RESEARCH SUMMARY

ADVANCES IN ENCEPHALITIS 2018

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Welcome to the Encephalitis Society's Research Summary 2018

The Research Summary – Advances in Encephalitis 2018 presents a collection of research papers published during that same year.

An increase in the number of autoimmune encephalitis cases comparable to infectious causes has been reported. This may be due to an improved awareness of clinical presentations of different types of autoimmune encephalitis, but also advances in the diagnosis of it. Efforts have been made to understand and characterise the movement disorders associated with neuronal antibodies with the aim of providing a diagnostic approach and hence guide treatment decisions. Nevertheless, differential diagnoses, especially in the case of anti-NMDAR encephalitis and psychiatric disorders, still pose a challenge.

The progress made in the field of identifying antibodies associated with autoimmune encephalitis means more antibodies are being discovered. The challenge now is to understand what their role in the pathogenesis of the disease is, especially in patients with atypical features or those with multiple antibodies. Other factors such as genetics have also been investigated to explain the pathogenesis of the disease.

Encephalitis as a travel health risk has been emphasised. Travellers and travel health practitioners need to be more aware not only of the risk of encephalitis, but also of the severity of the illness and the lack of treatment in most cases of infectious encephalitis. Presently, the epidemiology of infectious encephalitis is changing. Increasing number of cases, new virus strains and expanding or new endemic areas are reported. Co-circulation of viruses such as Zika, Chikungunya and Dengue in endemic areas can pose diagnostic challenges. The spectrum of neurological manifestations associated with these viruses is wider than previously thought.

Again, we noted a lack of studies on rehabilitation interventions in people with encephalitis. This is unfortunate as many people affected by encephalitis are left with difficulties that impact negatively on their quality of lives.

This year, we have continued our international work by supporting projects in India, Malawi, Brazil, Cameroon and Zambia. We have a new academic partner - Aston University - who will host and co-fund our new PhD on "Predictors of cognitive recovery in paediatric immune-mediated encephalitis". In December, we are pleased to once again host the now 'go-to' Encephalitis Conference at the prestigious Royal College of Physicians in London. At the time of writing we have participants from all over the world -12 speakers and 30 poster presenters from 13 countries and delegates registered from over 23 countries.

Thank you for your interest in encephalitis and our Society. Finally a big thank you from us to all those clinicians, scientists and researchers working hard to improve our understanding of this often devastating condition.

Dr Ava Easton
CEO, Encephalitis Society

Contents

Epidemiology of encephalitis

"Travellers and their healthcare providers need to balance the low risk of disease against the very high severity of disease if it does occur."
(Turtle and Driver, 2018)

Infectious and autoimmune encephalitis – a comparison of incidence and prevalence

Dubey et al. (2018) conducted a population-based comparative study of the incidence and prevalence of autoimmune and infectious encephalitis in Olmsted County, Minnesota, between 1995 and 2015. Patients of both sexes and all ages were included. There were 109 patients with encephalitis: 52 patients with encephalitis of unknown aetiology and immune-related disorders, 29 with infectious encephalitis (confirmed pathogen), and 28 with autoimmune encephalitis (definite and probable according to Graus et al. (2016) criteria). The incidence rates of autoimmune and infectious encephalitis were 0.8/100,000 and 1.0/100,000 person-years, respectively. There was a gradual increase in the incidence of autoimmune cases over time from 0.4/100,000 person-years (1995–2005) to 1.2/100,000 person-years (2006–2015), which coincided with identification of neuronal antibodies. The incidence of infectious encephalitis remained the same over time. The prevalence of autoimmune encephalitis (13.7/100,000) was slightly higher than that of infectious encephalitis (11.6/100,000). The prevalence and incidence of autoimmune encephalitis was higher among African Americans than Caucasians. The incidence of infectious encephalitis did not differ among ethnic groups. The authors concluded that the prevalence and incidence of autoimmune encephalitis are comparable to infectious encephalitis, and its detection is increasing over time.

Dubey D., Pittock S.J., Kelly C.R., et al. (2018) Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. Ann Neurol; 83: 166–177.

Graus F., Titulaer M.J., Balu R., et al. (2016) A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol; 15(4): 391–404.

Infectious causes of encephalitis in India, Japan and Brazil

Jain et al. (2018) conducted a study of 540 patients to ascertain the specific cause of Acute Encephalitis Syndrome (AES) in Bihar, India, where AES is a major seasonal public health problem. Half of the patients had both serum and cerebrospinal fluid (CSF) tested. The other patients had only serum (n=121) or only CSF (n=139) tested. Most patients (96.5%) were children less than 15 years-old. Overall, 33.3% of patients were positive for at least one pathogen, of which 23.3% were positive for more than one pathogen. *O. tsutsugamushi* was present in 25% of the patients, Japanese encephalitis virus (JEV) in 8.1%, West Nile virus (WNV) in 6.8%, Dengue virus in 6.1%, and Chikungunya virus in 4.5%. Other aetiological agents, more rarely identified were *M. tuberculosis, S. pneumoniae, H. influenzae*, adenovirus, herpes simplex virus 1, enterovirus, and measles virus. The diagnosis of scrub typhus was confirmed by polymerase chain reaction and sequencing. The authors explained the low incidence of Japanese encephalitis (JE) as a result of the successful JE vaccination programme. However, they emphasised the emergence of *O. tsutsugamushi* infection as an important cause of AES in Bihar, India.

Goto et al. (2018) undertook a nationwide survey of the paediatric departments of hospitals throughout Japan to determine the causes of paediatric acute encephalitis/encephalopathy (pAEE). pAEE was defined as being an acute onset of impaired consciousness following an infection. Overall, 636 children with pAEE were included in this study. More than half of cases (63.5%) had a cause identified. The most common causes were influenza virus (26.7%), exanthem subitum (ES) (12.3%), rotavirus (4.1%), mycoplasma (3.6%), adenovirus (2.8%), mumps virus (2.2%) and herpes simplex virus (HSV) (2.0%). The children were ≤ 15 years-old, with the peak incidence (among all causes) at one-year-old. Children with HSV were mostly newborns, while children with ES were between 8–15 months. In young children (< three years old), seizures were the most common symptoms, whilst in older children, abnormal speech and behaviour were more common. Fever was present in >90%, irrespective of age. Death occurred in 6.8% of patients, and 38.1% of survivors were left with neurological sequelae. The rate of unfavourable outcomes was higher in those with unknown cause of encephalitis.

Vieira et al. (2018) undertook a surveillance programme of patients with encephalitis, myelitis, encephalomyelitis or Guillain-Barré syndrome in Piaui, Brazil, to ascertain the role of arboviruses in these neurological syndromes. Serological and molecular tests of samples from 74 patients with these neurological syndromes, detected current or recent infection with Dengue (DENV), Zika (ZIKV) or Chikungunya (CHIV) virus in 35% of the samples. Positive cases were classified as probable (n=15) and confirmed (n=11) according to the Center for Disease Control laboratory case definitions for arboviral neuroinvasive diseases. The only symptoms which could have suggested arboviral infection in this cohort were fever and myalgia. Although some of these cases were detected only by serum immunoglobulin M (IgM), which suggested previous or unrelated infections, this study shows that arboviral infections by DENV, ZIKV and CHIV may play an important part in the aetiology of neurological diseases in Brazil. Various arboviral viruses were involved in the acute neurological presentations of 35 adults following suspected Zika virus infection in a study by Mehta et al. (2018). Twenty-two patients had evidence of recent arboviral infection: 12 Zika virus and ten chikungunya. Eleven patients had co-infection with two or three viruses. Neurological manifestations

included Guillain-Barré syndrome (GBS), meningoencephalitis, myelitis, radiculitis, or a combination of these syndromes. The authors concluded that co-infection can be very challenging. Zika virus has a wide range of neurological manifestations other than GBS, including disease of the central nervous system.

Goto S., Nosaka N., Yorifuji T., et al. (2018) Epidemiology of pediatric acute encephalitis/encephalopathy in Japan. Acta Med Okayama; 72(4): 351–357.

Jain P., Prakash S., Tripathi P.K., et al. (2018) Emergence of Orientia tsutsugamushi as an important cause of Acute Encephalitis Syndrome in India. PLoS Negl Trop Dis; 12(3).

Mehta R., Soares C.N., Medialdea-Carrera R., et al. (2018) The spectrum of neurological disease associated with Zika and chikungunya viruses in adults in Rio de Janeiro, Brazil: A case series. PLoS Negl Trop Dis 12(2).

Vieira M.A.C.S., Costa C.H.N., Linhares A.C., et al. (2018) Potential role of dengue virus, chikungunya virus and Zika virus in neurological diseases. Mem Inst Oswaldo Cruz, Rio de Janeiro; 113(11).

Encephalitis – a travel health risk

In a study conducted by Loconsole et al. (2018), international travellers who attended a travel clinic in Bari, Italy, were investigated for the prevalence of immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies specific for vector-borne diseases (VBD): Dengue virus (DV), West Nile virus (WNV), Chikungunya virus (CHIKV) and/or Zika virus (ZV). There were 156 participants with a median age of 33 years. The most visited continent was America, followed by Africa, Asia, and Europe. The most common reason for travel was tourism (51.9%), followed by volunteering (28.8%), work/study (15.4%), domicile (1.9%), and visiting family/friends (1.9%). The median length of the visit for seropositive participants was 21 days. Overall, 19 travellers had IgM and/or IgG antibodies specific for DV, nine for WNV, nine for CHIKV, and two for ZV. Ten participants had antibodies that were specific for more than one VBD. Half of the participants were asymptomatic, and none of the participants were hospitalised. The authors highlighted the risk of contracting VBDs, especially DV, in international travellers. They suggested systematic pre-travel counselling and surveillance of international travellers visiting endemic areas.

Amicizia et al. (2018) reviewed the risk of Japanese encephalitis (JE) for travellers. The risk of acquiring JE has evolved because of the changes in travellers' habits, such as being more likely to engage in outdoor activities, and the growing popularity of some of the JE endemic areas as tourist destinations. In addition, climate change could alter the seasonal character of JE transmission. The authors argued that the activity of the traveller is more important than the length of stay when assessing the risk. The current recommendations for travellers do not sufficiently emphasize the travel destination, the high morbidity and mortality rates of JE, the lack of available treatment, travel-related factors (itinerary, duration, season and activity), and the benefits of JE vaccination. Turtle and Driver (2018) also investigated the risk of JE in travellers. Longer stays, low altitude, high temperature, budget accommodation with low protection against mosquitos, evening outdoor activities, immunocompromised status, and the breach of the blood-brain barrier, could be considered risk factors for acquiring JE. Nevertheless, JE could be acquired outside these parameters (e.g., shorter stay, and cases in not so high epidemic areas). The authors concluded that as a general rule the risk of JE in travellers is low and difficult to calculate. However, there is a need for travellers to be informed about the severity of the outcomes: death and permanent severe disability.

Haditsch (2018) reported the challenges associated with tick-borne encephalitis (TBE) as a travel infectious health risk. Although it has the same incidence as typhoid fever (1/10000/month of stay in travellers staying in highly endemic areas), for which vaccination is recommended, it is unlikely that travel health advice personnel will recommend vaccination against TBE. The author argued that the indication 'outdoor activities during the tick-biting season' is too vague and sometimes misleading. The author also emphasised a new identified risk represented by event or mass gathering travellers, such as religious, sports, cultural or political events. These groups may completely miss the need to consult a travel health advice agency. Another issue is that vaccination is not widely available in all countries. Also, there is a misconception that Europe is a health-safe travel destination.

Amicizia D., Zangrillo F., Lai P.L., et al. (2018) Overview of Japanese encephalitis disease and its prevention. Focus on IC51 vaccine (IXIARO®). J Prev Med Hyg; 59: E99–E107.

Haditsch M. (2018) Ticks and tick-borne encephalitis in Europe: challenges for travel medicine. Travel medicine and infectious disease 26: 5–6.

Loconsole D., Metallo A., De Robertis A.L., et al. (2018) Seroprevalence of Dengue virus, West Nile virus, Chikungunya virus, and Zika virus in international travelers attending a travel and migration center in 2015–2017, Southern Italy. Vector-Borne and Zoonotic Diseases; 18(8).

Turtle L., Driver C. (2018) Risk assessment for Japanese encephalitis vaccination. Human Vaccines and Immunotherapeutics; 14(1): 213–217.

West Nile virus (WNV) and tick-borne encephalitis (TBE): increasing numbers and changes in epidemiology

Compared with 2017, an increase of WNV cases was reported in 2018 in Europe. Up to the end of August 2018, there were 361 cases reported in Italy, 286 in Serbia, 192 in Greece, 183 in Romania, and 155 in Hungary (Burki, 2018). Napp et al. (2018) argued that the epidemiology of WNV in Eastern Europe is complex due to the repeat introduction of WNV strains from both lineages 1 and 2, and the establishment of endemic cycles. The risk of WNV re-emergence in a given area increases proportionally to the number of human cases in the previous year, which may be explained through the level of viral circulation. Transmission usually happens between July–September; however cases were reported as early as May or as late as October. The WNV human epidemics

occurred in highly populated urban areas, but the drivers of these epidemics are not clear. In the USA, in 2017, there were 2097 WNV cases reported (92% of all nationally notifiable arbovirus diseases), out of which 1425 were neuroinvasive cases (0.44/100,000 population), including 714 encephalitis cases, 530 meningitis cases, 34 acute flaccid paralysis with meningitis/encephalitis cases, 55 acute flaccid paralysis cases, and 92 other neurological illnesses. Patients with neuroinvasive disease had a 10% mortality rate and 94% hospitalisation rate. The highest rates were in South Dakota, North Dakota, Mississippi, Arizona and Utah. The report concluded that WNV is the leading cause of domestically acquired arboviral disease in the continental United States (Curren et al., 2018).

