Welcome to the Encephalitis Society’s Research Summary 2016

The Advances in Encephalitis 2016 presents a summary of research papers published in 2016. This year, an increased incidence of tick-borne encephalitis has been reported. As this is a vaccine preventable disease there is a need for an increased awareness of the endemic areas, the existence of the vaccine and the effects of the illness on people affected. Enterovirus encephalitis continues to remain a significant cause of mortality and morbidity in children in many parts of the world, with researchers concentrating their efforts on serological surveillance, improving the accuracy and speed of the diagnosis, and characterising clinically the disease and the outcomes. Progress has been made in understanding the role of cytokines/chemokines as biomarkers of the CNS inflammation, but there is still more work to be done to fully understand the disease pathogenesis.

Herpes simplex virus is the most commonly identified cause of sporadic encephalitis worldwide, however, the diagnosis can still pose challenges, as shown by the studies in this review. Once more this year, the research world in encephalitis was still dominated by the work around autoimmune encephalitis: the discovery of new antibodies (neurexin-3α), the clinical characterisation of the existent syndromes, the role of therapies and also trying to ascertain the role of the antibodies in the mechanism of the disease. Guidelines for the diagnosis of autoimmune encephalitis, based on neurological assessment and more conventional tests widely available, have been developed. Nevertheless, the detection of specific autoantibodies is still very important for the management of these autoimmune syndromes.

As shown in this review, post-encephalitis sequelae are common in survivors of encephalitis. Irrespective of the type of encephalitis, improving the diagnosis and management (acute and postacute) is essential to reduce and manage these outcomes. Enhanced engagement and collaboration between doctors/researchers and patients/family members can also aid the management of this illness.

This review is available both in hard copy and electronically, along with a more detailed archive of papers we host on our website looking at everything from epidemiology to outcome.

This year, our half-day Professional Seminar becomes a full-day Conference with platform and poster presentations from the UK, USA, Indonesia and The Netherlands. We have also launched our Connect Professional Newsletter for our Professional Members featuring news about our Society and academic partners, along with profiles of researchers and their research projects. Our well-established website has a new look, and is more interactive and well-structured.

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

Dr Ava Easton
CEO The Encephalitis Society

Disclaimer
This review has tried to provide a succinct summary of the original papers. The full papers references are included in order to acknowledge the source, and for those who would like to read the articles, papers and books in full. The information presented in this summary should not be relied on to suggest an appropriate course of treatment for a particular individual. We strongly recommend you refer to the author’s original paper before altering practice in any way.
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Is encephalitis in Ontario different than encephalitis in England?

Parpia et al. (2016) assessed the incidence and trends of encephalitis in Ontario and compared them with those for England. The incidence of all cases of encephalitis was ≈4.3 cases /100,000 persons/year. Encephalitis was more frequent in males (15% higher) than females, except for the one to four year-old group. The highest incidence was in August/September. Children aged one to four years had the highest incidence of immune-mediated encephalitis. Viral encephalitis and encephalitis of unknown cause were more frequent in children under one year-old and adults aged 65 and over than in the other age groups.

The differences between the two locations (Ontario and England) consisted in: the presence of HHV-7, which was an unusual finding. After considering the high presence of HHV-7, which was an unusual finding, they recommended that the routine testing for this virus may need to be introduced in the diagnosis algorithm for suspected CNS infection in children.


Parisi S.G. (2), Basso M., Del Vecchio C., et al. Virological testing of cerebrospinal fluid in children aged less than 14 years with a suspected central nervous system infection: A retrospective study on 304 consecutive cases (3). HSV (two), CMV (two) and VZV (two). The other viruses found were EBV (six), human adenovirus (HAdV) (three), human parechovirus (HPeV) (three), HSV (three), CMV (one) and VZV (one). The authors concluded that only a small proportion of children had a cause identified. After considering the high presence of HHV-7, which was an unusual finding, they recommended that the routine testing for this virus may need to be introduced in the diagnosis algorithm for suspected CNS infection in children.

Viral infections in elderly patients and children under 14

Parisi et al. (1) (2016) studied the detection of viral infections of the central nervous system (CNS) in elderly patients. Their study included 502 cerebrospinal fluid (CSF) samples of patients with a suspected CNS infection. A total of 2,868 real-time polymerase chain reactions (RT-PCRs) were performed. Patients were divided into two groups: 65 to 79-year-old and ≥80 year-old. There were 59 positive RT-PCRs: 35 (9.6%) in the first group and 24 (17.4%) in the second group. Out of all positive samples, 23 were positive for herpes simplex virus (HSV), 15 for enterovirus (EV), 14 for Epstein-Barr virus (EBV), 12 for varicella-zoster virus (VZV) and one for cytomegalovirus (CMV). The second group was twice as likely to get infection with EV and EBV, than the first group. VZV was more common in the ≥80 year-old group (5.9%) than in the 65 to 79-year-old group (1.6%). However, HSV was the most common cause in this study.

Parisi et al. (2) (2016) investigated the presence of 11 viruses in the CSF of children younger than 14 with a suspected CNS infection. There were 304 children included in this study. The CSF in 64 patients (21%) was positive for a virus. Thirty-seven samples were positive for EV (12 of them being newborns). Six children were positive for human herpes virus 7 (HHV-7); all were immunocompetent and one had a concomitant bacterial infection. Eight children were positive for human herpes virus 6 (HHV-6). The other viruses found were EBV (six), human adenovirus (HAdV) (three), human parechovirus (HPeV) (three), HSV (three), CMV (one) and VZV (one). The authors concluded that only a small proportion of children had a cause identified. After considering the high presence of HHV-7, which was an unusual finding, they recommended that the routine testing for this virus may need to be introduced in the diagnosis algorithm for suspected CNS infection in children.

