18 (s)	I felt that I was rather touchy	0	1	2	3
19 (a)	I was aware of the action of my heart in the absence of physical exertion (e.g. sense of heart rate increase, heart missing a beat)	0	1	2	3
20 (a)	I felt scared without any good reason	0	1	2	3
21 (d)	I felt that life was meaningless	0	1	2	3

Scores on the DASS21 are multiplied by 2 to calculate the final score.

DASS21: Depression Anxiety Stress Scale-21

Table 1: Association of Depression Anxiety Stress Scale-21 with worst saturation recorded.

DASS21		Worst saturation recorded						p
		>90		81–90		≤80		
		n	%	n	%	n	%	
Depression	Absent	61.0	53.0	23.0	28.7	1.0	20.0	0.002
	Present	54.0	47.0	57.0	71.2	4.0	80.0	
Severity of depression	Normal	61.0	53.0	23.0	28.7	1.0	20.0	0.003
	Mild	25.0	21.7	19.0	23.8	0.0	0.0	
	Moderate	24.0	20.9	28.0	35.0	2.0	40.0	
	Severe	4.0	3.5	9.0	11.2	2.0	40.0	
	Extremely severe	1.0	0.9	1.0	1.2	0.0	0.0	
Anxiety	Absent	78.0	67.8	41.0	51.3	4.0	80.0	0.052
	Present	37.0	32.2	39.0	48.8	1.0	20.0	
Severity of anxiety	Normal	78.0	67.8	41.0	51.3	4.0	80.0	0.240
	Mild	21.0	18.3	21.0	26.3	0.0	0.0	
	Moderate	16.0	13.9	17.0	21.3	1.0	20.0	
	Severe	0.0	0.0	1.0	1.3	0.0	0.0	
Stress	Absent	103.0	89.6	70.0	87.5	3.0	100.0	0.660
	Present	12.0	10.4	10.0	12.5	0.0	0.0	
Severity of stress	Normal	103.0	89.6	70.0	87.5	3.0	100	0.970
	Mild	5.0	4.3	6.0	7.5	0.0	0.0	
	Moderate	4.0	3.5	3.0	3.8	0.0	0.0	
	Severe	2.0	1.7	1.0	1.2	0.0	0.0	
	Extremely severe	1.0	0.9	0.0	0.0	0.0	0.0	

DASS21: Depression Anxiety Stress Scale-21.

DISCUSSION

The COVID-19 pandemic was a dreadful pandemic, which had a devastating impact on almost all aspects of health. Though the waves of the pandemic have subsided, the literature suggests that the pandemic may have a long-term impact on the mental health of survivors of COVID-19, who might have faced immense trauma due to illness itself, isolation from family and friends, fear of death, etc.[10,11] Post-traumatic stress disorders (PTSD), depression, anxiety, etc. are documented among survivors of an outbreak.[9-11] The authors aimed to assess the level of depression, anxiety, and stress in survivors of COVID-19, and to correlate these problems with the severity of infection. The authors used the DASS21 scale for the assessment of mental disorders among the survivors, which is a valid and reliable scale

Table 2: Association of Depression Anxiety Stress Scale-21 with high-resolution CT severity.

DASS21		HRCT severity								p
		Normal		Mild		Moderate		Severe		
		n	%	n	%	n	%	n	%	
Depression	Absent	42.0	73.7	34.0	32.1	8.0	24.2	1.0	25	0.001
	Present	15.0	26.3	72.0	67.9	25.0	75.8	3.0	75.0	
Severity of depression	Normal	42.0	73.7	34.0	32.1	8.0	24.2	1.0	25	0.001
	Mild	7.0	12.3	30.0	28.3	7.0	21.2	0.0	0.0	
	Moderate	6.0	10.5	33.0	31.1	12.0	36.4	3.0	75.0	
	Severe	1.0	1.8	8.0	7.5	6.0	18.2	0.0	0.0	
	Extremely severe	1.0	1.8	1.0	0.9	0.0	0.0	0.0	0.0	
Anxiety	Absent	50.0	87.7	57.0	53.8	15.0	45.5	1.0	25.0	0.001
	Present	7.0	12.3	49.0	46.2	18.0	54.5	3.0	75.0	
Severity of anxiety	Normal	50.0	87.7	57.0	53.8	15.0	45.5	1.0	25.0	0.001
	Mild	3.0	5.3	28.0	26.4	8.0	24.2	3.0	75.0	
	Moderate	4.0	7.0	20.0	18.9	10.0	30.3	0.0	0.0	
	Severe	0.0	0.0	1.0	0.9	0.0	0.0	0.0	0.0	
Stress	Absent	53.0	93.0	94.0	88.7	28.0	84.8	3.0	75.0	0.510
	Present	4.0	7.0	12.0	11.3	5.0	15.2	1.0	25.0	
Severity of stress	Normal	53.0	93.0	94.0	88.7	28.0	84.8	3.0	75.0	0.001
	Mild	2.0	3.5	6.0	5.7	3.0	9.1	0.0	0.0	
	Moderate	1.0	1.8	4.0	3.8	2.0	6.1	0.0	0.0	
	Severe	1.0	1.8	2.0	1.9	0.0	0.0	0.0	0.0	
	Extremely severe	0.0	0.0	0.0	0.0	0.0	0.0	1.0	25.0	