Velay et al. (2018) reported an increase in the TBE cases in France. Of 1460 patients tested between 2013 and 2016, 54 patients (48 autochthonous and six imported) were confirmed as TBE, of which 29 were diagnosed in 2016 only. Cases were reported in Alsace region (n=43) and Alpine region (n=5). The imported cases were from Germany, Slovakia and Finland. Transmission occurred via leisure forest activities (n=30), agricultural occupational activities (n=3) and unknown (n=21). In one patient, the most likely transmission involved consumption of unpasteurised goat milk. In Lithuania, Radzisauskiene et al. (2018) reported an increase in TBE incidence rates of 8.5% per year for the 45-year period from 1970 to 2014. TBE is present throughout the whole country, but northeast and central parts have the highest incidence. Dai et al. (2018) described a new subtype of Eastern TBE virus discovered in wild rodent *Marmota Himalayan* in Qinghai-Tibet Plateau, China. They propose the name Himalayan (Him-TBEV), and suggest that the public health significance of Him-TBEV must be carefully evaluated. Tajima et al. (2018) reported a first case of TBE in a patient from the central part of Hokkaido Island (Japan).

Burki, T. (2018) Increase of West Nile virus cases in Europe for 2018. The Lancet; 392.

Curren E.J., Lehman J., Kolsin J., et al. (2018) West Nile virus and other nationally notifiable arboviral diseases —United States, 2017. Morbidity and Mortality Week Report, CDC; 67 (41).

Dai X., Shang G., Lu S., et al. (2018) A new subtype of eastern tick-borne encephalitis virus discovered in Qinghai-Tibet Plateau, China. Emerging Microbes & Infections; 7: 74.

Napp S., Petrić D., Busquets N. (2018) West Nile virus and other mosquito-borne viruses present in Eastern Europe. Pathogens and Global Health; 112(5): 233–248.

Radzisauskiene D., Zagminas K., Asokliene L., et al. (2018) Epidemiological patterns of tick-borne encephalitis in Lithuania and clinical features in adults in the light of the high incidence in recent years: a retrospective study. European Journal of Neurology; 25: 268–274.

Tajima Y., Yaguchi H., Mito Y. (2018) Fatal meningoencephalomyelitis due to the tick-borne encephalitis virus: the first detailed neurological observation in a Japanese patient from the central part of Hokkaido Island. Intern Med 57: 873–876.

Velay A., Solis M., Kack-Kack W., et al. (2018) A new hot spot for tick-borne encephalitis (TBE): A marked increase of TBE cases in France in 2016. Ticks and Tick-borne Diseases; 9: 120–125.

Preventive measures for La Crosse virus (LACV) and Nipah virus encephalitis

Byrd et al. (2018) reported 11 cases of LACV encephalitis linked either spatially by place of residence during the same or sequential epidemiologic weeks, or spatially but during different years. These cases prompted an interagency environmental assessment. The authors argued that LACV disease is highly focal, occurring in a limited geographical area. To reduce the risk of this disease, environmental assessments and modifications are necessary. In addition, raising awareness of the preventive measures among people living at a residence with a newly identified case of LACV disease, or in an area where the virus is known to occur, should help.

Nipah virus has been linked to fruit bats and sometimes pigs (Singapore, Malaysia) or horses (Philippines). Transmission occurs from person-to-person via close contact. It can cause encephalitis and pneumonia, and has a high mortality rate. Donaldson and Lucey (2018) call for anticipating, and preparing for, urban and larger rural outbreaks of Nipah virus. They suggest immediate and long-term preparation. Immediate plans include standardised guidance on infection prevention and control, and personal protective equipment. In addition, best clinical practices of experts in countries with multiple outbreaks such as Bangladesh and India should be considered. Long-term plans include accelerating development of field diagnostics, antiviral drugs, immune-based therapies, and vaccines. The authors argued that all these measures would help to prevent the consequences that the Ebola outbreak had in West Africa.

Byrd B.D., Williams C.J., Staples J.E., et al. (2018) Spatially associated coincident and noncoincident cases of La Crosse encephalitis —North Carolina, 2002–2017. MMWR; 67(39).

Donaldson H., Lucey D. (2018) Enhancing preparation for large Nipah outbreaks beyond Bangladesh: Preventing a tragedy like Ebola in West Africa. International Journal of Infectious Diseases; 72: 69–72.

Pathogenesis of encephalitis

"Cells participating in germinal center reactions might be a therapeutic target for the treatment of NMDAR-antibody encephalitis." (Makuch et al. 2018)

Advances in anti-N-methyl-D-aspartate receptor (NMDAR) pathogenesis

Makuch et al. (2018) investigated the mechanisms of NR1-IgG production and the contribution of germinal centre B cells to NR1-IgG levels in ten patients with anti-NMDAR encephalitis. Peripheral blood mononuclear cells from the patients, and two available ovarian teratomas, were tested for secretion of total IgG and NR1-specific antibodies. Clinical data and paired serum NR1-reactive IgM and IgG levels were also studied. Serum NR1-IgG antibodies were present in all patients. Six of them also had NR1-specific IgM antibodies, which were highest at disease onset and diminished (50% of their peak levels) after six months of the illness. NR1-specific B-cells could be detected in both the circulation and teratoma tissue. These cells produced NR1-IgG at levels proportional to serum NR1-IgM across the disease duration, suggesting ongoing production rather than persistence of NR1-IgM. Ovarian teratoma tissue contained infiltrating lymphocytes which produced NR1-IgG in culture. *In vitro*, the NR1-specific B cells were differentiated into specific antibody-secreting cells. The ongoing NR1-IgM production, and the presence of circulating B cells with the capacity to produce NR1-antibodies, may imply that lymph nodes are actively producing NR1-reactive B cells. The authors concluded that these data suggest that germinal centres have the capacity to generate NMDAR antibodies which could have huge implications for future treatments.

Iemura et al. (2018) analysed the neuroglial tissue in four cases of ovarian teratoma associated with anti-NMDA receptor encephalitis, and compared it with 12 control cases (six consecutive cases of immature teratoma and six cases of mature teratoma with an abundant neuronal component). NMDA receptor-expressing neurons were found in all cases. However, in the encephalitis-associated cases, they were significantly densely aggregated with a monotonous appearance, and were relatively smaller in size, than in the control cases. The number of NMDA receptor neurons and the Ki-67 labelling index in the area of NMDA receptor neurons were significantly higher in the encephalitis-associated cases. In addition, aggregation of B-cells within or around the neuroglial tissue was noted.

Shu et al. (1) (2018) investigated serum complement components (C3 and C4) levels, complement activation (CH50) and C-reactive protein (CRP), and their association with clinical course of the illness, in 40 patients with anti-NMDAR encephalitis and 40 controls. Patients with anti-NMDAR encephalitis (especially females and those with severe impairment) had significantly higher serum C4 levels and higher CRP levels than the controls. Serum C4 levels were associated with C3, CH50 and CRP levels. Serum C50 was associated with disease disability and CRP. In 11 patients followed up for six months, serum C3 levels were associated (significant negative correlation) with changes in modified Rankin Scale (mRS) score after treatment. Shu et al. (2) (2018) investigated the relation between serum cystatin C (CysC) and anti-NMDAR encephalitis, and found that the serum levels of CysC were significantly lower in patients with anti-NMDAR encephalitis than in controls. CysC levels were also associated with the disease's severity and duration. After treatment, patients with anti-NMDAR encephalitis had significantly increased serum CysC levels, and significantly decreased mRS scores, compared with before treatment.

Ai et al. (2018) analysed the cerebrospinal fluid (CSF) concentration of high-mobility group box protein 1 (HMGB1) and interleukin (IL)-6 and IL-17A in 33 patients with anti-NMDAR and 38 controls, using an enzyme-linked immunosorbent assay. They found that there were significant increases in CSF HMGB1, IL-6, and IL-17A in patients with anti-NMDAR encephalitis, which may reflect the underlying neuroinflammation. However, the study did not find a correlation between these CSF parameters and clinical outcomes.

In anti-NMDAR encephalitis, the underlying autoantibodies against the NR1 subunit are pathogenic. However, the antibody titre is not always correlated with clinical course. Ly et al. (2018) investigated the implications of antibody affinity for disease mechanisms and clinical course. The study found that patient-derived monoclonal NMDAR autoantibodies have variable binding curves, ranging from 1 to 74 µg/ml for monoclonal antibodies. These curves can be accurately measured with flow cytometry utilising NR1-expressing HEK293 cells with binding constants (half-maximal concentration, c50). When comparing values of individual monoclonal antibodies with human CSF samples, the authors found that the CSF signal is predominantly represented by higher-affinity antibodies, potentially in a concentration range of NR1 antibodies between 0.1 and 5 µg/ml, roughly reflecting 1–10% of total CSF IgG in NMDAR encephalitis. This suggests that low-affinity antibodies can remain undetected in routine cell-based assay, and may account for some of the symptoms.

Due to variable protocols for the diagnosis assay, the titres of NR1 antibodies may differ between laboratories, or even within the same laboratory, which makes the appraisal of treatment based only on antibody titre very difficult. The authors of this study suggest that a way to overcome this is normalisation of the data by comparing the binding of a human CSF sample to an assay standard comprising exactly determined concentrations of monoclonal human antibodies.

Rosch et al. (2018) explained fluctuating abnormalities in brain dynamics, observed in patients with anti-NMDAR encephalitis, by using patient electroencephalography (EEGs) and local field potential recordings in a mouse model of NMDAR-Ab encephalitis. The authors argued that NMDAR autoantibodies cause a specific shift in excitatory coupling within cortical circuits that places the circuits closer to pathological transitions between dynamic brain states. This proximity to the phase transition cause abnormal EEG responses.

Ai P., Zhang X., Xie Z., et al. (2018) The HMGB1 is increased in CSF of patients with an anti-NMDAR encephalitis. Acta Neurol Scand; 137: 277–282.

Iemura Y., Yamada Y., Hirata M., et al. (2018) Histopathological characterization of the neuroglial tissue in ovarian teratoma associated with anti-N-methyl-D-aspartate (NMDA) receptor encephalitis. Pathology International; 68: 677–684.

Ly L-T., Kreye J., Jurek B., et al. (2018) Affinities of human NMDA receptor autoantibodies: implications for disease mechanisms and clinical diagnostics. Journal of Neurology; 265: 2625–2632.

Makuch M., Wilson, R., Al-Diwani A., et al. (2018) N-Methyl-D-Aspartate receptor antibody production from germinal center reactions: therapeutic implications. Ann Neurol; 85: 553–561.

Rosch R.E., Wright S., Cooray G., et al. (2018) NMDA-receptor antibodies alter cortical microcircuit dynamics. PNAS; 115 (42).

Shu Y. (1), Chen C., Chen Y., et al. (2018) Serum complement levels in anti-N-methyl-D-aspartate receptor encephalitis. European Journal of Neurology; 25: 178–184.

Shu Y.(2), Chang Y., Wu H., et al. (2018) Serum cystatin C and anti-N-methyl-D-aspartate receptor encephalitis. Acta Neurol Scand; 137: 515–522.

Human leucocyte antigen (HLA) associations in patients with LGI1, CASPR2 and anti-NMDAR autoantibodies

Binks et al. (2018) compared the HLA alleles in patients with voltage-gated potassium channels (VGKC)-complex autoantibodies (n=111) with healthy controls (n = 5553). VGKC-complex antibodies comprise autoantibodies against leucine-rich, glioma-inactivated 1 (LGI1), contactin-associated protein 2 (CASPR2) and VGKCs. These antibodies are associated with different clinical syndromes: LGI1 and CASPR2 mostly with encephalitis and epilepsy, and VGKCs with various, often non-immune syndromes. The study included 68 patients with LGI1, 31 patients with CASPR2, three patients with both LGI1 and CASPR2, and nine patients with VGKCs. The authors noted that 28% of patients with LGI1 and 23% of patients with CASPR2 antibodies had co-existent autoimmune conditions (e.g., Hashimoto's thyroiditis, psoriasis, pernicious anaemia). In addition, patients with LGI1-antibody had a 47% rate of adverse drug reactions from corticosteroids, and a higher rate of drug-induced rashes secondary to antiepileptic drugs, antibiotics and immunosuppressants.

In patients with LGI1 antibodies, HLA-DRB1*07:01 was strongly represented; however, in patients with CASPR2 antibodies, HLA-DRB1*11:01 was over-represented. Other allelic associations for patients with LGI1 antibodies reflected linkage, and significant haplotypic associations included HLA-DRB1*07:01-DQA1*02:01-DQB1*02:02, in comparison with DRB1*11:01-DQA1*05:01-DQB1*03:01 in CASPR2-antibody patients. Patients with both LGI1 and CASPR2 antibodies, and patients with intracellular VGKC antibodies, did not show significant HLA associations. The authors argued that there were significantly different HLA associations for patients with LGI1 and CASPR2 antibodies, at both allelic and haplotypic levels, and a strong implication of T cells in disease initiation. However, the HLA associations did not distinguish among sub-phenotypes, outcomes or underlying tumours. Future research on the environmental factors that influence the presentation of peptides in genetically predisposed individuals is needed.

Shu et al. (2018) analysed the HLA loci of 61 patients with anti-NMDAR encephalitis, and 571 healthy controls, from the Chinese Han population. The DRB1*16:02 allele was associated with anti-NMDAR encephalitis with a higher allele frequency in patients (14.75%) than in controls (4.82%). The patients with DRB1*16:02 showed a lower therapeutic response to the treatment than patients with other HLA alleles. However, the underlying tumour did not influence the relation between DRB1*16:02 allele with anti-NMDAR encephalitis. The authors argued that their study proved the DRB8116:02 allele is a risk factor for anti-NMDAR encephalitis and a predictive factor for an unfavourable prognosis.

Binks S., Varley J., Lee W., et al. (2018) Distinct HLA associations of LGI1 and CASPR2-antibody diseases. Brain; 141: 2263–2271.

*Shu Y., Qiu W., Zheng J., et al. (2019) HLA class II allele DRB1*16:02 is associated with anti-NMDAR encephalitis. J Neurol Neurosurg Psychiatry; 0:1–7.*

Infectious encephalitis

"Despite the availability of vaccines, 69,000 cases of the disease are estimated to occur every year in Asia, and this figure is probably an underestimate." (Turtle and Solomon, 2018)

Japanese encephalitis (JE) – an overview

Turtle and Solomon (2018) presented an overview of JE, from epidemiology and clinical features to prevention and treatment. Considered the most commonly diagnosed epidemic encephalitis, JE is found in South and Southeast Asia. Recently, the distribution area has been considered larger than previously thought. The incidence of JE varies from 0.003/100,000 people in countries with established high-quality vaccination programmes (e.g., Japan and Korea) to 3.7/100,000 people (e.g., Cambodia, Indonesia and Malaysia). The risk of JE is 0.1–1% of all cases of infection with the virus.