The National Vaccination Program has reduced TBE morbidity in children and has reached significant vaccination coverage in children in highly endemic regions.” (Kunze, 2016)

Tick-borne encephalitis (TBE): awareness and vaccination

TBE has become a public health problem in Europe and Asia due to an increased incidence and spread of the disease. TBE virus is endemic in many parts of Europe (Estonia, Slovenia, Latvia, Lithuania, Czech Republic, Austria, Sweden, Switzerland, Slovakia, Hungary, Poland, Finland, Germany, France, Croatia and Norway), Siberia, Far-Eastern Russia, Northern China and Japan. Clinical manifestations of the infection vary from simple fever to severe encephalitis. There is no treatment for the cause. However, the infection can be prevented by avoiding tick bites and taking up vaccination. There are four TBE vaccines available: two Russian and two European. National Vaccination Programmes (e.g. Latvia, Austria) have considerably reduced the number of TBE cases. Although the number of TBE cases in travellers is underestimated, a risk to travellers is recognised. Increased awareness of TBE, vaccination, prevention measures and international recommendations for travellers are needed (Kunze, 2016).

Steffen (2016) investigated the extent of TBE in international travellers to Western and Central Europe. The author gathered data from the European Centre for Disease Prevention and Control (ECDC), individual experts and other surveillance databases. In 2012, there were 38 cases of TBE acquired internationally. Based on this figure, the author argued that vaccination should be recommended for travellers exposed to a risk of TBE outdoors in rural endemic areas during the period of transmission, but not for all visitors to endemic areas.

Aerssens et al. (2016) investigated the immune response to one booster vaccination in 88 travellers from non-endemic regions who had a primary TBE vaccination schedule more than five years before the study. Blood samples were taken on the day of the booster and at days 21 to 28 after the booster. Participants were divided into two groups: one group who received vaccination more than eight years ago and the second group who received vaccination more than five years ago but less than eight years. The analysis of the samples taken before the booster showed that 45 participants still had the primary antibody response as measured by seroconversion rates.
neutralising antibodies circulating before booster vaccination (measured with PRNT) and 66 participants had positive levels of antibodies (measured with ELISA IgG). No difference between the two groups was noted. After booster vaccination, 95.5% of participants had neutralising antibodies and all of the patients had positive levels of IgG antibodies. Again, there was no difference between the two groups. The authors conclude that young, healthy travellers only need a booster vaccination after a primary vaccination schedule in order to obtain positive antibodies, even if the primary vaccination happened more than the recommended time interval of five years. However, TBE can develop in the immunised patients in cases of missing the booster vaccination. Zlany et al. (2016) describe the case of a 13-year-old girl who developed TBE despite having been vaccinated against TBE virus, as recommended by the Austrian immunisation schedule, with three doses of vaccine. The last dose of the vaccine was received six years prior to onset of the symptoms and the patient did not receive a booster five years after the last dose. The patient lived in an endemic part of the country. The authors emphasised the risk of TBE even in immunised patients as the disease course is severe in these cases. A full history of the vaccination should be taken in the presence of typical symptoms.


Enterovirus (EV) – a growing presence in India and China

Enterovirus encephalitis (EVE) is a severe disease with high mortality and morbidity in children. Singh et al. (2016) prospectively analysed the cerebrospinal fluid (CSF) of 128 children with encephalitis in Uttar Pradesh aiming to determine the cause of their illness. There were 29 cases of EV, 14 of Japanese encephalitis virus (JEV), 11 of herpes simplex virus (HSV), four of dengue virus and two of measles virus. Regarding the types of EV strains, the authors identified echovirus 19 (ECV19) in 20 samples, echovirus 21 in three, ECV 69 in two, EV 101 in two, coxsackievirus B5 in one, and ECV 27 in one. The EV 101 and echovirus 19 were identified not through standard molecular typing methods, but using a sequence-independent single-primer amplification method and a modified enterovirus VP1 gene typing primer. According to the authors this is the first report of EV 69 and EV 101 in India.

Wei et al. (2016) conducted a molecular epidemiological study of enteroviruses in Hangzhou (China). They investigated CSF samples from 126 children with encephalitis by using reverse transcription polymerase chain reaction (RT-PCR) and gene sequencing of VP1 or 5’UTR region. Most of the children were ≥ three-years-old. EV was detected in 26 children (20.6%) of which 19 were boys and seven were girls. The types of EV strains identified were echovirus 30 (most cases), coxsackievirus B2, coxsackievirus B3, echovirus 5, echovirus 16, echovirus 18, and EV species B. June and July were the months with the highest incidence of the infection. The authors suggested that the EV 30 could play a major role in EV infection in this region of China. Wei L., Qiong, Z., Xiao-ting S., et al. Molecular epidemiological study of enteroviruses associated with encephalitis in children from Hangzhou, China. Medicine 2016; 95:40.


Mycoplasma pneumoniae surveillance in Switzerland

Sauter et al. (2016) investigated the cases of Mycoplasma pneumoniae-associated encephalitis in children in Switzerland. Cases seen at one centre between 2010 and 2013 were reviewed. A nationwide surveillance for 2013–2015 was also conducted. Seven cases with confirmed (one) or possible (six) M pneumoniae-associated encephalitis were found. All patients were male with a median age of 8.7 years. There was no M pneumoniae deoxyribonucleic acid (DNA) detected in the cerebrospinal fluid (CSF) of any patient. However, M pneumoniae DNA was present in the throat specimens of six patients with encephalitis. All patients tested had serum specific antibodies and one patient had M pneumoniae-specific immunoglobulin in CSF. All patients had prodromal respiratory symptoms for over at least five days and five patients presented infiltrates on chest radiographs. Six patients had pleocytosis and five patients had inflammatory process revealed on their neuroimaging findings. At follow-up (4–19 months), three children – one confirmed and two possible – presented neurological sequelae. The authors concluded by suggesting that the cause of the encephalitis was immune-mediated following the respiratory infection. Sauter P.M.M, Moeller A., Reilly C., et al. Swiss national prospective surveillance of paediatric Mycoplasma pneumoniae-associated encephalitis. Swiss Med Wkly 2016; 146:w14222.