DASS21: Depression Anxiety Stress Scale-21; HRCT: high-resolution CT.

for the assessment of depression, anxiety, and stress, with Cronbach's alpha values of 0.66, 0.29, and 0.52, respectively.[16]

COVID-19 infection was associated with various short-term and long-term morbidities among survivors. Psychological problems, including depression, anxiety, and stress have been reported to be common in patients who have recovered from COVID-19 infection.[16] The action of coronavirus infection on angiotensin-converting enzyme 2 (ACE2) receptors in the central nervous system (CNS) may lead to neurological symptoms. However, the role of cytokine storm associated with the infection has also been postulated.[17]

In the CNS, ACE2 is expressed in a physiologically appropriate manner. Whether ACE2 expression is increased in pathological

Table 3: Correlation of severity of COVID-19 with Depression Anxiety Stress Scale-21.

Severity		R	R^2	Adjusted R^2	Standard error of the estimate	p
Worst saturation	DASS21	0.375	0.140	0.136	11.817	0.0001
	Depression	0.398	0.158	0.154	5.968	0.0001
	Anxiety	0.286	0.082	0.077	3.375	0.0001
	Stress	0.179	0.032	0.027	5.925	0.0100
CT severity	DASS21	0.454	0.206	0.202	11.356	0.0001
	Depression	0.330	0.109	0.105	6.140	0.0001
	Anxiety	0.398	0.158	0.154	3.231	0.0001
	Stress	0.371	0.137	0.133	5.594	0.0001

DASS21: Depression Anxiety Stress Scale-21; R: Pearson's correlation coefficient; R^2: used in analysis of variance.

Table 4: Severity of depression, anxiety, and stress.

	Depression	Anxiety	Stress
Normal	0–9	0–7	0–14
Mild	10–13	8–9	15–18
Moderate	14–20	10–14	19–25
Severe	21–27	15–19	26–33
Extremely severe	28+	20+	34+

situations like SARS-CoV-2 infection is unknown. The presence of ACE2 in the CNS makes it possible for SARS-CoV-2 to invade neuronal cell membranes and cause neurological symptoms, as well as brain damage. A previous coronavirus study suggested that the coronavirus attaches to target cells' surfaces when the S1 unit of the spike protein on its surface interacts with the ACE2 receptor on neurons.[17] The spike protein is then activated by transmembrane protease, serine 2, which allows the virus to enter the neuron. Moreover, SARS-CoV-2 infection can attack endothelial cells in cerebral blood vessels via the ACE2 receptor and disrupt the blood–brain barrier (BBB), leading to increased BBB permeability, cerebral oedema, and intracranial hypertension. Endothelial cells of blood vessels also express ACE2 at high levels. A compromised BBB may also encourage invasion into neurons and brain tissues. One of the major causes of a higher proportion of mental illness is social isolation as a result of infection, leading to

loneliness and grief after bereavement, and financial worries. Vice versa, patients with pre-existing mental illness were more likely to get infected, and hospitalisation and death were reported to be higher among them.[18]

The authors reported depression in 57.5% of survivors of COVID-19, with severe and extremely severe depression in 7.5% and 1.0% of cases, respectively. Anxiety was documented in 38.5% of cases with mild-to-moderate anxiety in the majority of cases. Stress was reported in 11.0% of cases: mild in 5.5%, moderate in 3.5%, severe in 1.5%, and extremely severe in 0.5%.