JE can have a prodromal phase, with fever, coryza, diarrhoea or rigours, three to four days before the acute encephalitis. The syndrome manifests with alteration of consciousness, headache, vomiting and often seizures. Focal neurological signs will depend on the anatomical sites of damage: parkinsonian features, including mask-like blank staring faces and tremors; other movement disorders include lip-smacking, bruxism, choreoathetosis and hemiballismus; poliomyelitis-like flaccid paralysis; facial palsies, ptosis and abnormalities of eye movements. Generalised tonic–clonic seizures or subtle motor seizures can also be seen. Other features include: pulmonary oedema, hepatomegaly, splenomegaly, modestly raised liver enzymes, and thrombocytopenia. In some instances, JE virus has been associated with Guillain-Barré syndrome, immune-mediated transverse myelitis, and anti-NMDAR encephalitis.

Diagnosis is confirmed by finding JEV-specific immunoglobulin M (IgM) in cerebrospinal fluid (CSF), usually present in all patients by day seven of illness. Serum testing may show coincidental systemic infection in a patient who has another cause of acute neurological disease, so diagnosis based only on serum testing needs careful assessment. JEV is not detected by RT-PCR in urine or blood during the acute illness (with a few exceptions). Mortality has been estimated at a median of 18% and morbidity at 44%. Although typically an acute viral condition, very rarely the virus can persist in the nervous system for four to eight months after the initial illness.

There are five genotypes of JEV, whose distribution may be influenced by the climate. Most human cases are genotype III, although genotype I is gradually replacing genotype III. It is not clear why JEV virus is not present in other regions with similar conditions as in the endemic areas.

Vaccination against JEV has existed since the 1950s. Current vaccines are based on cell culture methods. There is a live attenuated Japanese encephalitis vaccine SA14-14-2 (against wild genotype III strains) and an inactivated, adjuvanted vaccine SA14-14-2 (marketed in Europe and North America as IXIARO, and in Australasia as JESPECT) (against genotypes I–IV). Lately, a new vaccine has been developed on the basis of an Indian genotype III strain, Kolar821564XY. Despite the availability of vaccination, it is estimated that 80% of cases still occur in areas with JE vaccination programmes. Lack of vaccine coverage, lack of vaccine efficacy, and waning immunity in areas with JE intermittent transmission, may affect incidence rates.

Although the pathogenesis is still not completely understood, there have been many advances which indicate that inhibition of viral replication, viral spread, and the host response, can guarantee a successful therapy. However, the authors emphasised the surprisingly lack of testing for treatments. Currently, there is only supportive management available, based on medication to control seizures, good nursing care, maintaining fluid balance, and avoiding aspiration pneumonia. The author reviewed the clinical trials of dexamethasone, intravenous immunoglobulin, and minocycline, which did not show a benefit or were underpowered, the current practice of giving corticosteroids or mannitol, and the unnecessary use of antibiotics. Compounds potentially suitable for JE trials have been tested in animal models and *in vitro*. The authors urged that these should be tested immediately within larger multicentre trials, with good quality diagnostic practice, and using a combination therapy of antiviral and anti-inflammatory drugs.

Turtle L., Solomon T. (2018) Japanese encephalitis-the prospects for new treatments. Nature reviews/Neurology. 14: 298-313.

Decompressive craniectomy in severe herpes simplex encephalitis (HSE)

The lack of clear guidelines on the management of severe brain oedema and intracranial pressure in HSE, and the lack of case series reports, contribute to the difficulty in knowing what the correct management of severe HSE is.

Todeschi et al. (2018) reported a severe HSE in a 26-year-old male with raised intracranial pressure (ICP), treated initially with midazolam, phenobarbital and therapeutic hypothermia. As the ICP remained high, right decompressive craniectomy combined with a right temporal polectomy was performed. The patient recovered well with only a mild depressive disorder reported at one-year follow-up. The authors also reviewed 68 patients described so far in the literature. The median age of the patients was 45 years, and six patients were children. All patients, except one, had acyclovir administered. For the acute management of intracerebral haemorrhage (ICH), the studies reported use of hyperventilation, osmotherapy, barbiturates and hypothermia. However, the best therapeutic option was considered to be surgical management. The procedures used included: standard hemicraniectomy with or without temporal lobectomy, and decompressive lobectomy without a craniectomy, with similar results. The timing for the surgery is debatable, usually a rise in ICP usually occurring on

about the 12th day of the illness. The surgery should be performed as soon as signs for herniation or refractory ICP are evident. The authors emphasised the risk implied by surgical management, suggesting that this should be resorted to only in cases of failure of conservative treatment. Byun et al. (2018) recommended monitoring with neuroimaging and surgical decompression if aggressive medical treatment fails in patients with HSE who show unchanged or worsened symptoms despite the initiation of acyclovir.

Byun Y.H., Ha E.J., Ko S-B, Kim K.H. (2018) Decompressive craniectomy for herpes simplex encephalitis complicated by frank intracerebral hemorrhage: a case report and review of the literature. BMC Neurology; 18:176.

Todeschi J., Gubian A., Wirth T., et al. (2018) Multimodal management of severe herpes simplex virus encephalitis: A case report and literature review. Neurochirurgie; 64: 183–189.

Significance of herpes simplex virus (HSV) in cerebrospinal fluid (CSF)

Alessandro et al. (2018) investigated the clinical features of patients with positive polymerase chain reaction (PCR) CSF due to HSE (n=16) and patients with positive PCR CSF due to other conditions not typically associated with HSV (n=3). Patients with HSE presented more often with headache, meningeal symptoms, pleocytosis, and suggestive findings on electroencephalography and magnetic resonance imaging. Patients with other diagnoses than HSE were more likely to be immunocompromised. Their symptoms were better associated with other neurological conditions than HSE, such as neuroimmune (multiple sclerosis, acute disseminated encephalomyelitis, NMO spectrum disorder, paraneoplastic syndrome), non-HSV infections, toxic-metabolic, neuro-oncological, or vascular diseases. The authors concluded that there are patients with central nervous system (CNS) disorders other than HSE who may have a positive HSV PCR in the CSF. The role of HSV in these patients is not yet established. A positive CSF result needs to be correlated with clinical symptoms, disease evolution, and radiology.

Otto et al. (2018) compared the clinical course of HSE in four neonates who presented HSV deoxyribonucleic acid (DNA) in the CSF after 21 days of treatment with acyclovir, with that of 14 neonates with clearance of the CSF after 21 days of therapy. All patients in the first group were male and were infected with HSV2. Patients who still presented with HSV DNA had a more severe course of the illness, with refractory seizures despite treatment, raised total bilirubin in the first week of therapy, and raised protein CSF after three weeks of treatment. They were more likely to be left with cortical blindness and visual difficulties, and overall more likely to have moderate-to-severe impairment.

Alessandro L., Wilken M., Farez M.F., et al. (2018) Clinical correlations of positive herpes simplex PCR in cerebrospinal fluid. The Neurologist; 23 (6).

Otto W.R., Myers A.L., LaRussa B., et al. (2018) Clinical markers and outcomes of neonates with herpes simplex virus deoxyribonucleic acid persistence in cerebrospinal fluid in disseminated and central nervous system infection. Journal of the Pediatric Infectious Diseases Society; 7(2).

Herpes simplex encephalitis (HSE) followed by autoimmune encephalitis (AE)

Armangue et al. (2018) investigated the frequency, risk factors and outcomes of AE after HSE. Patients with HSE (n=51) were followed up for two, six and 12 months. Patients with autoimmune encephalitis following HSE (n=44) were studied retrospectively. None of the patients with HSE had antibodies to neuronal antigens initially. During follow-up, 14 patients developed AE with neuronal antibodies (nine had NMDAR antibodies and five had other antibodies). Of the remaining patients, 11 developed antibodies (three to NMDAR and eight to unknown antigens), but they did not develop AE. A risk factor for developing AE was the development of antibodies within three weeks of HSE. In the group of patients with AE following HSE, 34 had anti-NMDAR antibodies and ten had other antibodies. Patients with AE older than four years were more likely to present with psychosis and cognitive changes. Children aged four years or younger were more likely to have shorter intervals between onset of HSE and onset of AE, choreoathetosis, decreased level of consciousness, and worse outcome at one year. The authors concluded that AE can develop after HSE and manifests with different symptoms depending on age. Prompt diagnosis is important as patients (older children and adults) may respond to immunotherapy.

Armangue T., Spatola M., Vlagea A., et al. (2018) Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. Lancet Neurol; 17: 760–72.

Neurological complications of Chikungunya infection

Mehta et al. (2018) reviewed 856 cases of Chikungunya-associated neurological disease: 796 patients infected by mosquito bites and 60 neonates infected from the mother. Chikungunya virus is an alphavirus transmitted by *Aedes* mosquitos (more often) and from mother to child (rarely). Between 3 - 47% of infected people are asymptomatic. If symptoms are present, after an incubation period of three days (median), these may include an acute onset of fever, headache, rash, arthralgia, and myalgia, which typically last for one to two weeks. There are no specific antiviral drugs or vaccines against chikungunya virus. Treatment is intensive care management, including intubation, ventilator support, correction of electrolyte abnormalities, management of raised intracranial pressure, and enhancement of cerebral perfusion pressure.

Although complications of chikungunya infection vary, the neurological complications are the most severe complications. Neurological involvement can be demonstrated by detecting viral ribonucleic acid (RNA) in the cerebrospinal fluid (CSF) by polymerase chain reaction (PCR), or by culture or autopsy material in fatal cases. However, in many patients, the virus has cleared from the CSF by the time they are seen by a doctor; in which case, detection of CSF IgM antibody by enzyme-linked immunosorbent assay confirms the diagnosis. The most frequent neurological manifestations include encephalopathy and encephalitis, myelopathy and myelitis, encephalomyelopathy, myeloneuropathy, encephalomyeloneuropathy, Guillain-Barré syndrome, acute

disseminated encephalomyelitis, neonatal hypotonia, and neuro-ocular disease. Out of all the patients with encephalopathy in this review (40.5%), 78% presented with encephalitis, 20.5% had encephalopathy, and 0.6% had acute disseminated encephalomyelitis. At follow up, 48.8% of patients had complete or near-complete recovery, 19.7% had residual neurological deficit and 31.5% had died.

Co-circulation of Chikungunya virus with Zika and Dengue viruses has often been reported in South America. The authors suggested that in the endemic areas, patients presenting with a neurological presentation, and pregnant patients with a fever-arthralgia-rash syndrome, should be tested for all three viruses. Neonates should be monitored for neurodevelopmental delay for at least two years, irrespective of the initial presentation.

Maria et al. (2018) reported clinical characteristics of 13 babies with chikungunya: ten congenital (associated with maternal infection within the last week before delivery), two acquired and one unknown. All patients presented with fever and encephalopathy, with a duration between ten and 15 days. Seizures were present in six patients. Ten patients had peri-oral rashes spreading to trunk and limbs. Only one child had a positive PCR. Neuroimaging abnormalities were seen in eight out of ten patients. At discharge, 12 patients presented with hypotonia. At three months follow-up, four children had delayed milestones with hypotonia (n=2) and hypertonia (n=2). The authors suggested that neonates presenting with fever, encephalopathy and perioral rashes, within the first week during outbreaks, should be suspected for Chikungunya. If diagnosis is confirmed, patients need a detailed neurodevelopmental follow-up.

Maria A., Vallamkonda N., Shukla A., et al. (2018) Encephalitic presentation of neonatal Chikungunya: A case series. Indian Pediatrics; 55.

Mehta R., Gerardin P., de Brito C.A.A, et al. (2018) The neurological complications of chikungunya virus: A systematic review. Rev Med Virol; 28.

Prognosis factors in human immunodeficiency virus (HIV)-infected patients with encephalitis

Hvozdetska et al. (2018) investigated the prognosis factors of encephalitis due to opportunistic infections in 53 patients HIV positive. Of them, 22 patients died. Patients were between 18 and 61-years-old and had HIV-infection in the fourth clinical stage. Only 12 patients received antiviral treatment prior to admission (32.3% of survivors and 9.1% of the fatal cases). The group of patients who survived were more likely to have a gradual onset of the illness (58.1%), whilst the group of patients who died were more likely to have a rapid onset (68.2%). Regarding clinical manifestations, the non-survivor group had more frequent neck stiffness, aphasia, dysphasia, anisocoria, ptosis, fever, positive Kerning's sign, sphincter disturbance, pathological foot signs, and eyeball movement abnormalities. Survivors more often reported vision reduction and asymmetry of limb tendon reflexes. Other risk factors associated with fatality cases were the severity of the patient's condition during admission, the prolonged time to treatment initiation, the high degree of co-morbidity, the degree of cellular immunity depression, viral load level of HIV in blood, and the absence of previous antiviral treatment.

Hvozdetska M., Kozko V., Yurko K. et al. (2018) Factors affecting the fatal outcome in HIV-infected patients with encephalitis. Georgian Medical News; 7-8: 280–281.

Case reports

- Vieira et al. (2018) presented a case of encephalitis associated with Zika virus infection and reactivation of varicella-zoster virus in the central nervous system in an eight-year-old child in Brazil. They suggested that reactivation of varicella-zoster virus could be a result of Zika virus infection.
- Russell et al. (2018) reported the first isolation and whole genome sequencing of Murray Valley encephalitis virus genotype 2 from cerebrospinal fluid (CSF) of a patient with encephalitis in the Northern Territory in Australia.
- Crawshaw et al. (2018) reported three cases of encephalitis in the UK cohort of patients with human T-cell lymphotropic virus (HTLV)-1-associated myelopathy (HAM). Patients presented with reduced consciousness, fever/hypothermia, headaches, seizures, focal neurology, raised CSF protein, pleocytosis and raised CSF peripheral blood mononuclear cell HTLV-1 proviral load ratio. Magnetic resonance imaging revealed normal or white matter changes in the brain and spinal cord. The authors also reviewed another six reported cases of encephalopathy in HTLV-infected patients, four of whom also had HAM. Most patients were female (n=8/9), and all patients with HAM manifested a deterioration of the spastic paraparesis before development of encephalitis. The authors proposed that HTLV-associated encephalopathy may be part of the spectrum of HTLV-1-induced central nervous system disease.
- Li et al. (2018) reported the first case of autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy, five months after full recovery from herpes simplex encephalitis (HSE), in a 35-year-old Chinese female. The authors suggested that autoimmune GFAP astrocytopathy may be a differential diagnosis in cases of HSE relapse.