Case classification at the point-of-care

Because of the challenges in recognising and diagnosing some of the acute infections of the central nervous system (CNS), the classification of clinical cases may not always be accurate and some cases are missed or misclassified. Obermeier et al. (2016) undertook a study of the accuracy and efficiency of the Vienna Vaccine Safety Initiative Automated Case Classification-Tool (VACC-Tool) and compared it to the ICD-10 coding and retrospective analysis of electronic health records. The VACC-Tool is a mobile application allowing immediate case ascertainment based on consensus criteria at the point-of-care. The authors believed that having pre-defined case criteria implemented universally, immediately at the point-of-care would add value to the classification of the diseases which is very important for clinicians and public health. This study used retrospective paediatric hospital discharge summaries from a hospital in Switzerland who have already applied case criteria for aseptic meningitis, acute disseminated encephalomyelitis (ADEM), encephalitis and myelitis in a previous study. Collected data was compared with the case criteria integrated into VACC-Tool and the results were given straight away at the patient’s bedside. The cases were divided into three categories according to the level of certainty: level 1 close to the standard, level 2 and 3 evident but less stringent ; and level 4 (insufficient data) and 5 (define ‘no’). Five hundred and twenty-one patients were studied at the point-of-care and 34.6% were successfully classified as aseptic meningitis, encephalitis or ADEM using VACC-Tool. None of the cases was classified as myelitis. One hundred and ninety-four were a definite ‘no’. When applying the same algorithm to electronic health records retrospectively, 33 cases would have been missed, 38 cases would have been misclassified and 33 patients did not have important clinical data. By using ICD-10 coding, 116 cases of the 180 confirmed cases by VACC-Tool would have been missed. The most frequently missed was ADEM (89/116). Thirty-eight cases would have been classified as aseptic meningitis instead of encephalitis. The authors concluded by highlighting the successful implementation of VACC-Tool for the automated case classification of aseptic meningitis, encephalitis, myelitis and ADEM at the point-of-care. Obermeier P., Muehlhans S., Hoppe C., et al. Enabling precision medicine with digital case classification at the point-of-care, E Bio Medicine (2016).
Cytokines/chemokines—biomarkers of central nervous system (CNS) inflammation

Kothur et al. (2016) reviewed 83 studies on cytokines/chemokines and their role in the pathogenesis of neuroinflammatory disorders. Studies of viral encephalitis showed that cytokines and chemokines involved in Th1-mediated immunity were often elevated, the pattern of elevation depending on the type of encephalitis. For example, IFN-γ and TNF-α were prominently also elevated in herpes simplex encephalitis (HSE) and IL-1β was elevated in enterovirus encephalitis (EV). In HSE, the continuous cytokine elevation could imply the presence of persistent intrathecal immune activation in the CNS. In viral encephalitis, IFN-γ was elevated as part of T cell mediated viral control in the CNS. Studies on the role of cytokines in autoimmune encephalitis were limited. The available studies described a lack of IFN-γ elevation. Another finding was related to CXCL13, which could be considered a biomarker of the disease course, as it was increased in the early stages of anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis and relapses. In acute disseminated encephalomyelitis (ADEM), Th2 and Th17 cytokines were frequently elevated.

In a study conducted by Liba et al. (2016), CXCL10 and CXCL13 cerebrospinal fluid (CSF) levels were elevated in patients in the early stages of the illness with anti-NMDAR encephalitis and in patients with a severe course of this disease. These levels were also correlated with the presence of pleocytosis. The CSF levels of T cell-related cytokines (INFγ, TNFa and ILL17A) and IL15 were slightly elevated throughout the illness. The CSF BAFF levels remained unchanged. The authors concluded that their study showed that anti-NMDAR encephalitis was restricted to the CNS.

Michael et al. (1) (2016) investigated the relation between cytokines and associated mediators in serum and CSF and clinical disease severity, blood-brain barrier (BBB) permeability, neuroimaging findings and outcomes. The levels of 38 mediators in serum (78 samples) and CSF (37 samples) were measured. Patients were recruited prospectively from 24 centres. Markers of clinical disease severity were Glasgow coma scale (GCS) score (admission), Glasgow outcome scale (GOS) (discharge) and magnetic resonance imaging (MRI) findings for patients with herpes simplex virus (HSV) encephalitis. The ratio of CSF to serum albumin levels was used as a marker for BBB permeability.

The mediator most closely associated with the GCS score on admission was IL-10, the concentration of which was significantly higher in those with a normal GCS score (same finding for the subgroup of HSV encephalitis patients). The serum mediator associated most significantly with outcome was IL-1RA. Higher serum concentrations of IL-1RA were seen in those with a good outcome (same finding for the HSV encephalitis patients). The study also showed that in patients with a good outcome greater concentrations of the anti-inflammatory mediators IL-1RA and IL-10 were associated with lower concentrations of the pro-inflammatory mediators, IL-1α and IL-1β. Analysing the mediators associated with BBB permeability, the authors found that the CSF mediator with the strongest negative correlation with the ratio of CSF to serum albumin levels was IL-10. In patients with HSV encephalitis, temporal lobe volume had a positive correlation with serum IL-1α level and CSF VSF IL-1β level and a negative correlation with serum IL-1RA level. The conclusion of this study was that the balance between the IL-1 level and the level of its antagonists, IL-1RA and IL-10, was associated with clinical severity, BBB permeability and the volume of temporal lobes in HSV encephalitis.