As the study participants were from a younger age group and did not have a significant past history of any respiratory illness, specifically chronic obstructive pulmonary disease, that could also change the overall burden of psychiatric illness in this study, as anxiety, depression, and stress have been associated with lung diseases, specifically chronic obstructive pulmonary diseases.

In this study, diabetes and hypertension were the common comorbidities observed in 19.5%, and 17.0% of survivors of COVID-19, respectively. Siddiqui et al.[19] reported diabetes, hypertension, chronic lung disease, and coronary artery disease in 61.5%, 47.1%, 3.8%, and 24.0% of survivors of COVID-19, respectively.

These study findings were supported by the findings of Shah et al.,[20] who reported anxiety and depression in 68.7% of survivors of COVID-19. Khademi et al.[16] reported anxiety, depression, and PTSD in 5.8%, 5.0%, and 3.8% of survivors. Uvais et al.[21] reported depression, anxiety, and PTSD in 26.2%, 12.1%, and 3.7% of cases, respectively.. Huang et al.[22] reported the prevalence of anxiety, depression, and PTSD after 12 months of infection as 6.26%, 11.94%, and 6.07%, respectively. Chen et al.[23] documented the prevalence of depression at 21.0%, anxiety at 16.4%, and PTSD at 13.2% among patients with COVID-19 who were hospitalised.

The correlation of health disorders was assessed with respect to the severity of infection. The severity of the infection was determined using the worst saturation and CT severity score. In this study, the worst saturation below 80% was significantly associated with depression, as well as increased severity of depression; whereas HRCT severity showed a significant association with depression as well as anxiety, with increasing severity of depression, anxiety, and stress ($p<0.05$). The authors also documented a moderate positive statistically significant correlation between the severity of COVID-19 infection with stress and DASS21 overall score ($r=>0.40$; $p<0.05$). However, a weak, significant correlation of severity with depression and anxiety was noted ($r=0.20–0.40$; $p<0.05$). These study findings were supported by the findings of Parker et al.,[24] in which the authors documented a higher rate of PTSD in cases with severe physical illness (not particularly COVID-19). The present study's findings are concordant with the findings of Liu et al.,[7] in which mental and neurological disorders among survivors were significantly associated with the severity of illness. Similarly, Magnúsdóttir et al.[25] in their study documented a significantly higher risk of depression, as well as anxiety, in patients with COVID-19 who were bedridden for more than 7 days, as compared with patients who were not bedridden ($p<0.05$). Pappa et al.[26] found that the majority of cases suffered from severe COVID infection (48.25%), followed by 34.97% and 13.99% with moderate and critical illness, respectively.

LIMITATION

The present study was conducted as an observational cross-sectional study; however, a prospective study with follow-up of patients after discharge might have revealed the long-term outcomes.

Since this study was cross-sectional, there is no comparison/control for people who lived through the COVID-19 pandemic with the same stresses, and there is no baseline data on mental health disorders, which may bias the result.

This is a limited and selective sample of patients, which does not appear to control for variables such as false or unverified information; this would also be impacting people who have not had the COVID-19 virus.

CONCLUSIONS

COVID-19 has long-term effects, especially in the form of psychological morbidity. Patients have recovered from the physical illness, but psychological distress and mental problems are still persistent among the survivors as the prevalence of depression, anxiety, and stress is reported to be high among them. Mild illness is less likely to have an impact on the mental health of affected individuals, but severe illnesses have been linked with a higher risk of long-term mental health morbidities. All survivors of COVID-19 must be screened for mental problems periodically, as these illnesses may significantly negatively impact the quality of life of the affected individual, and their family members.

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Lymphoma of Nervous System or the Great Imitator in Neurology

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Abstract

Background: Lymphoma of the central nervous system (CNS), both primary and secondary, represents a very rare part of patients with non-Hodgkin lymphoma.

Methods: Exams included a neurological exam, laboratory blood tests, MRI, biopsy, and electromyography.