Crawshaw A. A., Dhasmana D., Jones B., et al. (2018) Human T-cell lymphotropic virus (HTLV)-associated encephalopathy: an under-recognised cause of acute encephalitis? Case series and literature review. Journal of Neurology; 265: 871–879.

Li J., Xu Y., Ren H., et al. (2018) Autoimmune GFAP astrocytopathy after viral encephalitis: A case report. Multiple Sclerosis and Related Disorders 21: 84–87.

Russell J.S., Caly L., Kostecki R., et al. (2018) The first isolation and whole genome sequencing of Murray Valley encephalitis virus from cerebrospinal fluid of a patient with encephalitis. Viruses; 10: 319.

Vieira M.A.C.S, Castro A.A.S, Henriques D.F., et al. (2018) Encephalitis associated with Zika virus infection and reactivation of the varicella-zoster virus in a Brazilian child. Rev Soc Bras Med Trop; 51(3): 390–392.

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis

"This clinical constellation of phenomenologies, with the unusual triad of dystonia, stereotypies and chorea, should, in the correct clinical context, provide clinicians with greater confidence in diagnosing this common cause of encephalitis." (Varley et al., 2018)

Anti-NMDAR encephalitis in children

Favier et al. (2018) investigated the clinical presentation of anti-NMDAR encephalitis in young children (<12-years-old) and compared them to a series of previously published female adult patients. This retrospective study included 50 children (27 females and 23 males). In 40% of children, there was a prodromal phase with fever, headache, ear, nose and throat disorders, digestive symptoms, cough and sleep disturbances, or deterioration of the general health, seven days before neurological symptoms appeared.

The first initial symptoms were seizures (72% of children), especially focal seizure (42%), behavioural abnormalities with agitation and aggressiveness (26%) and cerebellar syndrome (one child). Other symptoms followed within a median of 15 days. The authors highlighted the difficulty in diagnosing the seizures due to the transient unilateral dystonic or tonic posturing presentation, or sudden unilateral pain in the absence of clonic movements. The cerebrospinal fluid (CSF) was abnormal in 87% of patients (oligoclonal bands, pleocytosis, high protein level). Electroencephalography (EEG) was abnormal in 89% of patients (asymmetric slowing, focal spikes and/or extreme delta brush pattern) and magnetic resonance imaging (MRI) abnormal in 38% of patients. Only one patient (a ten-year-old boy) presented with a tumour (pineal dysgerminoma) 11 months before encephalitis.

Diagnosis was confirmed at a median of 25 days after the first neurological symptoms. First-line immunotherapy was administered in all patients, and consisted of intravenous immunoglobulin (IVIG) (96%), IV corticosteroids (86%), plasma exchange (PE) (29%), and immunoadsorption (16%). Second-line therapy was reported in 84% of patients and included rituximab, and rituximab associated with cyclophosphamide. Azathioprine and intrathecal therapy with methotrexate and methylprednisolone were administered in 18% and 14% of patients, respectively, as long-term immunosuppressive to prevent relapses.

The initial presentation in this cohort of children differed substantially from the presentation in adult female patients, who initially presented with mainly psychiatric disorders (67%) or cognitive impairment (19%), and less frequently seizures (14%). Frequency of tumour was lower in children (2%) than in the adult female patients (41%). Second-line therapy was used more in children (84%) than in adult women (48%). However, 14% of adult females had a relapse, compared with none in children. The authors concluded that a diagnosis of anti-NMDAR encephalitis should be considered in young children (female and male) who present with neurological symptoms suggesting recent seizures (focal or generalised) without any other obvious aetiology.

Generalised seizures and cognitive changes were also the initial symptoms in 16 children (aged six months to 14 years) with anti-NMDAR encephalitis in a study conducted by Konuskan et al. (2018). Movement abnormalities (dyskinesia, tremor or chorea) were also frequent. The only factor associated with a good prognosis was early treatment (within three months). Age, sex, onset, MRI, EEG and CSF findings did not influence the outcome.

In a study conducted by Granata et al. (2018), the initial symptoms of children with anti-NMDAR encephalitis differed according to their ages: neurological presentation in children and psychiatric symptoms in teenagers. However, movement disorders were distinctive symptoms in all patients: hyperkinetic movement disorders in children and a constellation of symptoms consistent with catatonia in teenagers. The authors emphasised that several movement disorders may coexist in one child with anti-NMDAR encephalitis and can persist during sleep. Stereotyped motor phenomena (e.g., perseveration, reproduction of acquired complex motor activities, and orofacial dyskinesia) were present in all patients.

In a study conducted by Ho et al. (2018) of 15 children (aged one to 17 years) with anti-NMDAR encephalitis in Hong Kong, most children developed a constellation of symptoms (median five) over time: seizures (93%), abnormal psychiatric behaviour and cognitive dysfunction (93%), speech dysfunction (87%), movement disorder (80%), decreased level of consciousness (67%), and autonomic dysfunction or central hypoventilation (33%). Initially, more children developed psychiatric or behavioural symptoms (60% of patients) than neurological symptoms (40% of patients), but the rate of psychiatric presentation did not increase with age. Most children (80%) presented with a premorbid infection (upper respiratory tract infection or non-specific febrile illness). One child developed anti-NMDAR after HSV encephalitis. All children except one were Chinese, and 67% were female. Antibody testing was positive in the CSF (all patients) and serum (67% of patients). Other CSF findings included pleocytosis (73% of patients) and oligoclonal band (15% of patients). MRI was normal in 80% of patients. EEG abnormalities (87% of patients) included electrographical seizures, generalised slowing, focal slowing and/or epileptiform discharges. No tumour was reported in any child. All patients received immunotherapy (IVIG in one, steroids in one, or a combination in 13), at a median time of two to 2.5 weeks from initiation of symptoms. Plasmapheresis and rituximab were administered in three patients unresponsive to first-line immunotherapy. Intensive

care unit admission was necessary in 67% of children, with a median stay of ten days. Full recovery was observed in ten out of 14 patients (median follow-up was 20.5 months). Mild behavioural problems were reported in two patients, and severe behavioural problems in one patient. The child who developed anti-NMDAR post HSE, and had a delayed diagnosis, was left with dyskinesia, epilepsy, severe global developmental delay and oromotor dysfunction. The authors remarked on the higher incidence of anti-NMDAR (2.2/million children per year) in their study compared to other reported studies, and also the ethnicity feature.

Favier M., Joubert B., Picard G., et al. (2018) Initial clinical presentation of young children with N-methyl-D-aspartate receptor encephalitis. European Journal of Paediatric Neurology; 22: 404–411.

Granata T., Matricardi S., Ragona F., et al. (2018) Pediatric NMDAR encephalitis: A single center observation study with a closer look at movement disorders. European Journal of Neurology; 22: 301–307.

Ho A.C-c., Chan S.H-s, Chan E., et al. (2018) Anti-N-methyl-D-aspartate receptor encephalitis in children: Incidence and experience in Hong Kong. Brain & Development; 40: 473–479.

Konuskan B., Yildirim M., Topaloglu H., et al. (2018) Clinical presentation of anti-N-methyl-D-aspartate receptor and anti-voltage-gated potassium channel complex antibodies in children: A series of 24 cases. European Journal of Paediatric Neurology; 22: 135–142.

Treatment with intrathecal methotrexate in severe anti-NMDAR encephalitis

Yang et al. (2018) investigated the response to treatment with intrathecal methotrexate in four patients with severe anti-NMDAR encephalitis, refractory to first-line immunotherapy. Patients were between 13 and 23-years-old. Three patients had unilateral ovarian teratoma removed. Mean time from presentation to treatment was 11 days. All patients progressed rapidly into a state of unresponsiveness within two weeks. The treatment regimen included weekly intrathecal immunotherapy for four weeks and systemic immunotherapy (low-dose steroids and mycophenolate mofetil). Patients were assessed periodically and followed up for at least 12 months. Three patients experienced improvement and a decrease of cerebrospinal fluid (CSF) anti-NMDAR antibody titres after the fourth intrathecal administration. At two months follow-up, they were able to follow simple commands and had appropriate interactions with people. At 12 months follow-up, all of them had returned to their previous daily activities (modified Rankin scale of 0) with no relapses reported. One patient showed no clinical improvement, persistent high level of antibodies in CSF, and died of neurological complications two months later. No neurological complications associated with intrathecal administration were observed in any of the patients. The authors concluded that despite the small number of patients in this cohort, these findings may suggest that intrathecal administration could have a direct impact on the inflammatory process by suppressing the intrathecal synthesis of antibodies, which results in decreasing antibody titres and resolution of symptoms.

Yang X-Z., Zhu H-D., Ren H-T., et al. (2018) Utility and safety of intrathecal methotrexate treatment in severe anti-N-methyl-D-aspartate receptor encephalitis: a pilot study. Chin Med J; 131:156–60.

Challenges in diagnosis anti-NMDAR encephalitis

In a retrospective series of 221 patients with clinically suspected autoimmune neurological disorders who underwent testing for autoantibodies against neuronal cell-surface antigens, 41 patients met the diagnostic criteria of Graus et al. (2016) for probable anti-NMDAR encephalitis (Kaneko et al. 2018). Anti-NMDAR antibodies were detected in 85% of patients with the probable criteria. Two of the patients who were antibody-negative had ovarian teratoma. The antibody-negative group had a higher median age at onset of symptoms than the antibody-positive group. Of 180 patients who did not fulfil the probable criteria, five patients had anti-NMDAR antibodies detected. They presented with isolated epileptic syndrome (n=2), atypical demyelinating syndrome (n=2), and autoimmune post-herpes simplex encephalitis (post-HSE) (n=1). The authors concluded that the probable criteria are useful and valid. However, the diversity of clinical phenotype should also be considered in patients who display fewer symptoms, which are not explained by other causes or a previous seizure or psychiatric disorder.

During the initial illness, when psychiatric presentation predominates, the condition may be misdiagnosed as a psychiatric disorder. Conroy et al. (2018) described a patient with anti-NMDAR encephalitis misdiagnosed as chronic schizophrenia, concluding that anti-NMDAR encephalitis should be considered in patients with psychosis who manifest with altered mental status, abnormal movements, and poor response to conventional antipsychotic medication. In the present case, the patient had a long-standing diagnosis of schizophrenia (four years).

Janmohamed et al. (2018) reported a patient who manifested with primary lateral sclerosis-like picture after a probable anti-NMDAR encephalitis 22 years before (the longest follow-up of a patient with anti-NMDAR encephalitis). After a severe illness, resembling anti-NMDAR, with a long and complicated intensive care unit admission but without immunotherapy, the patient had gradually improved. Nine years after her initial illness she was diagnosed with an ovarian teratoma. Her current episode manifested with difficulty with balance, multiple falls, leg stiffness and mild emotional lability. Cerebrospinal (CSF) anti-NMDAR antibodies test was positive. Treatment with immunoglobulin, rituximab, bortezomib, and oophorectomy did not improve her condition. The authors argued that this case shows that some anti-NMDAR encephalitis patients may spontaneously recover. The second episode with ongoing progression of the symptoms and the lack of treatment response prompted the authors to question the pathogenesis of this condition, with a possible role of anti-NMDAR antibodies

in neurodegeneration. The risk of misdiagnosing anti-NMDAR encephalitis is also highlighted by Kobayashi et al. (2018), especially mild cases that improve spontaneously. This is important as these cases may relapse involving different lesions without symptoms (e.g. brainstem in this study). Careful assessment for appropriate treatment is recommended.

Bacchi et al. (2018) undertook a systematic review of published studies on the use of magnetic resonance imaging (MRI) and positron emission tomography (PET) in the diagnosis of anti-NMDAR encephalitis. MRI did not show abnormalities in over half of the patients. If present, abnormal findings included T2/FLAIR medial temporal and frontal hyperintensity, and leptomeningeal contrast enhancement, cortical grey matter changes and subcortical white matter changes. FDG-PET has been reported as used very rarely, but showed abnormality in all reported studies, even in cases where MRI was normal. Given the high rate of abnormal EEG findings in patients with anti-NMDAR encephalitis, Miao and Wang (2018) investigated if there were specific electrographic features other than the extreme delta brush (EDB) and high beta/delta power ratio (BDPR) already described in the literature. The authors reported the presence of an ictal electrographic pattern of 'rhythmic alpha sinusoidal wave' (RASW), which lasted up to two minutes with evolution in frequency, amplitude, morphology, or field, and mingled with a few sharp waves. During RASW, no clinical symptoms were observed in any of the three patients studied. The authors argued that RASW may be specific for anti-NMDAR encephalitis. Baykan et al. (2018) drew attention to delta brush patterns, which may not be unique to anti-NMDAR encephalitis. They found this specific pattern in one patient (out of 76) with mesial temporal lobe epilepsy with good prognosis after surgery, and in three patients (out of 106) from ICU who have a high mortality rate (hypoxic encephalopathy, brain tumour, stroke, and metabolic derangements).

Varley et al. (2018) analysed the movement disorders associated with anti-NMDAR encephalitis in 34 patients. Patients were aged between two months and 32-years-old, and had a severe course of the illness (modified Rankin Scale median 5). Movement disorders were an early feature, which persisted for a median of 112.5 days. Seven experts established a consensus glossary of terms followed by rating each of the 76 video recordings. The authors noted the experts' difficulty in characterising each movement disorder included in those videos. Overall, the movement disorders associated with anti-NMDAR encephalitis were characterised by diverse, widely distributed hyperkinetic phenomenologies, with prominent dystonia, chorea and stereotypes, with almost complete absence of tics and tremor and relative lack of myoclonus. The authors argued that this classification, in the context of adequate clinical context, may help diagnose this disorder promptly and initiate therapy.

Bacchi S., Franke K., Wewegama D., et al. (2018) Magnetic resonance imaging and positron emission tomography in anti-NMDA receptor encephalitis: A systematic review. Journal of Clinical Neuroscience; 52: 54–59.