The study by Michael et al. (2) (2016) of the characteristic cytokine and chemokine profiles in encephalitis of infectious, immune-mediated and unknown aetiology showed that cytokine/chemokine-mediated host response was different for infectious and immune-mediated cases. However, the unknown aetiology group was similar to the infectious cause group. Myeloperoxidase (MPO) concentrations were high in infectious encephalitis, both in serum and CSF compared with the ones in immune-mediated encephalitis. MPO was also high in serum of encephalitis cases of unknown origin. CSF concentrations of MPO correlated with CSF neutrophil count which could imply that CSF neutrophils may be the primary source of MPO identified. The authors suggested that MPO may be regarded as a biomarker for a potential infectious cause in patients with encephalitis. Differences in the concentration of other mediators between the aetiological groups were also noted (higher concentration of IL-8 in infectious and unknown origin compared with the immune-mediated). However, no substantial differences in the mediators’ concentration were found between the infectious and unknown origin.
Infectious encephalitis

"While great progress has been made in the treatment of this life-threatening infection, a majority of patients will not return to their previous neurologic baseline, indicating the need for further research efforts aimed at improving the long-term sequelaes." (Bradshaw and Venkatesan, 2016)

Herpes simplex virus 1 (HSV 1) encephalitis in adults: an overview

Bradshaw and Venkatesan (2016) presented an overview of HSV 1 encephalitis in adults considering epidemiology, pathophysiology, diagnosis, treatment, complications and outcomes. HSV 1 is the most common identified cause of sporadic encephalitis worldwide. HSV 1 is one of the eight human herpes viruses (HHV). HSV initially gains access to host tissues through mucous membranes or damaged skin. The mechanisms by which HSV gains access to the central nervous system (CNS) in humans are not well understood. Solfactory or trigeminal spread are possible routes of entry. There is a debate around herpes simplex viral encephalitis (HSVE) being a reactivation of a latent virus or caused by a primary infection. In support of the second theory, the authors noted that the viral strains responsible for encephalitis are different from the strain that causes herpetic skin lesions in the same patient in at least half of HSV cases.

Prodromal symptoms are common in HSVE and are associated with upper respiratory tract or other systemic infections. Symptoms of encephalitis develop over several days and include encephalopathy, fever, seizures, headache, and focal neurological deficits. HSV 1 in immunocompromised patients may present differently than in immunocompetent ones. Patients may lack prodromal symptoms or pleocytosis and can show brain involvement outside the temporal lobes.

A comprehensive history and medical and neurological examination are essential for a prompt diagnosis as they can eliminate other illnesses that mimic signs and symptoms of HSVE. Lumbar puncture should be performed in all patients if it is not contraindicated. Other laboratory studies include complete blood count, HIV testing, Mycoplasma pneumoniae and Epstein-Barr virus serologies (in children), opening pressure, cell count and differential, protein, glucose, Gram stain, oligoclonal bands, IgG index, bacterial cultures, HSV 1/HSV 2 polymerase chain reaction (PCR), varicella zoster polymerase chain reaction (VZV-PCR), enterovirus PCR, cryptococcal antigen or India ink staining, and Venereal Disease Research Laboratory test.

For diagnosis purposes and evaluation of the disease, magnetic resonance imaging (MRI) is preferred to the computerised tomography (CT) scan. MRI is abnormal in most of the patients with HSV 1 encephalitis with asymmetric hyperintense lesions on T2-weighted sequences corresponding to areas of oedema in the mesiotemporal and orbitofrontal lobes and the insular cortex. Diffusion restriction on diffusion-weighted imaging (DWI) is frequently seen early in the course of HSVE. Therefore, DWI changes in the temporal or frontal lobes could be a marker for the diagnosis of HSVE. Periodic discharges, focal or generalised slowing, and electrographic seizures, including status epilepticus (SE) are associated with electroencephalography (EEG) findings for HSV 1 encephalitis. Differential diagnosis can include other infections and autoimmune syndromes as well as vascular, toxic or metabolic disease, trauma, malignancy and nonconvulsive status epilepticus. Failure to recognise encephalopathy, absence of CSF pleocytosis and false-negative PCR studies can further complicate the diagnosis.

Initially, management of any emergent issues should take place, ideally on the neurological intensive care unit (ICU) if the patient presents with decreased level of consciousness, severe comorbidities and autonomic dysfunction. A multidisciplinary medical team should be involved. Empirical treatment with aciclovir and broad spectrum antibiotics should be commenced in all patients with suspected encephalitis. Aciclovir is the first-line treatment for HSVE (10 mg/kg/8h; 14–21 days). Very rarely in immunocompetent and, sometimes, in immunocompromised patients, there is a resistance to aciclovir. In this situation, foscarnet is preferred. The administration of corticosteroids in HSVE is not supported yet by the research. The authors argued that their experience is to administer corticosteroids in patients with significant oedema and mass effect.

Complications of HSVE include seizures and elevated intracranial pressure associated with brain oedema and herniation. Mortality is high if HSVE is not treated and post-encephalitis morbidities are frequent. The risk factors for a poor outcome are older age, coma at presentation, restricted diffusion on DWI and delay in aciclovir administration. Some patients may present with an apparent clinical relapse after completing treatment, usually less severe than initial illness. This relapse can be a viral relapse or an immune-mediated process. Many patients who relapse were recently found to have anti-N-methyl-D-aspartate receptor (NMDAR) antibodies. These patients respond well to immunotherapy, so it is essential for clinicians to be aware of this new entity. The authors concluded their review by highlighting the need to improve the diagnostic approach, to investigate the role of host immune response in the disease pathogenesis, to develop a vaccine and to improve the long-term outcomes.

Post-neurosurgery herpes simplex encephalitis (HSE) - a rare occurrence but rather challenging

Jaques et al. (2016) described three cases of post-neurosurgery HSE. They also undertook a literature review and identified 23 cases of postoperative HSE. There were no specific features regarding age, gender or type of neurosurgery among the patients. Only eight patients had a previous history of HSE. All documented patients were treated postoperative with steroids.