Results: Three different clinical cases of patients with lymphoma of the nervous system are presented. The first patient is a 44-year-old male admitted to the emergency room because of neck stiffness, with MRI data for a tumour in the left cavernous sinus area. Biopsy was performed 3 months prior to hospitalisation, showing connective tissue, partially hyalinised. Lumbar tap was performed to exclude CNS infection. Cerebrospinal fluid (CSF) examination showed lymphocytic pleocytosis, atypical cells in different phases of mitosis, and the result did not confirm lymphocytic choriomeningitis. Flow cytometric measurement (FCM) of CSF led to the diagnosis of T-lymphoblastic lymphoma of CNS.

The second patient is a 50-year-old female hospitalised in the authors' neurological department because of lower limb weakness and decreased sensation, dysphagia, and facial nerve palsy. Brain MRI showed no abnormal lesions. Guillain–Barré syndrome was considered after performing electromyography and electroneurography. CSF showed lymphocytic pleocytosis and 47% of them were atypical. FCM of CSF helped the authors diagnose the patient with B-lymphoblastic lymphoma.

The third case presents a 63-year-old male with right sided hemiparesis and progressive cognitive impairment. Previously performed CTs and MRIs of the brain showed both hemispheres and left cerebellar peduncle diffuse lesions. Ischaemic stroke, tumour, and CNS infectious disease were considered. Most of these were excluded because CSF showed no pathological findings. Brain tissue biopsy of one of the lesions was performed, and the patient was diagnosed with diffuse large B cell lymphoma.

Conclusion: Lymphoma of the CNS is rare disease. Differential diagnoses include different conditions. FCM of CSF and biopsy could be useful in complicated patients and unknown diagnosis affecting the CNS.

Key Points

1. Lymphoma of the central nervous system (CNS), both primary and secondary, represents a very rare part of the patients with non-Hodgkin lymphoma. CNS lymphoma is associated with poor outcome, with an overall survival of 1.5 months when untreated, and a 5-year survival rate of 30% when treated.
2. These cases show the significance of varied examinations in diagnostic process.
3. Flow cytometric measurement of cerebrospinal fluid and biopsy could be useful in complicated patients with unknown diagnosis affecting the CNS.

INTRODUCTION

Primary and secondary lymphoma of the central nervous system (CNS) is a rare case of non-Hodgkin lymphoma. The World Health Organization (WHO) classifies primary CNS lymphoma as extranodal non-Hodgkin lymphoma typically confined to the brain, eyes, and cerebrospinal fluid (CSF), without evidence of systemic spread.[1] Affected CNS areas could be different in each patient, as well as clinical signs and symptoms, requiring consideration of a lot of differential diagnoses. CNS lymphoma is associated with poor outcome, with an overall survival of 1.5 months when untreated, and a 5-year survival rate of 30% when treated.[2]

Primary CNS lymphoma (PCNSL) occurs at an incidence of 0.47 per 100,000 person-years, for 4–6% of extranodal lymphomas and 4% of newly diagnosed CNS tumours. PCNSL is more typical in males.[3] The clinical and neuroimaging presentation of CNS lymphoma can be varied. The patients should not be treated for PCNSL without cytologic confirmation of diagnosis with CSF examination or biopsy of the brain. Differential diagnoses includes brain tumour, neurological infections, peripheral nerve disease, neurosarcoidosis, and vascular disease.

Most cases with PCNSL (approximately 90%) are associated with diffuse large B cell lymphomas (DLBCL), while the other 10% are T cell, mantle cell, Burkitt, or indolent B cell lymphomas.[4] A 2–27% risk of developing secondary CNS disease is observed in patients with aggressive systemic non-Hodgkin's lymphoma.[5] In patients who are immunocompetent, incidence of PCNSL is approximately 51 per 10,000,000 cases per year.[6]

Definitive diagnosis of CNS lymphoma could depend on a positive CSF.[7] New studies have showed the usefulness of flow cytometric measurement (FCM) for detecting CNS disease in B cell lymphoma.[8,9] The greater sensitivity of FCM was presented in other analyses when series of CSF-stabilised samples used 4–8 colour FCM.[10]

CNS T-lymphoblastic lymphoma is a rare disease. Differential diagnosis is difficult, and includes varied conditions like aseptic meningitis, brainstem glioma, granulomatous angiitis, neurological infections, neurosarcoidosis, and neurosyphilis.[11]