Baykan B., Tuncer O.G., Vanli-Yavuz E.N., et al. (2018) Delta brush pattern is not unique to NMDAR encephalitis: evaluation of two independent long-term EEG cohorts. Clinical EEG and Neuroscience; 49(4): 278–284.

Graus F., Titulaer M.J., Balu R., et al. (2016) A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol.; 15(4): 391–404.

Janmohamed M, Knezevic W., Needham M., Salman S. (2018) Primary lateral sclerosis-like picture in a patient with a remote history of anti-N-methyl-D-aspartate receptor (anti-NMDAR) antibody encephalitis. BMJ Case Rep; 28 May.

Kobayashi Y., Sato S., Takasone K., Takamatsu R. (2018) Anti-N-methyl-D-aspartate receptor encephalitis relapse in the brainstem. BMJ Case Rep. 22 March.

Kaneko A., Kaneko J., Tominaga N., et al. (2018) Pitfalls in clinical diagnosis of anti-NMDA receptor encephalitis. Journal of Neurology; 265: 586–596.

Conroy M.A., Finch T., Levin T.T. (2018) Chronic schizophrenia later diagnosed with anti-NMDA receptor encephalitis: case report and review of the literature. Clinical Schizophrenia and Related Psychosis; Winter 2018.

Miao A., Wang X. (2018) Ictal rhythmic alpha sinusoidal waves in 3 cases of anti-NMDAR encephalitis. Clinical EEG and Neuroscience; 49(5): 302–305.

Varley, J.A., Webb A.J.S., Balint B., et al. (2018) The movement disorder associated with NMDAR antibody-encephalitis is complex and characteristic: an expert video-rating study. J Neuro Neurosurg Psychiatry, 0; 0.

Case reports

- Metzger et al. (2019) reported two patients (both female aged 19 and 24-years) with anti-NMDAR encephalitis, which featured Balint syndrome (optic ataxia, psychic paralysis of gaze, and lateralised disorder of attention) in addition to other clinical features specific to this illness.
- Cai et al. (2018) reported a case of anti-NMDAR encephalitis in a nine-year-old girl, associated with acute acquired *Toxoplasma gondii* infection.
- Randall et al. (2018) presented a case of anti-NMDAR encephalitis in an immunosuppressed patient who was found to have a non-Hodgkin's B cell lymphoma.

Cai X., Zhou H., Xie Y. et al. (2018) Anti-N-methyl-D-aspartate receptor encephalitis associated with acute Toxoplasma gondii infection. A case report. Medicine; 97:7.

Metzger A., Pisella L., Vighetto A., et al. (2019) Balint syndrome in anti-NMDA receptor encephalitis. Neurol Neuroimmunol Neuroinflamm; 6.

Randall A., Huda S., Jacob A., Larner A.J. (2018) Autoimmune encephalitis (NMDAR antibody) in a patient receiving chronic post-transplant immunosuppression. Pract Neurol; 18: 320–322.

Leucine-rich glioma-inactivated 1 (LGI1) and contactin-associated protein-like 2 (CASPR2) antibody encephalitis

"The striking syndrome similarities, coexistence of two otherwise rare antibodies and molecular insights suggest the VGKC complex may yet be a common functional effector of antibody action." (Binks et al., 2018)

LGI1 and CASPR2 antibody encephalitis – advances

Establishing the specific antibody directed against the voltage-gated potassium channel complex (VGKCc) – LGI1 or CASPR2 – enhances clinical diagnosis and management of these patients. Binks et al. (2018) investigated the clinical characteristics of patients with LGI1 and CASPR2 antibody encephalitis. Similar features include male gender of older age predominance, focal seizures, prominent amnesia, dysautonomia, neuromyotonia, and neuropathic pain. However, faciobrachial dystonic seizures are a characteristic of anti-LGI1 encephalitis. In both types, magnetic resonance imaging (MRI) and electroencephalography (EEG) can be normal, but can also present characteristic features including: frontocentral cortical slow waves and subclinical seizures (EEG) and unilateral or bilateral hippocampal swelling with hyperintensities on T2 and FLAIR sequences (MRI). Another similarity was high prevalence of antigen-specific antibodies of the IgG4 subclass. Antibody testing was more sensitive in serum than in the cerebrospinal fluid (CSF).

LGI1-associated faciobrachial dystonic seizures (FBDS) respond well to corticosteroids, whilst CASPR2 antibody-associated seizures have been reported as less responsive to immunotherapy, requiring more than one drug, and taking longer to cessation. Other immunotherapies used were immunoglobulin and plasma exchange (PLEX), although in LGI1 antibody encephalitis, there was no evidence that combination therapy was more efficient than corticosteroids alone. In addition, there is no evidence that second-line immunotherapies such as azathioprine, mycophenolate and cyclophosphamide are efficient. However, immunoadsorption showed benefit on CSF antibodies. Relapses (14–40%) were associated with rapid corticosteroid tapers. The authors suggested early and relatively assertive use of corticosteroids with PLEX, followed by gradual corticosteroid taper over about 18 months. In both antibody types, there was evidence of immune dysfunction combined with a predisposing event or antigenic exposure. The authors emphasised the high degree of clinical similarities between these two entities, mechanistic commonalities and the coexistence of anti-LGI1 and CASPR2 antibodies in some patients – all suggesting a role for the VGKC complex, which the two proteins are linked to.

Nantes et al. (2018) assessed functional brain activity in patients affected by autoimmune encephalitis with FBDS. Their study included eight patients and eight controls, who underwent multimodal 3T MRI scans, including structural neuroimaging (T1-weighted, diffusion weighted) and functional neuroimaging (involving a scene-encoding task known to activate hippocampal regions). The authors established that patients high peak seizure frequency did not have the expected hippocampal activity when performing a complex scene-encoding task. They suggested that frequent seizures can have a long-term impact on hippocampal functional activity. On-going monitoring of medial temporal lobe performance can direct patient management and future clinical trials.

Binks S.N.M., Klein C.J., Waters P., et al. (2018) LGI1, CASPR2 and related antibodies: a molecular evolution of the phenotypes. J Neurol Neurosurg Psychiatry; 89: 526–534.

Nantes J.C., Thomas A.G., Voets N.L., et al. (2018) Hippocampal functional dynamics are clinically implicated in autoimmune encephalitis with faciobrachial dystonic seizures. Front. Neurol. 9: 736.

LGI1 antibody encephalitis in Chinese patients

Addressing the lack of reports of LGI1 antibody encephalitis in the Chinese population, Wang et al. (2018) and Li et al. (2018) investigated clinical features of LGI1 antibody encephalitis in this population. The first study (Wang et al., 2018) included 13 patients, of whom eight were female, aged between 18 and 66 years. Four patients presented with fever as the prodromal symptom. Initially, six patients developed psychiatric symptoms, such as visual and auditory hallucinations (46%), delusions (62%) and apathy (54%), and four patients were seen by a psychiatrist. After hospitalisation, 39% and 54% of patients respectively, developed impulsive or bizzarre behaviour (e.g., talking to themselves, unprovoked laughter). Seizures were reported in 77% of patients. All patients experienced faciobrachial dystonic seizures (FBDS) and memory deficits. No tumours were detected in any of the patients. The time from initial symptom to diagnosis ranged from ten to 240 days. Antibody testing was positive in serum (n=7), cerebrospinal fluid (CSF) (n=4) or both serum and CSF (n=2). Electroencephalography (EEG) was abnormal in eight patients and magnetic resonance imaging (MRI) in four patients (temporal lobe abnormalities). Treatment consisted of corticosteroids (n=5), intravenous

immunoglobulin (IVIG) (n=4) or a combination of both (n=4), and resulted in favourable functional outcome in ten patients after two months. Three patients who did not improve were treated with corticosteroids only. The authors suggested that psychiatrists need to recognise these clinical features of anti-LGI1 encephalitis, as rapid diagnosis and treatment has favourable prognosis.

In the second study (Li et al., 2018), out of eight patients, five were males and three females with ages between 41 and 73 years, characteristics more similar to the European reports of this illness than in the first study. The initial symptoms were cognitive disorders (short-term memory problems) and seizures (tonic-clonic, partial and FBDS). Four patients had FBDS before cognitive impairment. Other symptoms included spatial disorientation, hallucinations, emotional changes, sleeping disorders and autonomic dysfunction. Antibody testing was positive in CSF and serum in all patients. MRI was abnormal in five patients, revealing abnormalities on insula, hippocampus and basal ganglia. Treatment consisted of antiepileptic drugs and glucocorticoids in all patients. Four patients had additional IVIG. Two patients relapsed at three months. Patients were left with mild memory impairments, spatial disorientation and sleep disorders. One patient was left with seizures.

Li W., Wu S., Meng Q., et al. (2018) Clinical characteristics and short-term prognosis of LGI1 antibody encephalitis: a retrospective case study. BMC Neurology; 18:96.

Wang D., Hao Q., He L., et al. (2018) LGI1 antibody encephalitis – Detailed clinical, laboratory and radiological description of 13 cases in China. Comprehensive Psychiatry 81: 18–21.

Autoimmune movement disorders

"The approach to treatment of immune mediated movement disorders requires an understanding of the immunopathogenesis, whether the disease is destructive or 'altering', and the natural history of disease." (Mohammad and Dale, 2018)

Balint et al. (2018) reviewed the movement disorders associated with neuronal autoantibodies, highlighting the red flags of the main syndromes associated with these autoantibodies. Dyskinesias are specific for anti-NMDAR encephalitis. Mild orofacial dyskinesia may also suggest neurexin-3α antibody encephalitis, whose red flags are dysautonomia, decreased consciousness and seizures preceded by a prodromal phase (fever and headache), and neuropsychiatric disturbance. Chorea is seen in relapses following herpes simplex encephalitis (HSE) associated with anti-NMDAR antibodies. LGI1 or CASPR2 antibodies are also associated with chorea with/without neuropsychiatric symptoms, usually without any underlying cancer. Dystonia is usually a combined feature of an antibody-associated encephalitis. Nevertheless, dystonia as a main feature has been reported in paediatric anti-NMDAR encephalitis. Myoclonus was described as a main characteristic in anti-DPPX encephalitis, but also in anti-LGI1 and CASPR2- antibody encephalitis. Specific for anti-LGI1 are faciobrachial-dystonic seizures, episodic bradycardia and serum hyponatremia. A red flag for DPPX antibody encephalitis is the prodromal phase with prolonged diaarrhoea, weight loss and dysautonomia. CASPR2 antibodies are associated with male gender, old age, cognitive impairment and neuropathic pain. In addition, myoclonus can be present in steroid-responsive encephalopathy with thyroid antibodies (SREAT) with thyroid, gliadin or tissue transglutaminase antibodies. The authors drew attention to the fact that the latter antibodies are not pathogenic; however, $GABA_A$R antibodies, which may be associated with thyroid autoimmunity, and are pathogenic, can manifest with myoclonus, epilepsy, and T2 – weighted MRI changes (cortical and subcortical hyperintensities). Parkinsonism is present in anti-Ma2, Ri, CRMP5- antibody associated syndromes, and has also been described in patients with anti-LGI1, DPPX and GAD antibodies. Children with anti-NMDAR and D2R antibodies can also present with acquired Parkinsonism. Ataxia is a main feature in patients with GAD antibodies associated with a slowly progressive course or sub-acutely, with either isolated cerebellar signs or additional signs, such as pyramidal tract involvement or features of stiff person syndrome. Ataxia has also been described in children with anti-NMDAR encephalitis, and combined with encephalopathy and/or brainstem dysfunction in patients with CASPR2 or $GABA_B$R antibodies. Hyperekplexia associated with trunk prominent cerebellar ataxia and various degrees of dysautonomia, somatosensory disturbances, and cognitive decline was reported in DPPX encephalitis. Stiff person spectrum disorder was associated mostly with GAD and GlyR antibodies. It has also been reported in association with DPPX, $GABA_A$R and GlyT2 antibodies. Tremor can be part of a wider encephalopathic picture in association with LGI1/CASPR2, NMDAR and DPPX antibodies. Sleep behaviour disorders including RBD (in anti-Ma 2 encephalitis and anti-LGI1 encephalitis), status dissociatus and agrypnia (in Morvan syndrome, anti-NMDAR encephalitis, and $GABA_B$R antibody-associated encephalitis) are also described.

The authors suggested that clinicians should use neuronal antibody panels based on the predominant movement disorder presentation, age at onset, and the presence or absence of other neurological signs. In assessing results, consideration should be given to type of assays and specimen used, and different laboratory practices. The authors emphasised the importance of identifying the clinical presentations of different antibodies in patients with movement disorders. Future treatment avenues, such as tailored

antigen-specific immunotherapy, engineering a non-pathogenic monoclonal antibody that binds to the same target and displaces the autoantibodies, targeting the pathophysiological cascades downstream of the antibody–antigen interaction need to be explored.

Fearon and O'Toole (2018) argued that isolated autoimmune movement disorders are rare. There are a few factors that may raise suspicion of an autoimmune aetiology, such as female gender, subacute onset, fluctuating course, multifocal neurological disease, personal or family history of autoimmunity, personal history of cancer or suspicion of new cancer, abnormal supportive tests (e.g., CSF, imaging), and response to immunotherapy. If autoimmune cause is suspected then key diagnostic tests should be performed: serum antibody testing with matched CSF sample; CSF testing for leucocytosis, raised protein, increased IgG index and oligoclonal bands; MRI of the brain and/or spinal cord with and without gadolinium; electroencephalogram (EEG); a movement disorder laboratory evaluation if available. If any of these tests confirm the autoimmune suspicion, then there is a need to look for a cancer: mammography, testicular ultrasound, pelvic ultrasound, computed tomography (CT) of the chest/abdomen/pelvis, gastroscopy, colonoscopy, digital rectal exam, serum prostate-specific antigen, and cervical smear testing depending on the presenting clinical features. If no cancer is detected, then a positron emission tomography-computed tomography (PET-CT) of the body should be considered, and potentially repeated serially in case the movement disorder appears before the cancer. Treatment consists of immunotherapy: intravenous pulsed steroids, intravenous immunoglobulin, and plasmapheresis. Use of the second-line therapy depends on the type of antibody, the condition, and the response to treatment. If the disorder is prone to relapses (e.g. anti-NMDAR) then a long-term therapy is recommended. Other treatments such as tocilizumab and bortezomib may also be used in anti-NMDAR refractory cases. Currently, the new drug ephrin B2 is in early-phase experimentation. The disorders associated with an extracellular antibody, and without cancer, have a better prognosis than those associated with cancer and intracellular antibody.