Diagnosing post-neurosurgery HSE appeared to be challenging as there were no specific characteristics to point to this diagnosis. Symptoms commenced both early (a few hours) and later after the operation (three weeks). MRI findings varied from typical findings in a few patients only (medial temporal lobe and insular involvement) to atypical and even normal findings. CSF analysis showed lymphocytic pleocytosis in most of the cases, but also normal findings in some others. HSV-1/2 polymerase chain reaction (PCR) proved to be the most accurate diagnosis test. The type of HSE was mostly HSV-1 with only two patients having HSV-2 encephalitis.

Regarding the pathogenesis of this entity, the authors discuss various hypotheses: primary infection by the time of surgery, relapse of previous herpetic infection with or without viral replication, surgical stress and trauma as well as corticosteroids as triggers for HSV reactivation postoperative and host factors (specific immunological defects) facilitating HSVE relapses.

Prompt accurate antiviral treatment was linked with the clinical outcome. Death or neurological sequelae were the outcomes in all non-treated patients, but only in 43% of all those treated. Full recovery was associated with initiation of treatment within two days of symptoms onset. The conclusion of this study is that clinicians should not disregard the possibility of post-operative HSVE despite the normal MRI findings and the rather long time (weeks) to the symptoms onset. The authors recommend that empirical treatment should be started in patients with a history of HSVE undergoing neurosurgery.


Aiding the diagnosis of herpes simplex encephalitis (HSE)

Gennai et al. (2016) undertook a multicentre retrospective case-control study in four French hospitals between 2007 and 2013 aiming to elaborate a clinical and paraclinical score which can estimate the probability of HSE in patients with febrile, acute neurological impairment. Thirty-six patients with confirmed HSE were compared with 103 patients with febrile acute neurological impairment without herpes simplex virus (HSV) detection by cerebrospinal fluid (CSF) polymerase chain reaction (PCR). They analysed demographic data, patient past medical history, clinical features at presentation, and biological and magnetic resonance imaging (MRI) findings.

The study found that the factors associated with a diagnosis of HSE were: absence of past neurological history (score 1), normal/high blood pressure (≥140 mmHg) (score 1), normal C-reactive protein (<10 mg/L) (score 2) and the presence of seizures (score 2). A total score of 6 was associated with a 71% risk of HSV encephalitis. The authors argued that, despite the study’s limitations, this score could help clinicians recognise HSE in patients with acute, febrile neurological impairment who need prompt antiviral therapy while waiting for the results of CSF PCR. However, this score must not replace the classic diagnosis methods such as HSV PCR on CSF or the antiviral therapy.


Enteroviruses (EV): severe neurological syndromes in children

Lee et al. (2016) characterised the neurological manifestations of EV 71 in a cohort of patients from Ulsan University Hospital (Korea). They looked retrospectively at the clinical features, magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) findings of 31 children with EV 71 associated with acute neurological manifestations. The median age of the patients was 2.9 ± 5.5 years. Regarding symptoms, 58.1% of the patients presented myoclonus, 54.8% lethargy, 54.8% irritability, 48.4% vomiting, 38.7% ataxia and 35.5% tremor. CSF analysis showed pleocytosis in 86.7% of the patients. MRI scan in 14/25 patients revealed increased T2 signal intensity in the posterior region of the brainstem and bilateral cerebellar dentate nuclei. Based on the clinical features, the patients were diagnosed as having brainstem encephalitis (21), meningitis (seven), encephalitis (two) and acute flaccid paralysis (AFP) (one). Thirty patients recovered completely and one died. The authors acknowledge the good prognosis for the patients in this study compared with other studies of EV 71 infection and explain this difference through particularities in the enterovirus 71 subgenotypes during epidemics, absence of medulla oblongata lesion on MRI findings, the treatment with IVlg and milrinone, environmental factors, and the ethnicity or genetic background.

Teoh et al. (2016) conducted a prospective study of 61 children with EV-related neurological disease at two hospitals in Australia. Symptoms included fever in all patients, myoclonic jerks in 86%, ataxia in 54%, and vomiting in 54%. MRI showed increased T2-weighted signal in the dorsal pons and spinal cord. Four patients died within several hours of presentation. The neurological manifestations were encephalomyelitis in 40%, brainstem encephalitis in 35%, encephalitis in 11%, acute flaccid paralysis in 7% and autonomic dysregulation with pulmonary oedema in 7%. Brainstem and motor dysfunction were resolved in 51 patients at 12 months followup. Long-term functional neurological morbidity of focal paressis linked to the involvement of gray matter in the brainstem and spinal cord was an outcome in five children. One child required invasive ventilation.

Brainstem encephalitis is a severe neurological manifestation of EV 71 and can often result in death. Zeng et al. (2016) aimed to establish if standardised histograms of signal intensities of T1 signal and T2 signal on sagittal view without enhancement during acute and convalescence stages of children with EV 71 brainstem encephalitis can provide diagnosis information. They analysed 25 cases in acute stage and 13 cases in convalescence stage and compared them with a healthy group of 25 children. The authors argued that their study found that the standardised histograms of T1 and T2 intensity can help to identify brainstem encephalitis patients and assess the severity of the disease which is of greater importance for saving the lives of these patients.

Recently, steroid-pulse therapy has been suggested for patients with EV 71 infection involving central nervous system aiming to reduce the severity of outcomes of this disease. Zhang et al. (2016) investigated the efficacy of high-dose steroid pulse
therapy in EV 71 encephalitis. Their cohort included 80 children with EV 71-caused hand, foot and mouth disease (HFMD). Half of the patients received steroid pulse therapy (high-dose methylprednisolone) when encephalitis or meningoencephalitis had developed. The course of the disease (the duration of fever and the length of hospitalisation), age, sex, weight, vital signs, laboratory tests and the outcomes between the steroids therapy group and the non-steroids therapy group were compared. The differences between these two groups were not statistically significant. The authors concluded that there was no evidence to sustain the steroids pulse therapy. Furthermore, the side effects of this therapy, which might aggravate the disease, should be considered. In this study the heart rate, respiratory rate, white blood cell counts and blood glucose were significantly higher in the steroids therapy group than the non-steroids therapy group.