The current preferable standard method for determining the tissue diagnosis of CNS lymphoma is stereotactic biopsy, since these lesions are usually deeply positioned and their resections were shown to be associated with poorer prognosis.[12,13] However, histopathological evaluation of stereotactic biopsies also has some restrictions, not only because of slight sample sizes, but also due to comprehensive spectrum of differential diagnoses, including inflammatory conditions such as vasculitis, multiple sclerosis, and infection. The dense cellularity of the tumour causes isodense or hyperdense occurrence on non-enhanced CT scan and hypointense occurrence on long repetition time-weighted

MRI imaging. Primary lymphoma of the CNS is supposed to be diffusely infiltrative at the time of showing, and is reckoned a 'whole brain' disease. The regions of disease are not visible on neuroimaging studies because they are behind a comparatively intact blood–brain barrier.[14,15] For this reason, prior administration of corticosteroids (CS) represents the major diagnostic provocation. Because of the high susceptibility of lymphoma cells to CS-induced apoptosis, administration of CS can camouflage the morphology and it was even reported to cause tumours to disappear.[16]

Three different cases of CNS lymphoma are presented.

METHODS

The patients described were hospitalised in the authors' clinic of neurology with different clinical presentations. Somatic and neurological exams were performed, as well as laboratory tests, including flow cytometric immunophenotyping of cerebrospinal fluid, MRI, CT scan, trepan biopsy of bone marrow and brain tissue, electromyography, chest X-ray, and coronary angiogram.

RESULTS

The described clinical cases are of patients with different neurological symptoms as an effect of CNS lymphoma.

The first case is of a 44-year-old patient admitted to the emergency department with complaints of progressively increased headache, stiffness of the neck, impaired co-ordination, nausea, sickness, and extreme sensitivity to light. Neurological examination revealed neck stiffness, double vision on the left, and downward and right limb hypoesthesia. The patient had no change in consciousness. MRI of the head was performed 4 months before admission in the neurological clinic with data showing a tumour in the area of left cavernous sinus (Figure 1A). Biopsy was performed 3 months earlier and the histology examination showed in part hyalinised connective tissue. Performed laboratory tests showed no significant abnormalities. Systemic infection and autoimmune disease were excluded by performing additional laboratory and imaging tests.

No stenosis or thrombosis of coronary blood vessels were found.

Examination of CSF showed increase in the amounts of lymphocytes. Atypical ones were observed in different phases of mitosis. CSF was tested for lymphocytic choriomeningitis, herpes simplex, varicella zoster virus (VZV), and Epstein–Barr virus (EBV). No infection agent was identified. Trepan biopsy of bone marrow was without pathological cells. FCM of CSF gave the diagnosis of T-lymphoblastic leukaemia/lymphoma. The studied materials identified: 1.5% of the CD45-positive cells were mature lymphocytes and 93% of the CD45-positive cells were T-lymphoblasts which have the following expression patterns: CD45 (+), low sCD3 (J+); partial CD2 (+); CD5 (+); CD7 (+); CD4 (+); CD8 (+); CD34 (-); CD56 (-); CD10 (-); CD19 (-); and CD20 (-). Intrathecal chemotherapy was started with high-dose methylprednisolone, vincristine, methotrexate, and cytarabine. It was combined with hyper-cyclophosphamide, vincristine sulfate, doxorubicin, plust dexamethasone.