Honnorat and Joubert (2018) also differentiated between movement disorders with antibodies targeting cell-surface antigens and movement disorders with antibodies targeting intra-cell antigens. In the first category, are patients with acute or subacute encephalitis when abnormal movements are associated with other neurological symptoms (e.g. NMDAR, DPPX, GlyR) and patients with a more progressive encephalitis and symptoms that develop gradually over a few weeks (e.g. LGI1, CASPR2). Sometimes, it may be difficult to differentiate between movement disorders and epileptic manifestations. In young children, the first sign of NMDAR-Ab encephalitis, may be transient unilateral dystonic or tonic posturing, with no clonic movements as the first evidence of focal epilepsy, followed by the development of generalised chorea or stereotypical movements together with mutism and orofacial dyskinesia. In the second category, the authors differentiate between onconeuronal antibodies (anti-Hu, CV2/CRMP5, Ri, amphiphysin and Yo-Abs) associated most frequently with cerebellar ataxia, but also isolated chorea and dystonia, and two antibodies difficult to categorise: GAD65 (stiff person

syndrome, cerebellar ataxia and limbic encephalitis) and IgLON5 (neurodegenerative disease). The importance of identification of each particular autoantibody subtype is again highlighted, as it influences the treatment regimen: immunotherapy (cell-surface antibodies) and cancer treatment followed by immunotherapy (intracellular antibodies).

In their review of immune-mediated movement disorders, Mohammad and Dale (2018) established principles that can guide the therapy: early initiation of treatment, reducing the impact of the inflammation (severity and duration of the illness, relapses), achieving a complete remission, diminishing the provoking factors, conventional symptomatic treatment, and support for the whole family to avoid/minimise the post-traumatic stress.

Balint B., Vincent A., Meinck H-M., et al. (2018) Movement disorders with neuronal antibodies: syndromic approach, genetic parallels and pathophysiology. Brain; 141: 13–36.

Fearon C., O'Toole O. (2018) Autoimmune movement disorders. Semin Neurol; 38: 316–329.

Honnorat J., Joubert B. (2018) Movement disorders in autoimmune encephalitis and paraneoplastic neurological syndromes. Revue Neurologique; 174: 597-607.

Mohammad S.S, Dale R.C. (2018) Principles and approaches to the treatment of immune-mediated movement disorders. European Journal of Paediatric Neurology; 292–300.

Other autoimmune encephalitis

"When antibodies targeting intracellular and cell-surface antigens are detected together, investigation and treatment of syndromes associated with intracellular antibodies should be prioritized, acknowledging the link between these antibodies and irreversible neuronal injury." (Kim et al., 2018)

Autoimmune encephalitis with multiple autoantibodies

Myelin oligodendrocyte glycoprotein (MOG)-ab disease and AQP4-IgG-positive neuromyelitis optica spectrum disorder (NMOSD can coexist (simultaneously or sequentially) with anti-NMDAR encephalitis (NMDARe). Fan et al. (2018) compared patients with overlapping MOG-ab disease and NMDARe (MNOS) and patients with AQP4-IgG-positive NMOSD and NMDARe (ANOS). MOG-ab disease co-exists with anti-NMDARe more than AQP4-IgG-positive diseases (11.9%–0.6%). Patients with MNOS were younger at onset (aged three to 25-years-old) than patients with ANOS (aged 16 to 62-years-old). MOG-ab disease followed anti-NMDAR encephalitis in one patient and preceded anti-NMDAR encephalitis in two patients. Two patients had the diseases simultaneously. In patients with ANOS, anti-NMDARe occurred before the episode of NMOSD in two patients, and simultaneously in one patient. A literature research found that the main features of anti-NMDARe in both syndromes were psychiatric behaviour and cognitive dysfunction. None of the patients had tumours. MNOS patients responded better to steroids and immunoglobulin. Patients with ANOS were more likely to be treated with second-line therapy (rituximab and cyclophosphamide).

Kim et al. (2018) investigated the challenge in determining the clinical relevance of each antibody in autoimmune encephalitis with multiple autoantibodies. They presented a 67-year-old man with anti-NMDAR, Hu and CRMP-5 antibodies who died ten months after initiation of the symptoms. The clinical presentation included symptoms specific for each of these antibodies. The lack of response to immunotherapy, in addition to a progressive neurological deficit, suggested anti-HU antibody encephalitis diagnosis, which was confirmed by neuropathological assessment. No tumour was discovered, though the authors acknowledged a disease-associated malignancy as the cause of the neurological symptoms. The authors recommended that clinicians should use thorough screening of serum and cerebrospinal fluid using diagnostic panels that test for intracellular and cell-surface antibodies, rather than testing for individual antibodies. If both types of antibodies (intracellular and cell-surface) are identified, treatment of the intracellular antibodies should be prioritised. Comprehensive screening for tumours should be carried out in patients with multiple disease-associated antibodies, as the tumour treatment is very important in stabilising the neurological disease. If no tumour is discovered, staged provision of immunomodulatory therapies targeting B and T lymphocytes is suggested (e.g., cyclophosphamide, rituximab).

Fan S., Xu Y., Ren H., et al. (2018) Comparison of myelin oligodendrocyte glycoprotein (MOG)-antibody disease and AQP4-IgG-positive neuromyelitis optica spectrum disorder (NMOSD) when they co-exist with anti-NMDA (N-methyl-D-aspartate) receptor encephalitis. Multiple Sclerosis and Related Disorders 20: 144–152.

Kim A.E., Kang P., Bucelli R.C., et al. (2018) Autoimmune encephalitis with multiple autoantibodies a diagnostic and therapeutic challenge. The Neurologist; 23: 55–59.

Anti-alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor encephalitis

Samad and Wong (2018) reported a case of anti-AMPA receptor encephalitis associated with medullary thyroid cancer who experienced a full recovery due to prompt diagnosis and treatment. The patient, a 69-year-old woman, had a three-week history of paranoid delusions, short-term memory impairment and confusion. Cerebrospinal fluid and serum were positive for anti-AMPAR antibodies. She had a history of medullary thyroid cancer. A literature search identified 66 cases of AMPAR-associated encephalitis. There were 42 females and 24 males with a median age of 50 years. Most of the patients presented with a subacute onset of the illness. Thirty-eight patients presented with symptoms of limbic encephalitis (e.g., short-term memory loss, seizures, confusion, and psychiatric symptoms). In addition to limbic encephalitis, 18 patients presented with multiple areas of central nervous system involvement (e.g., optic neuropathy, sensory deficits, motor symptoms, ataxia, and dyskinesias). Isolated neurological symptoms without limbic encephalitis were described in five patients. The remaining four patients manifested with new-onset psychosis. Half of the patients had underlying cancer including lung cancer, thymomas, breast cancer, ovarian cancer, and seminoma. Treatment with immunotherapy and/or cancer treatment resulted in partial or complete recovery in most patients (72%). The authors argued that prompt recognition of this syndrome is important as the response to immunotherapy is positive.

Samad N, Wong J. (2018) Anti-AMPA receptor encephalitis associated with medullary thyroid cancer. BMJ Case Rep 2018. 6 August.

Glioblastoma (GBM) or autoimmune encephalitis (AE)

There is no standard protocol for differential diagnosis of AE from brain tumours. Diagnosis delay may mean unnecessary and potentially dangerous immunotherapy treatment. Vogrig et al. (2018) compared AE and AE-like presentation of glioblastoma. Out of 306 patients with suspected AE, six (2%) developed pathologically confirmed glioblastoma. The authors reviewed clinical and radiological features of these six, and also seven patients previously reported in the literature. There were nine males and four females, with a median age of 63 years. The median time from symptoms to GBM diagnosis was 3 months (range 1.5–24). One patient was diagnosed post-mortem.

The initial symptoms included working memory deficits (77%), seizures (62%) (including status epilepticus in 23%), and psychiatric symptoms (46%). Initial magnetic resonance imaging (MRI) showed bilateral or unilateral selective limbic involvement with initial sight contrast enhancement in five patients. CSF work-up revealed inflammation in five patients and three patients had antibody present (NMDAR, VGKC, GluRepsilon2). Retrospectively, all patients initially fulfilled the 2016 criteria for diagnosis of AE: 38% as definite limbic encephalitis, 15% as probable AE, and 46% as possible AE. MR spectroscopy performed later in the course of the disease revealed increased Cho/NAA ratio.

The authors argued that GBM can incorrectly suggest a diagnosis of AE. Therefore, an alternative diagnosis of glioblastoma may be considered in patients presenting initially as AE, especially in middle-aged/elderly male patients who do not fulfil the criteria for definite AE, and in those with a poor clinical evolution despite initial improvement. Brain biopsy should be considered in indeterminate cases. Advanced MRI techniques and close MRI follow-up could also be beneficial.

Vogrig A., Joubert B., Ducray F., et al (2018) Glioblastoma as differential diagnosis of autoimmune encephalitis. Journal of Neurology. 265: 669–677.

Seizure characteristics in autoimmune encephalitis

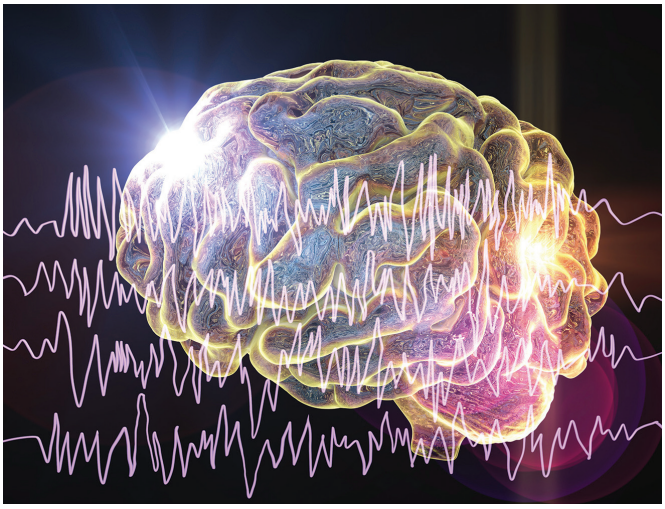
Steriade et al. (2018) investigated the evolution of electroclinical features of autoimmune epilepsy over time, in 19 patients with autoimmune encephalitis. Seizures were the exclusive, or the predominant clinical feature, and were frequently and rapidly refractory to antiepileptic drugs (AEDs). The median time to second AED was 9.5 days, and the median number of AEDs was three. Ten patients presented with status epilepticus (refractory in nine) as the initial symptom. Sixteen patients had multiple daily seizures.

On magnetic resonance imaging (MRI) and FDG-PET, 74% and 75% of the patients respectively presented with medial temporal lobe abnormalities. These correlated with seizure semiology (abdominal in 16%, psychic in 42%, and olfactory auras in 6%), interictal temporal epileptiform discharges (42%), and ictal onset in the temporal region (63%). Multimodal auras with somatosensory (26%), autonomic (26%), gustatory (11%), and visual (16%) features were seen in 82% of patients with focal aware seizures, suggesting broader involvement of the perisylvian regions. Subclinical seizures were observed in 58% of the patients.

On electroencephalography (EEG) seizure onset was frequently localised over the temporal region (63%) with frequent involvement of the temporoparietal and/or frontotemporal regions. Interictal epileptiform discharges (IEDs) were present in 53% of patients, and were most frequently distributed over the temporal regions (42%). Changes in seizure semiology and EEG findings were often seen. Seizures in antibody-negative and antibody-positive patients were very similar. However, faciobrachial dystonic seizures were only seen in patients with anti-LGI1 encephalitis.

At the last follow-up (median 2.2 years), the median number of AEDs was reduced to two. Eight patients presented with medically intractable seizures. These seizures were associated with initial generalised tonic-clonic seizures, temporal lobe involvement, interictal EEG and MRI changes. Initial status epilepticus was not associated with persistence of seizures. The authors concluded that seizures associated with autoimmune encephalitis are dynamic and exhibit common electroclinical features. Temporal and perisylvian regions as common pathways for these seizures are suggested. This may have implications for epilepsy surgery.

Steriade C., Moosa A.N.V., Hantus S., et al. (2018) Electroclinical features of seizures associated with autoimmune encephalitis. Seizure: European Journal of Epilepsy; 60: 98–204.



Hashimoto's encephalopathy, Rasmussen's encephalitis and Bickerstaff brainstem encephalitis

"In Rasmussen's encephalitis, a shorter interval from seizure onset to surgery may help in reducing the decline in functions subserved by the unaffected hemisphere." (Rudebeck et al., 2018)

Hashimoto's encephalopathy (HE) in children

Lee et al. (2018) reported six children with HE; five females and one male, between 10 and 17-years-old. Initial symptoms included altered consciousness (n=6), behavioural and psychiatric changes, such as aggression, severe irritability, hallucinations, insomnia, and agitation (n=6), seizures, such as generalised tonic-clonic, automotor, psychic aura, somatosensory aura (n=4), tremor and dystonia (n=2).

Only one patient had pre-morbid hypothyroidism. Laboratory testing showed antithyroid antibody titre increased with various levels (anti-thyroglobulin, 20.5–2318.0 U/ml in five patients; anti-thyroid peroxidase, 12.5–2231.0 U/ml in two patients). Remarkably, two patients initially had normal or low-titre antithyroid antibody. Electroencephalogram was abnormal in five patients. Brain magnetic resonance imaging was normal. Diagnosis was made based on encephalopathy and elevated serum antithyroid antibodies. Treatment included high-dose corticosteroid (all patients) followed by immunoglobulin (IVIG) (three patients). One patient refractory to corticosteroids and IVIG responded to plasmapheresis. Autoantibody titres decreased with clinical improvement in the acute stage. After the acute stage, three patients showed elevated antibody titre, despite complete recovery of their symptoms.

All patients improved substantially within three months of the onset. Two months after recovery, one patient had a relapse with disorientation and aggressive behaviour. Treatment with corticosteroids resulted in complete recovery.