Nonprimary West Nile virus (WNV) infection - a new clinical entity

The case of an 81-year old man with clinical picture of WNV encephalitis, very high WNV-specific IgG titers measured in serum and cerebrospinal fluid (CSF) (15-fold above the standard cut-off) and negative WNV-specific IgM in CSF and serum, led Rahav et al. (2016) to investigate the features of nonprimary WNV infection (NPI) and compared them with primary WNV infection (PI). Patients with confirmed PI were characterised by one of the following: the development of anti-WNV IgG between the acute and convalescent phases of illness in serum or CSF, the presence of anti-WNV IgM in CSF or the detection of anti-WNV IgM and IgG in serum or CSF with low serum WNV specific IgG avidity (<30%). Patients with possible PI had anti-WNV IgM detected in serum, with or without IgG. Patients with NPI had clinical manifestations of WNV infection with initial high levels of anti-WNV IgG (10-fold above the cut-off, or higher when performed during the first week of disease) and a high WNV-specific IgG avidity (≥55%).

One hundred and twenty-four patients from a hospital in Israel were included in this study. Seventy-one patients had PI and 53 patients had NPI. 97% of PI cases occurred during summer and autumn. 20% of NPI occurred during winter and spring. Fever was more often found in the NPI group than PI group. Patients with NPI had a significantly higher frequency of psychiatric and neurological comorbidities. The mortality rate in the NPI group was 20% compared with 9% in the PI group. Both groups had similar neurological sequelae. The authors discuss the two possible causes of NPI: persistent virus or reactivation of low-level persistent virus and reinfection by a different lineage. Regardless of the pathology, the authors highlighted the possibility of NPI being a new clinical entity with a high mortality rate.


Single case studies

• Carteaux et al. (2016) reported a case of Zika virus (ZIKV) infection associated with meningoencephalitis in an 81-year-old man, highlighting the possibility of meningoencephalitis associated with this virus.

• Soares et al. (2016) presented the first fatal case of ZIKV infection associated with encephalitis in a 47-year-old non-pregnant woman, concluding that ZIKV could be suspected as aetiological agent in cases of encephalitis in the endemic areas.

• Jacobs et al. (2016) reported a first case of late Ebola virus relapse causing meningoencephalitis. The authors emphasise the serious implications of this case: the possibility of relapse of thousands of Ebola survivors and furthermore the potential of spreading the disease.

• Verma et al. (2016) reported a case of rhombencephalitis associated with dengue fever emphasising the possibility of this diagnosis in endemic zone of dengue fever.

• Fong et al. (2016) described a case of enterovirus rhombencephalitis presenting with ocular flutter and truncal ataxia. The patient, a 23-year old male was initially treated for bacterial meningitis and viral encephalitis until PCR-CSF tested positive for enterovirus.


Acute disseminated encephalomyelitis (ADEM)

“Age-specific guidelines for ADEM diagnosis and treatment may be valuable, and vigilance for other, mostly rare, diseases is imperative.” (Koelman et al., 2016)

ADEM: distinctive features, outcomes and relapses

Koelman et al. (2016) conducted a retrospective multicentre study of the largest cohort of patients with ADEM (228) diagnosed at four hospitals in the USA. The patients were aged 1 to 72 years and 122 were children. There were 106 males. The majority of patients had an infection or vaccination less than four weeks before the onset of the illness. ADEM in adults was characterised by sensory abnormalities, elevated cerebrospinal fluid (CSF) protein, periventricular lesions and corpus callosum involvement. ADEM in children was associated with encephalopathy, fever, headache and nausea or vomiting.

In the patients with a final diagnosis of monophasic ADEM, magnetic resonance imaging (MRI) findings included spinal cord lesions (37%), brainstem lesions (54%), cerebellum/peduncle lesions (42%), infratentorial lesions (62%), deep gray matter lesions (42%), periventricular lesions (39%), corpus callosum involvement (34%) and other supratentorial lesions (85%). Pleocytosis was present in 71% of patients and CSF elevated protein in 53%. Treatment included steroids (188 patients), IV immunoglobulin G (IVIg) (37 patients) and plasma exchange (PLEX) (17 patients). Patients who required additional treatment with IVIg or PLEX had a low chance of a favourable outcome.

The patients were followed-up for a median of 24 months. The follow-up was longer in children than in adults and longer for patients who experienced a relapse than for those who didn’t relapse. Seven patients died. One hundred and fifty-six patients (72 adults and 84 children) had a monophasic disease course without any diagnostic revision at follow-up. Seventeen patients were given other diagnosis than demyelinating disease at follow-up. A relapsing demyelinating syndrome was experienced by 55 patients (31 children and 24 adults). The first relapse was reported within two years of initial presentation in 85% of patients. The risk of relapse was correlated with female sex, the absence of encephalopathy and fever at initial presentation and the presence of ataxia. Children with relapses were more often diagnosed with multiphasic ADEM and adults were more often diagnosed with multiple sclerosis (MS). Patients with multiphasic ADEM presented more often with fever, and encephalopathy than the patients with MS (no patient with MS presented with meningeal signs). The outcomes were more favourable in the multiphasic group than the MS group. The clinical utility of International Paediatric MS Study Group criteria was not evident in the adult population (only 47% of adult patients had diagnosis on initial presentations in line with these criteria). The authors concluded that future age-specific guidelines for management of ADEM may help the diagnosis and the treatment of this rare – sometimes relapsing – disease.


Single case studies

• Macerollo et al. (2016) described a case of ADEM in a pregnant woman with extensive, rapidly progressing bilateral white matter lesions needing decompressive craniectomy complicated by a concomitant asymptomatic Cytomegalovirus infection.
• Marziali et al. (2016) presented a case of ADEM following Campylobacter jejuni gastroenteritis in a 25-year-old male. MRI findings (hyperintense T2 signal with some areas of contrast enhancement in the deep and cortical white matter and spinal cord) in the early course of the disease could help clinicians make an early diagnosis.