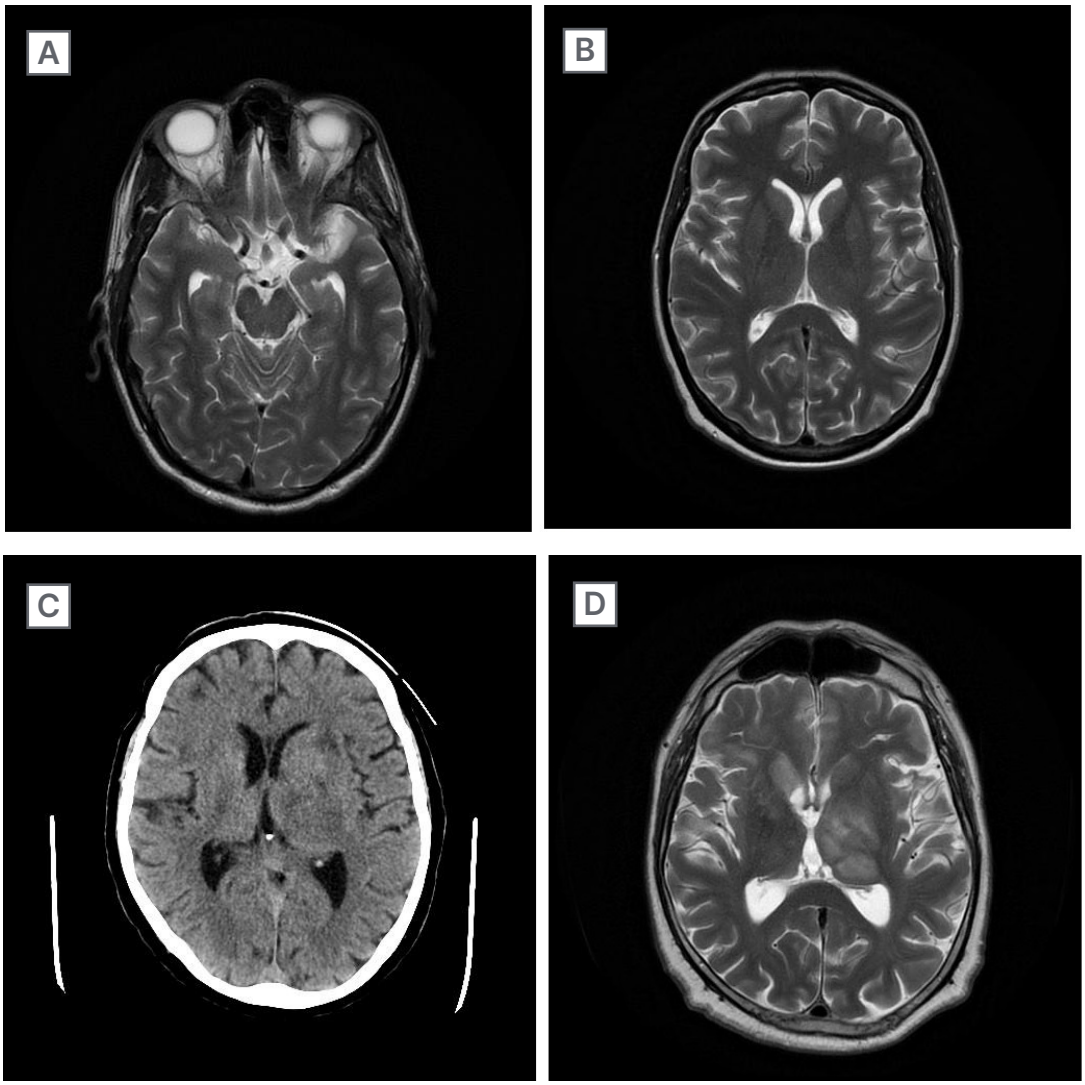
The second case is of a 50-year-old female with complaints starting 3 days prior, including weakness in the legs, inability to walk alone, and tingling of the lower limbs from the knees down, as well as in the palms and fingers of the hands. They reported worsening of the condition this morning when they had difficulty swallowing, deteriorated speech, no taste, difficulty breathing, fatigue, and chills.

Neurological examination showed positive Kernig sign, bilateral ageusia, peripheral lesion of facial nerve on the right, and weakened muscle strength for both legs with manual muscle testing 4/5. Biceps, radial, knee, and Achilles reflexes were missing bilaterally. The patient performed dysmetria finger to nose probe with both hands and Romberg test was positive. They had decreased sensation for touch and pain in the lower extremities, and Lasègue test was positive bilaterally. Joint-muscle sensation was preserved and the patient scored 15 points on the Glasgow Coma Scale (GCS). Brain tumour was excluded by performing MRI of the brain (Figure 1B). The patient was suspected of Guillain–Barré syndrome because of the clinical presentation. EMG data showed sensory-motor axonal polyneuropathy.

CSF examination showed lymphocytic pleocytosis (403 $\times 10^6$/L), 47% atypical ones, and high protein level (1.98 g/L [0.00/0.45]) and lactate level (3.7 mmol/L [1.10/ 2.20]). Laboratory tests did not reveal an infectious agent (EBV, cytomegalovirus, VZV, HIV, or COVID-19). FCM of CSF was performed. In total, 122 546 cells were identified in CSF: 95.9% of all cells were CD45-positive, CD19-positive, CD10-positive, CD20-positive, CD3-negative, and CD34-megative cells with B-lymphocyte phenotype, corresponding to B-lymphoblastic lymphoma. The authors decided that lower motor neuron symptoms (missing reflexes and weakness in four limbs) could be associated with a peripheral neuropathy, mainly as a result of direct infiltration. Treatment was continued with intrathecal chemotherapy (cytarabine and methotrexate).