The authors argued that despite various levels of antibody titres, patients showed a similar clinical course of the illness. Changes in the antibody titers were correlated with the response to treatment in the acute stage, but did not predict relapses in the recovery stage. They suggested further re-testing if the antibody titer is normal, or levels are low initially, but there is a suspicion of HE.

Lee J., Yu H.J., Lee J. (2018) Hashimoto encephalopathy in paediatric patients: homogeneity in clinical presentation and heterogeneity in antibody titers. Brain & Development; 40: 42–48.

Rasmussen's encephalitis (RE): how to improve the outcomes

Rudebeck et al. (2018) tried to establish the best timing for surgery in patients with RE, by assessing their cognitive features pre- and post-surgery. The retrospective case-note review study included 32 children. Pre-surgery, 50% of the children had an intelligence quotient (IQ) below 80, with the left hemisphere group (LHG) having a lower verbal IQ (VIQ) and a higher performance IQ (PIQ) than the right hemisphere group (RHG). Cognitive abilities declined with the progress of the illness, suggesting bilateral hemispheric involvement, a fact confirmed using magnetic resonance imaging (MRI) morphometry. Early onset of epilepsy was associated with greater decline in PIQ scores over time.

Post-surgery, cognitive decline was observed in both groups. The children in the LHG presented with a lower VIQ, whilst the children in the RHG had similar scores as pre-surgery. However, PIQ declined in both groups. The children with a higher IQ pre-surgery had greater losses than the children with a lower IQ pre-surgery. The cognitive changes from pre- to post–surgery were not influenced by age at onset, surgery, or the duration of the disease. Postoperative seizure control influenced the cognitive changes.

While pre-surgery children in both groups attended similar schools, post-surgery children in the LHG were more likely to attend special educational needs schools, with post-surgery verbal skills being the deciding factor.

The authors also looked at the global hemispheric volume (GM) across the groups, and compared it with a control group. GM volume of the affected hemisphere was smaller than the GM volume of the unaffected one; however, both hemispheres experienced a decrease in GM during follow-up. Volume loss on the affected side exceeded the atrophy of the unaffected hemisphere. There was also a connection between VIQ loss and left GM reduction. Compared with the control group, a voxel-based morphometry analysis confirmed a pattern of cortical atrophy with significant changes in frontal and insular cortices.

The authors concluded by suggesting that minimising the time from seizure onset to surgery can have a great impact on the cognitive abilities post-surgery, by maintaining the functions of the unaffected hemisphere.

Kuki et al. (2018) suggested that functional neuroimaging should be added to the diagnostic criteria for RE in order to improve the diagnosis and neurological outcomes. Their study of 23 patients with RE evaluated the use of cerebral blood flow (CBF)-single photon emission computed tomography (SPECT), central benzodiazepine receptor (BZR)-SPECT, and fluorine-18 fluorodeoxy glucose-positron emission tomography (FDG-PET) and correlated their results with MRI and histological findings. Functional neuroimaging detected abnormalities in patients with RE. In addition, abnormal findings on functional neuroimaging were reported in five patients in the absence of any MRI abnormalities.

Rudebeck S.R., Shavel-Jessop S., Varadkar S., et al. (2018) Pre- and postsurgical cognitive trajectories and quantitative MRI changes in Rasmussen syndrome. Epilepsia; 59: 1210–1219.

Kuki I., Matsuda K., Kubota Y., et al. (2018) Functional neuroimaging in Rasmussen syndrome. Epilepsy Research; 140: 120–127.

Bickerstaff brainstem encephalitis (BBE) in children

Santoro et al. (2018) conducted a systematic review of literature to characterise BBE in children. The study included 47 cases identified in the literature, and five unreported cases: 32 cases of 'definitive' BBE and 20 cases of 'probable' BBE. The median age of patients was ten years, and there was a 2.6:1 male-to-female ratio. Most patients (90%) had a pre-BBE illness (flu-like illness, upper respiratory tract infection and/or gastroenteritis) with a median time to neurological symptom development of nine days. The neurological manifestations included BBE characteristics (e.g., altered mental status, ataxia, and ophthalmoplegia), hypo/areflexia, extremity weakness, bulbar palsy, and visual deficits or disturbances, including diplopia, facial palsy, hyperreflexia, altered sensorium and/or paraesthesia.

Patients with magnetic resonance imaging (MRI) abnormalities (41%) had the longest median time to symptom resolution (120 days). Cerebrospinal fluid (CSF) abnormalities were found in 60% of patients. Of those tested, 68% of patients had anti-GQ1b positivity, and 44% had abnormal electromyography (EMG) or nerve conduction studies (NCS). One third of the patients received supportive therapy; the others received steroid, immunoglobulin (IVIG), plasma exchange, or a combination of them. The median time to resolution of symptoms was shorter in those treated with steroids or IVIG.

The study concluded that despite more abnormal lumbar puncture, MRI, EMG/NCS and EEG findings, BBE in children has a similar clinical profile to that in adults. Immunotherapy could be useful; however further randomised controlled studies are necessary.

Santoro J.D., Lazzareschi D.V., Campen C.J., Van Haren K.P. (2018) Pediatric Bickerstaff brainstem encephalitis: a systematic review of literature and case series. Journal of Neurology; 265: 141–150.

Diagnosis, treatment and outcomes

"Despite reports of good outcomes following paediatric anti-NMDAR encephalitis, many children experience cognitive problems and fatigue, even up until adolescence, which impact negatively on academic achievement and QoL." (de Bruijn et al., 2018)

Management of acute encephalitis – key facts

Ellul and Solomon (2018) reviewed the management of suspected acute encephalitis, which can present significant clinical challenges. A neurological emergency, which can lead to death and disability, encephalitis requires prompt and accurate diagnosis. The definition of encephalitis refers to encephalopathy and central nervous system infection evidenced by at least two of the following: fever, seizures or focal neurological signs, cerebrospinal fluid (CSF) pleocytosis (more than 4/µL), electroencephalography (EEG), and magnetic resonance imaging (MRI) findings of encephalitis. Clinical assessment of the patient should include a full history of the illness (e.g., symptoms such as personality or behaviour changes, seizures, drowsiness, subtle symptoms, travel history, contact with animals, bites, exposure to illnesses, risk factors for human immunodeficiency virus-HIV), and examination looking for seizures, movement disorder, consciousness level, and any focal neurological deficits. The initial management involves stabilising the patient and ruling out severe life-threatening conditions such as herpes simplex encephalitis, which requires urgent treatment. A lumbar puncture (LP) should be performed as soon as possible to examine the CSF. With a few exceptions (focal neurological signs, presence of papilloedema, continuous or uncontrolled seizures, Glasgow Coma Score ≤12), imaging is not necessary before LP. MRI is the most appropriate imaging technique. If a paraneoplastic cause is suspected, ultrasonography, computed tomography of the body and positron emission tomography imaging may be performed. An HIV test is recommended in all patients with suspected brain infections. If viral causes are eliminated, or patients have clinical manifestation of an autoimmune encephalitis associated with a particular antibody, then antibody testing should be performed. Acyclovir should be started immediately after the LP, or even before, if an LP is delayed for more than six hours. Acyclovir should be continued for at least 2 weeks or until the polymerase chain reaction (PCR) is negative. As many people (50–60%) have seizures in the acute stage, seizure control is important. The authors acknowledged that the care of this group of patients is challenging for the nursing staff, due to patients' physical, neuropsychological, and communication difficulties. Most of the survivors are left with neuropsychological difficulties. Access to information and referrals to neuropsychology services is essential.

Backman et al. (2018) investigated if a tailored multifaceted implementation strategy improves the initial management of patients with suspected encephalitis. A two-arm cluster, randomised, controlled trial with twenty-four hospitals (13 intervention and 11 controls) and 489 patients was performed. The intervention strategy included: local action planning, education and training, feedback on performance, an LP pack, and a range of optional components. All intervention sites received on-going support. There were two outcomes to be measured: the proportion of patients with suspected encephalitis undergoing an LP within 12 hours of admission and starting acyclovir treatment within six hours, and the proportions of adults and children who had an LP, appropriate CSF investigations and radiological imaging within 24 hours of admission. After assessing these data, the authors ascertained that the intervention strategy did not have any effect on the initial hospital management of patients with suspected encephalitis; all hospitals' practices being similar. However, there was a slight improvement in practice in all hospitals, which may reflect overall progress in management of encephalitis through wider awareness and education.

Backman R., Foy R., Diggle P.J., et al. (2018) A pragmatic cluster randomised controlled trial of a tailored intervention to improve the initial management of suspected encephalitis. PLoS ONE 13(12).

Ellul M., Solomon T. (2018) Acute encephalitis-diagnosis and management. Clinical Medicine; 18(2): 155–9.

Autoimmune encephalitis (AE) within an intensive care unit (ICU)

Schubert et al. (2018) reported on the management and outcomes of patients with AE in the ICU. Their study included 120 patients with a median age of 43 years. Neuronal antibodies were detected in 85 patients. Complications included disorders of consciousness (n=101), autonomic disturbances (n=54), status epilepticus (n=42), and severe sepsis (n=39). Sixty-eight patients were mechanically ventilated. Predictors of unfavourable outcomes included mechanical ventilation, tracheostomy, tumour, sepsis, and autonomic dysfunction. Autoantibody type, inflammatory changes in cerebrospinal fluid (CSF) or pathologic magnetic resonance imaging (MRI) had no influence on the outcomes. The authors concluded that classic ICU complications, rather than autoimmune type, determine the short-term outcomes of patients with AE requiring ICU treatment.

Schubert J., Bramer D., Huttner H.B., et al. (2018) Management and prognostic markers in patients with autoimmune encephalitis requiring ICU treatment. Neurol Neuroimmunol Neuroinflamm; 6.

Therapeutic plasma exchange (TPE) in children with neurological conditions

According to the American Society of Apheresis Guidelines 2016, acute disseminated encephalomyelitis (ADEM) is a category II indication (second-line therapy) for TPE, and anti-NMDAR encephalitis is a category I indication (first-line therapy). Özkale et al. (2018) reported the use of TPE in 22 children with neurological conditions of which four children had ADEM and four children had autoimmune encephalitis (AE). The other 14 children had acute inflammatory polyneuropathy, chronic inflammatory demyelinating polyneuropathy, or neuromyelitis optica spectrum disorder. TPE was performed as second- or third-line therapy after steroids and/or intravenous immunoglobulin (IVIG). Fresh frozen plasma was used as replacement fluid due to its lower costs than albumin.

In the ADEM group, the median number of sessions of TPE was five. Neurological symptoms improved in three patients, and one patient was left with neurological sequelae (hemiparesis and neurogenic bladder). In the autoimmune encephalitis group, there were a median of six sessions/patient. Two patients had improved neurological symptoms (one patient with anti-NMDAR and one patient who was seronegative), one patient was left with neurological deficit (three years follow-up) and one patient was lost at follow-up, but showed partial recovery immediately after TPE. In this group of patients, none developed major complications after TPE. Three out of the 22 patients developed minor complications: mild allergic reactions and hypotension. The authors concluded that TPE is safe and efficient in children with immune-mediated neurological diseases, although further investigation on large cohorts is necessary.

Özkale M., Erol I., Özkale Y., Kozanoğlu I. (2018) Overview of therapeutic plasma exchange in pediatric neurology: a single-center experience. Acta Neurologica Belgica. 118: 451–458.

Neuropsychological assessment (NA) – an objective tool in monitoring treatment responses

Sieg et al. (2018) assessed the usefulness of neuropsychological assessment in monitoring treatment response in anti-NMDAR encephalitis. They reported a 28-year-old female, diagnosed with anti-NMDAR encephalitis and treated with immunosuppression. Periodic neuropsychological assessments to guide the treatment and inform her response to treatment were performed. At one month, NA indicated incomplete global aphasia and receptive vocabulary less than the two-years-old age equivalence. The patient received speech and language therapy as an outpatient twice weekly. At three months follow-up, a qualitative exam reported limited improvement in speech and functions, with fluctuations in cognition and behaviour during the day. An NA showed clinical improvement in receptive language function, equivalent to that of a six-year-old. As electroencephalography (EEG) did not show any epileptiform activity, the antiepileptic drugs were reduced to one. Although considered, cyclophosphamide was not initiated. The following NAs, at six months and one year, reported a return to 70% of her baseline functioning, with language equivalent to that of a 19-year-old. The authors concluded that this case, demonstrated that a comprehensive neuropsychological assessment, can be a clinically relevant biomarker to guide treatment decisions. In this case the neuropsychological assessment helped to avoid complex treatment with more toxic medications and a wide range of antiepileptic drugs.

Sieg E., Brook M., Linnoila J., Van Haerents S. (2018) Neuropsychological assessment as an objective tool to monitor treatment response in anti-N-methyl-D-aspartate receptor encephalitis. BMJ Case Rep. June 8.

Outcomes of paediatric anti-NMDAR encephalitis

De Bruijn et al. (2018) performed a study of Dutch children diagnosed with anti-NMDAR encephalitis, which aimed to determine their long-term neuropsychological outcomes, and the influence of these on their quality of life (QoL). Twenty-eight children aged four years or older were included in the study. Median age at onset was 14 years. Twenty-one patients were female (75%). Median time from symptom onset to maximum disease severity was 30 days. Nearly half of the patients (46%) were admitted to the intensive care unit (ICU), with a median stay of 13 days. First-line immunotherapy was administered in all patients, and 46% received either rituximab or cyclophosphamide. Three patients relapsed. Seventeen patients were discharged home, of whom ten were referred to an outpatient rehabilitation programme. Eleven patients (39%) were transferred directly to an inpatient rehabilitation centre. Median rehabilitation time was 98 days.

Most of the patients (93%) returned to school; however three patients stopped school prematurely because of fatigue or anxiety. Five children had special educational needs, and 18 returned consistently to their previous school level. Twenty-two patients participated in the follow-up study, with a median follow-up time after symptom onset of 31 months. The follow-up study consisted of a detailed interview and a standardised neuropsychological assessment. Problems with sustained attention and fatigue were reported. The mean score on long-term verbal memory tended to be low. QoL was strongly correlated with fatigue, but not with cognitive deficits. Sustained attention, long-term verbal memory, or fatigue were not influenced by treatment delay, follow-up time, age at onset, ICU stay, maximum paediatric cerebral performance category (PCPC), and PCPC at follow-up.