Autoimmune encephalitis

"It is possible to proceed through a logical differential diagnosis of autoimmune encephalitis using criteria based on conventional clinical neurological assessment and standard diagnostic tests (MRI, EEG and CSF studies)"

(Graus et al., 2016)

**Diagnosing autoimmune encephalitis without or before antibody testing**

Graus et al. (2016) developed diagnostic guidelines for autoimmune encephalitis which are based on a practical syndrome-based diagnostic approach. Rather than rely on antibody testing and the response to immunotherapy, the guidelines recommend neurological assessment and more conventional tests that are widely available to clinicians. The aim of these guidelines is to enable clinicians to establish a quick initial diagnosis and commence treatment if necessary. The guidelines apply strictly to autoimmune encephalitis cases who present with subacute onset of memory deficits or altered mental status which may be associated with (not always) other symptoms. The authors recommend caution when applying them to children, especially children younger than five-year-old.

According to these guidelines, there are three levels of clinical evidence for autoimmune encephalitis: possible, probable and definite. For the first two levels, autoantibody status is not needed in most of the cases. However, antibody status is often needed for level three. Possible autoimmune encephalitis is characterised by the following features:

- subacute onset of working memory deficits, altered mental status or psychiatric symptoms
- at least one of the following: new focal central nervous system (CNS) findings, seizures not explained by a previously known seizure disorder, CSF pleocytosis, magnetic resonance imaging (MRI) findings suggestive of encephalitis
- reasonable exclusion of alternative causes

Autoimmune encephalitis can present as various clinical syndromes. Some of them have no recognisable features and their diagnosis relies on the antibody-testing. However, the authors argue that there are some autoimmune syndromes that can have a probable or definite diagnosis based on clinical manifestations and MRI findings, before the antibody-testing results are known. These include limbic encephalitis, acute disseminated encephalomyelitis (ADEM), anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis and Bickerstaff’s brainstem encephalitis. For each one of these syndromes the authors have developed criteria for both probable and definite diagnosis. Criteria were also developed for Hashimoto’s encephalopathy and probable autoimmune encephalitis antibody-negative (autoimmune encephalitis cases which do not fit within the recognisable syndromes).

Nevertheless, the authors argued that the detection of specific autoantibodies is very important in the management of many autoimmune syndromes. However, caution should be taken in differentiating between different antibodies (e.g. antibodies against neuronal cell-surface proteins and classic onconeural) and interpreting the results of the antibody testing.

Albert et al. (2016) investigated the role of imaging in diagnosing autoimmune encephalitis in children with and without anti-neuronal antibodies. Eighteen children were included in this study. Nine children had a definite diagnosis via antibody-testing: anti-NMDAR antibodies were present in five children and four patients had antibodies against glutamic acid decarboxylase 65 (GAD65). Seven of those with definite encephalitis and five of those with suspected encephalitis had abnormal MRI findings. The most prominent finding was increased T2 signal on fluid-attenuated inversion recovery images. Abnormal contrast enhancement was present in 54% of those with an abnormal MRI. Seven of the nine definite cases, and one of the suspected, had involvement (predominantly bilateral and asymmetric) of the limbic areas. Deep gray matter signal abnormality was reported in both definite and suspected cases. 81% of those who had an electroencephalography (EEG) had abnormal findings: abnormal background rhythm (63%), generalised slowing (50%), focal slowing (43%), and focal epileptiform discharges (31%). Abnormal sleep spindle abnormalities were found in 38% of the patients (a novel finding), however, delta brush patterns were not observed in any of the patients. The authors concluded that the majority of children with autoimmune encephalitis showed abnormalities on MRI or EEG. In definite cases, the MRI showed involvement of the limbic area is most cases, however, the EEG abnormalities were non-specific.

Baysal-Kirac et al. (2016) did not find any significant differences between EEG findings of patients with autoimmune epilepsy (with or without autoimmune encephalitis) with anti-neuronal antibodies and patients without antibodies. However, there were a few particularities for the antibody-positive group: the presence of non-convulsive status epilepticus or focal motor status epilepticus in a fifth of the seropositive patients, but not in the seronegative group; continuous theta and delta rhythms in 71% of the seropositive group compared to 24% of the seronegative group; frontal intermittent rhythmic delta activity pattern in 40% of the seropositive patients compared to 24% of the seronegative patients.

Wagner et al. (2016) investigated white matter changes by diffusion tensor imaging (DTI) in 14 patients with GAD-associated limbic encephalitis and compared them with 16 patients with VGKC complex antibodies. Age-matched control group data were also obtained. They found widespread changes of fractional anisotropy and all diffusivity parameters in patients with GAD antibodies, but preserved white matter integrity in those with VGKC complex antibodies. The authors argued that limbic encephalitis shows distinct imaging features depending on the associated antibody.
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Authors concluded that, overall, studies are combined (e.g. IVIg and steroids). The intravenous immunoglobulin (IVIg), are very rarely found. Immunotherapy—

Face, and less frequently, the leg. Tumours mainly the arm, the ipsilateral side of the movement with dystonic features involving a brief and very frequent involuntary is mostly associated with faciobrachial and treatment responses. This syndrome to symptomatology, immunopathology of anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis with regards to autoimmune LE who did not respond to first-line immunotherapy. The response to the rituximab might not depend on the antibody status. Regarding the safety of the drug, there were only infrequent severe adverse effects reported. Gastaldi et al. (2016) suggested in their study that intrathecal Rituximab administration could be more effective in reducing central nervous system (CNS) NMDAR Abs production.

Suppiej et al. (2016) investigated the protocol of using plasma exchange (PE) in the paediatric population by doing a systematic literature review of papers published between 2007 and 2015. Seventy-one articles met the inclusion criteria. In total, 242 children with anti-NMDAR encephalitis with ages between 1 and 18 years were reported as having PE. The time from the disease onset to initiation of immune therapy was 30 days or less in 57.1% of patients. PE was given with steroids and IVIg in 89/128 patients, with steroids only in 23/128 patients and with IVIg only in 9/128 patients. Only PE was given in 7/128 patients.