The third case is of a 63-year-old male with weakness in the right limbs and progressive cognitive impairment. Tremor occurred initially in their left arm, after which right arm was affected and the gait changed. Neurological examination revealed dysarthria, mild right central hemiparesis, spasticity for the left limbs, exaggerated reflexes in four limbs without pathological reflexes, right-sided hypesthesia for

Figure 1: MRI and CT scans.



A) MRI of the brain of the first presented patient. **B)** MRI of the brain of the second presented patient. **C)** CT of the brain of the third presented patient. **D)** MRI of the brain of the third presented patient.

touch and pain, and confusion and disorientation for time and place. Several CTs and MRIs of the brain were performed with disseminated lesions in both hemispheres and left cerebellar peduncle (Figure 1C and 1D). Ischaemic stroke, tumour, and CNS infectious disease were discussed as possibilities. Laboratory tests did not reveal an infectious disease, including EBV, cytomegalovirus, VZV, HIV, or COVID-19. Examination of CSF showed no pathological changes. Treatment with steroids was started and the condition of the patient improved. Due to suspicion for lymphoma, trepan biopsy of bone marrow was performed. Fragment of a spongy bone was with hypocellular age-related bone marrow. The three haematopoietic lines were represented by maturation.

Normocellular granulocyte cells, including all maturation forms, are observed, along with normocellular erythrocyte cells. Megakaryocytes had an unincreased number and normal morphology. The reticulin network was unincreased. Bone marrow was without diagnostically significant histological changes. Patient was diagnosed after brain tissue biopsy of one of the lesions. In order to determine the histogenesis and possible primary focus, an immunohistochemical study was performed.

The result showed a CD45 and CD20-positive reaction in tumour cells; CD10-negative reaction in tumour cells; Ki67-positive reaction in approximately 80% of tumour cells; an adverse reaction to cytokerarin AE1/AE3; glial fibrillary acidic protein; S100 and synaptophysin-negative reaction in tumour cells with positive internal control in astrocytes; and CD3 and CD5-positive reaction in a small number of mature T lymphocytes.

The constellation was for DLBCL (Table 1).

CONCLUSION

CNS lymphoma is a rare but socially significant disease. Early diagnosis improves the survival rate of the patients. FCM of CSF could be beneficial to make the right diagnosis. FCM is a highly sensitive technique, efficient for finding malignant cells.[17-19] It can find CNS disease before the presentation of clinical symptoms, and the routine use of FCM and cytology may enable the earlier detection of neoplasm. Many studies have proven the value of FCM for detecting CNS disease in DLBCL.[20-23] More recent results of larger series of CSF-stabilised samples using 4–8 colour FCM[22-24] demonstrated very little false-negative FCM results (range: 0–<1 %), further fortifying its greater diagnostic productivity with regard to conventional cytology. CSF examination should also be done in existence of neurological symptoms, in suppletion to imaging methods (MRI and CT).[25] The differential diagnosis of CNS lymphoma is vast. High-grade gliomas, meningioma, granulomatous and demyelinating diseases, and vasculitis should all deserve attention.

Table 1: Clinical cases comparison.

	Patient 1	Patient 2	Patient 3
Neurological findings	+	+	+
Brain imaging pathological finding	+	-	+
Performed biopsy	+	-	+
Typical for lymphoma biopsy	-	N/A	+
FCM of CSF	+	+	-

CSF: cerebrospinal fluid; FCM: flow cytometric measurement; N/A: not applicable.

Metastatic lesions from systemic malignancies, as well as infections within the nervous system, can also present alike, and must be excluded with a careful medical history and appropriate diagnostic tests.