The authors argued that, despite reports of good outcomes following paediatric anti-NMDAR encephalitis, many children experience cognitive problems and fatigue, even up to adolescence, which impact negatively on academic achievement and QoL. Greater awareness of these problems among physicians is needed so they can provide advice to patients and caregivers in the acute and follow-up phase, and consider early neuropsychological input.

Nicolle and Moses (2018) reviewed studies on the neuropsychological profile of people with anti-NMDAR encephalitis, to establish the cognitive characteristics associated with anti-NMDAR at presentation and during the chronic stage. Ten papers were included in the review: five case studies and five case series, with a total of 54 participants. During the acute stage, memory was the most tested cognitive function. The impairments included delayed verbal memory and difficulties with immediate, visual and short-term memory. Other cognitive difficulties reported were: attentional and processing speed difficulties, executive dysfunction, such as difficulties with problem solving, rule finding and set shifting, language impairments, and visuospatial difficulties. During the chronic stage (>12 months), studies reported delayed verbal memory, short-term memory difficulties, immediate recall difficulties, visual memory difficulties, executive dysfunction, attention/processing speed difficulties, and visuospatial difficulties. The authors argued that the results of these studies are consistent with the role of NMDA receptors in domains such as learning and memory. The authors emphasised the need for high-quality neuropsychological and psychological studies on the impact of anti-NMDAR encephalitis on cognitive function and psychosocial wellbeing, both of adults and particularly those under 18 years.

de Bruijn M.A.A.M., Aarsen F.K., van Oosterhout M.P., et al. (2018) Long-term neuropsychological outcome following pediatric anti-NMDAR encephalitis. Neurology; 90.

Nicolle D.C.M., Moses J.L (2018) A systematic review of the neuropsychological sequelae of people diagnosed with anti N-methyl-D-aspartate receptor encephalitis in the acute and chronic phases. Archives of Clinical Neuropsychology 33: 964–983.

Rehabilitation after encephalitis

"Of additional benefit would be studies spanning internationally, taking into account the capacities of different healthcare systems when addressing rehabilitation care for encephalitis." (Christie et al., 2018)

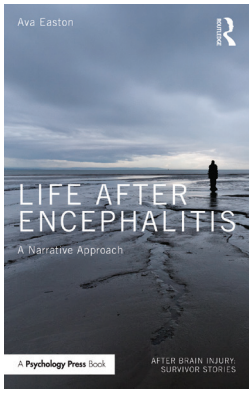
Corallo et al. (2018) reported a 50-year-old female with limbic encephalitis who undertook cognitive rehabilitation that resulted in improved cognitive and behavioural functions. They used a multidimensional approach in a personalised, intensive and short-term training programme. The programme included psychotherapy and neuropsychological methods for four months, with a total of 24 hours in sessions. External devices such as calendar, clock, family photos, city map, and diaries were also used. The patient underwent magnetic resonance imaging and neuropsychological assessment before and after rehabilitation training. Initially, the patient presented a global cognitive impairment, including disorientation on the spatial-temporal and autobiographic parameters, alteration in attention, learning, and immediate and delayed memory, language, speech, visuo-spatial abilities and executive functions, and emotional lability. At the end of the rehabilitation, the patient showed improved memory, attention, metacognition and relational aspect.

Christie et al. (2018) undertook a systematic review of rehabilitation outcomes among patients (adults and children) with residual impairments of neurological functions following infectious encephalitis. A literature research was performed and 20 studies were included in this review. Most studies presented case reports, and no studies with more than 25 patients were included. The studies included a wide range of interventions from cognitive therapy (nine studies), behavioural therapy (five studies), physical therapy (two studies), or two or more therapies (four studies). There wasn't enough evidence to make a connection between age, sex and baseline functional abilities, and outcomes. The authors concluded that overall, there is evidence for the benefit of rehabilitation interventions in patients with infectious encephalitis; however, there is still a need to understand the natural course of recovery and what else influences the recovery.

Christie S, Chan V, Mollayeva T, Colantino A. (2018) Systematic review of rehabilitation intervention outcomes of adult and paediatric patients with infectious encephalitis. BMJ Open; 8.

Corallo, F., Lo Buono, V., Di Cara M., et al. (2018) The role of cognitive rehabilitation in limbic encephalitis. A case report. Medicine; 97: 48.

Book review

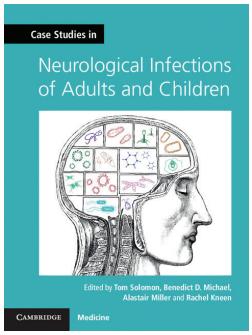


Life After Encephalitis. A Narrative Approach by Dr Ava Easton

Life After Encephalitis provides a unique insight into the experiences of those affected by encephalitis, sharing the rich, perceptive, and often powerful, narratives of survivors and family members. It shows how listening to patient and family narratives can help us to understand how they make sense of what has happened to them, and also help professionals better understand and engage with them in practice. The book will also be useful for considering narratives associated with brain injuries from other causes, for example traumatic brain injury. Life After Encephalitis will appeal to a wide range of people: professionals working in neurology and rehabilitation, and also to survivors of encephalitis, their families, and carers.

"Easton's book makes you think about identity. If our brains hold our memories that largely determine our personality and effectively define us, what does it mean if part of our brain is destroyed? Personality creates relationships - so when someone you love changes, what happens to the relationship? Encephalitis is undoubtedly a thief, and Easton does an excellent job at explaining why." Jules Morgan, The Lancet Neurology

Available from the Encephalitis Society (www.encephalitis.info/shop)



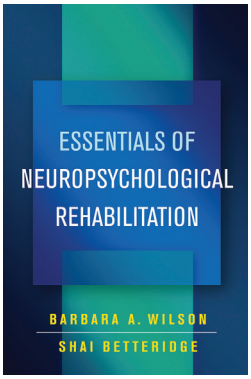
Case Studies in Neurological Infections of Adults and Children

Edited by Prof. Tom Solomon, Dr Benedict Michael, Alastair Miller and Dr Rachel Kneen

The book, published by Cambridge University Press, features over 60 case studies which work through the history, examination, and investigation findings to the diagnosis and treatment pathway. Each chapter also includes discussion of the key issues and historical or quirky facts to add further depth.

"The global burden of neurological infectious diseases is huge. Sometimes the diagnosis is straightforward. On other occasions it may be difficult, especially because of the overlap with inflammatory neurological conditions. Delays or missed diagnoses can have devastating consequences for patients. This book brings together adult and paediatric clinical cases in neurological infection and inflammation, including important conditions for both developed countries and resource-poor settings. Clinical case studies are recognized as a useful learning tool for clinicians at all stages in their careers." Prof. Tom Solomon

www.cambridge.org



Essentials of Neuropsychological Rehabilitation by Barbara A. Wilson and Shai Betteridge

For people with disabilities caused by nonprogressive brain injury, challenges in everyday living can be multifaceted and overwhelming. This book presents key principles of holistic neuropsychological rehabilitation, helping practitioners stay on track through complex terrain. Leading authorities Barbara A. Wilson and Shai Betteridge provide a framework for effective intervention based on a collaborative understanding of clients' strengths and needs. They describe essential strategies for assessing and remediating the impact of cognitive and psychosocial problems in everyday life. Detailed case examples illustrate the process of building partnerships with families, setting meaningful goals, developing skills and supports, and addressing emotional and mental health concerns. Innovative uses of technology are highlighted.

"Clinicians and researchers who want to know about holistic neuropsychological rehabilitation, this is the book for you! Wilson and Betteridge distill their knowledge gained over decades of clinical and research experience. The book explains the concepts and models underpinning neuropsychological rehabilitation, offers practical advice on assessment and goal setting, describes new intervention approaches, and provides case illustrations and visual aids. The authors have produced a valuable, highly accessible 'how-to' resource." Robyn Tate, PhD, Professor Emerita, John Walsh Centre for Rehabilitation Research, University of Sydney, Australia

www.guilford.com

About the Encephalitis Society

How we help

We are an international charity and the only resource of our kind in the world, dedicated to supporting those affected by encephalitis, their families and professionals involved in their care. Our work involves:

- Supporting adults, children, families and carers of those affected by encephalitis.
  Support Line: +44(0)1653 699599
  support@encephalitis.info
- Producing high quality, evidence-based and peer-reviewed information about encephalitis
  www.encephalitis.info
- Raising awareness about encephalitis, its consequences and the need for improved services.
- Conducting and funding research and working in partnership with other researchers.

Professional membership

Welcome to the world's leading network of encephalitis experts!

Professional membership of the Encephalitis Society is open to all professionals worldwide. Membership is free and it takes only two minutes to complete online. Being one of our members means you get priority access to our services and you will be kept up to date by our regular communications.

Some of the ways we support you and your work:

- We deliver the only accredited international Encephalitis Conference for health, social and educational professionals.
- We bring together and collaborate on research into the condition, and provide trusted support and information to the people in your care.
- We have an extensive database of over 5000 people affected by encephalitis. We work in partnership with researchers putting them in touch with people who meet the criteria for their studies as well as collaborating on research projects.

For more information about professional membership or if you would like to become a member please visit our website www.encephalitis.info/professional-membership or contact us at mail@encephalitis.info or +44 (0)1653 692583.

World® Encephalitis Day 22nd February 2020

Can you help us to raise awareness of brain inflammation this World Encephalitis Day?

This World Encephalitis Day we want to team up with encephalitis experts like YOU.

Our aim on 22nd February 2020 is to provide resources, support and information that can make a positive difference to lives affected by encephalitis.

We will do this by highlighting your expertise and letting the public know how their healthcare professionals are working for them.

We want to talk about all the great research that you are carrying out.

We want to talk about the support that is out there for survivors and their families.

We want them to know that they are not alone.

So, how can you help?

We want you and your institution to join us in going #RED4WED and talking about encephalitis and World Encephalitis Day.

Wearing red on World Encephalitis Day has become a fun way for our professional supporters to get involved on 22nd February and can cause quite a splash on social media.

You can find out more at www.worldencephalitisday.org and by signing up to become a professional member.

Encephalitis: a global issue with a human solution

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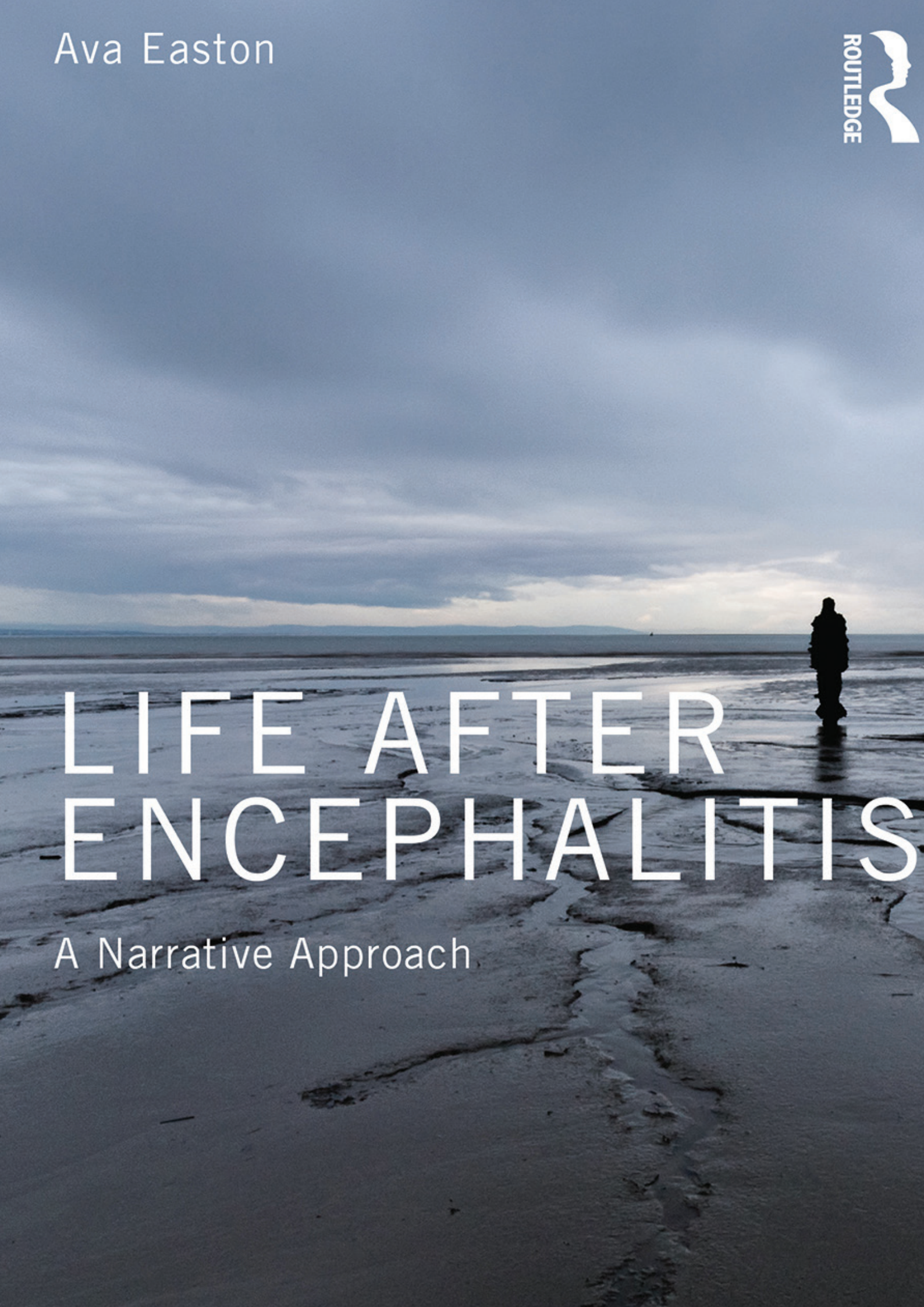
Third Sector Awards Winner 2019

Third Sector Awards Highly Commended 2019

Ava Easton

ROUTLEDGE



LIFE AFTER ENCEPHALITIS

A Narrative Approach