CSF cytology can ensure certain diagnostic information in CNS lymphoma, and with the aid of immunohistochemical studies, it has been likely to identify atypical or neoplastic lymphocytes. Sensitivity increases when a larger volume (≥10.5 mL) is analysed and when serial CSF probes are examined.[26] Sensitivity is decreased when there are delays in working, or after exposure to CS, causing cytolysis.[27]

CNS lymphoma often presents with atypical symptoms, which are either unrecognised or difficult to differentiate from other diseases. So, whenever manifest, neurological symptoms should provoke further CNS imaging and/or CSF analysis, depending on the clinical context of the patient and the results of additional diagnostic tests.

The authors believe that when B cell lymphoma is suspected, CSF examination is the first method of choice because of its safety and high diagnostic value. Although biopsy is still the gold standard in the diagnosis of CNS lymphoma, periprocedural risk can be avoided by CSF examination. It also requires a highly skilled neurosurgical team, which is not always possible and can lead to false negative results.

Anomalies of the peripheral nervous system come about in 5% of patients with lymphoma. Some of the drugs used in lymphoma commonly cause neuropathy. Compression or infiltration of nerve roots by lymphoma is a rare presenting distinction, but becomes more common with forward disease. Either multifocal infiltration of nerves or lymphoma-associated vasculitis may present as a peripheral neuropathy. The frequency of Guillain–Barré syndrome, and possibly chronic idiopathic demyelinating polyradiculoneuropathy, appears to be enlarged in association with lymphoma. Treatment of the hidden lymphoma is only rarely followed by recovery of the associated neuropathy.[28]

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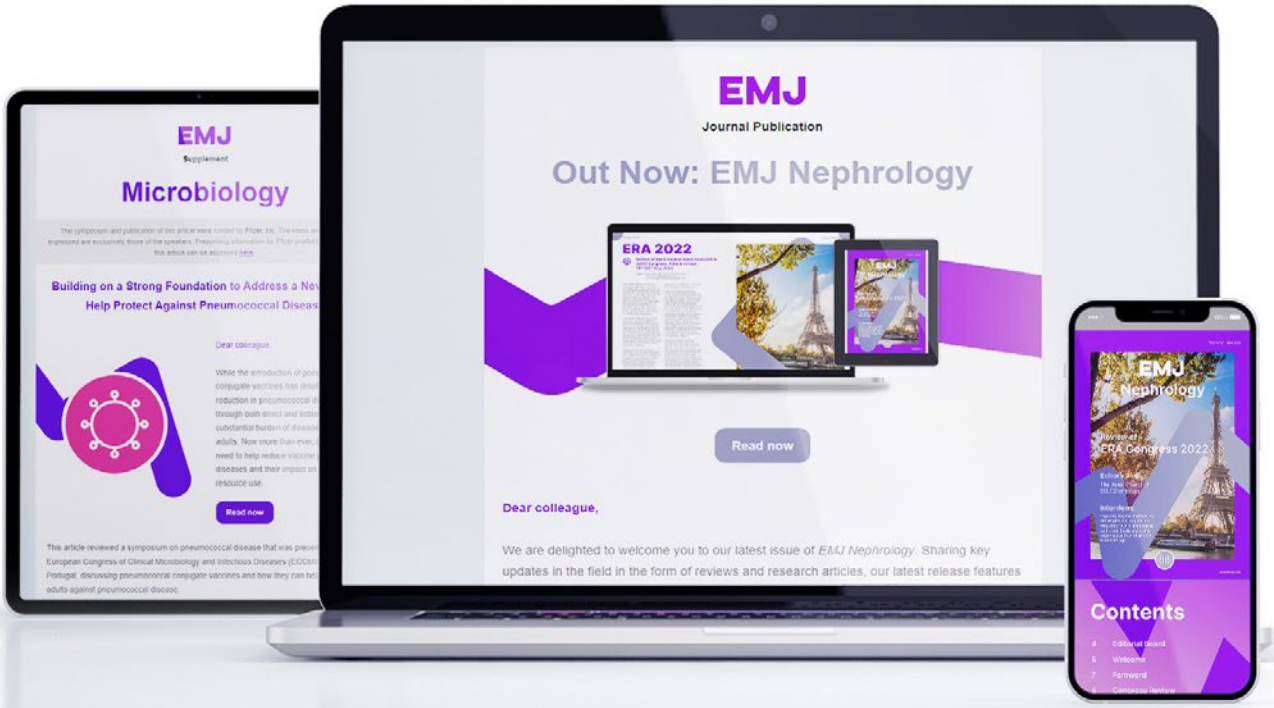

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