Compared with the order of other first-line immune therapy, PE was given after steroids and intravenous immunoglobulin (IVIg) in 54.6% of the patients, after only steroids in 23.5% or after only IVIg in 7.6%. In 14.3% of the children PE was given as the first choice. Regarding the second-line immunotherapy, PE was administered before them in 91.34% of the patients and after them in 8.5% of the patients (a third of these patients after a relapse). The follow-up after the first-line immune therapy showed a higher rate of full/substantial recovery in patients treated with PE, steroids and IVIg or PE and steroids compared to PE and IVIg or PE alone. After second-line immune therapy, the outcomes were similar with those of patients who received only first-line. The authors explained this finding through the fact that the second-line immune therapy was administered to patients with severe course of the disease. When considering the time to initiation of the immune therapy/PE, the outcomes were better in the patients treated early in the disease.

Serious side effects of PE were reported in six patients: transient hypotensive episodes (two patients), anaphylactic reaction (one patient), worsening of autonomic instability resulting in hypotensive shock (one patient), pulmonary artery thromboembolism (one patient) and non-tolerance (one patient) (the cause was not described). The authors concluded that more studies are needed to control the outcomes in subgroups of children receiving PE. However, their study showed that PE was increasingly used in paediatric populations, although the use of it varied greatly. The outcomes were better when PE was used with steroids and given early in the disease. In a case study by Miyauchi et al. (2016), the authors drew attention to the use of PE as first-line therapy in patients with autonomic instability due to the risk of hypotensive shock.


treatment outcomes of autoimmune encephalitis

Gastaldi et al. (2016) reviewed the treatment responses in adult patients with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis and voltage-gated-potassium-channel (VGKC) complex-related antibodies (LG1 antibody-associated limbic encephalitis). The treatment in anti-NMDAR encephalitis consists in tumour resection and immunotherapy and can result in a substantial improvement of patient’s condition. Options for first-line and second-line therapy are discussed. The authors highlighted the significant rate of prolonged recovery in these patients, even years following the treatment. Nevertheless, the risk of early or late relapses needs to be considered, even if, currently, there is no clinical or paraclinical predictive marker for relapses. A recent recognised entity is anti-NMDAR encephalitis following herpes simplex virus encephalitis (HSVE), characterised by choreoathetosis in children and behavioural/psychiatric features in adults.

The LG1 antibody-associated limbic encephalitis is a very different entity than anti-NMDAR encephalitis with regards to symptomatology, immunopathology and treatment responses. This syndrome is mostly associated with faciocervical dystonic seizures (FBDS) which consist of brief and very frequent involuntary movement with dystonic features involving mainly the arm, the ipsilateral side of the face, and less frequently, the leg. Tumours are very rarely found. Immunotherapy—

intravenous immunoglobulin (IVIg), steroids, plasma exchange (PLEX)—is beneficial, especially when these drugs are combined (e.g. IVIg and steroids). The authors concluded that, overall, studies showed a substantial improvement in these patients which can be a very good reason to use immunotherapy. However, each one of these syndromes requires a specific treatment protocol.

Lee et al. (2016) compared a group of 80 patients with autoimmune limbic encephalitis (LE) who received rituximab as second-line immunotherapy with 81 control patients. The patients were recruited from the Korea Autoimmune Synaptic and Paraneoplastic Encephalitis Registry. Thirty patients had synaptic autoantibodies, 15 had paraneoplastic and 35 were antibody-negative. Twelve patients had tumours for which they had surgery or chemotherapy. All patients had first-line immunotherapy. The patients from the first group with a median rituximab cycle of five weeks were followed up for 22.5±12.2 months. More functional improvement was noted in the rituximab group than in the control group. The authors concluded that rituximab is an effective second-line treatment for patients with autoimmune LE who did not respond to first-line immunotherapy. The response to the rituximab did not depend on the antibody status. Regarding the safety of the drug, there were only infrequent severe adverse effects reported. Gastaldi et al. (2016) suggested in their study that intrathecal Rituximab administration could be more effective in reducing central nervous system (CNS) NMDAR Abs production.
one neural-specific IgGs associated with autoimmune encephalitis detected in serum, cerebrospinal fluid (CSF) or both; the second group (12 patients) had at least three features associated with autoimmune encephalitis. Patients presented with subacute confusion or cognitive decline (13), seizures (12), craniofacial pain (five), personality change (four), myoclonic jerks (two), ataxic symptoms (two), coma (one), fever (one) and sensory problems (one). The time from initiation of symptoms to admission to ICU was a median of 4.5 weeks. Twelve patients were admitted directly to ICU from the Emergency Room. Initially, 10 patients had the diagnosis of autoimmune encephalitis before admission to neurological ICU, four were diagnosed with viral encephalitis and other three with rapidly progressing neurodegenerative dementia, vasculitis and vestibular neuritis.

Magnetic resonance imaging (MRI) was abnormal in 21 patients, the most common finding being T2-signal abnormalities suggestive of inflammation in 14 patients. Electroencephalography (EEG) was abnormal in 24 patients, but not specific for autoimmune diseases. CSF findings showed central nervous system (CNS) inflammation in 20 patients. Seven patients had been diagnosed with cancer and 12 patients had coexisting autoimmune diseases. The median stay in ICU was three days. Eleven patients had a prolonged ICU stay (longer than three days). Those with a longer stay presented with neurological or medical complications. Nine of them received immunotherapy: corticosteroids in seven with improvement in five; seven received plasma exchange with improvement in three and three received intravenous immunoglobulin with no improvement. Rituximab was administered in three patients, but only one patient improved.

At the follow-up, 10 patients died (six in hospital and four after discharge). Death in hospital was associated with severe encephalopathy, status epilepticus, sepsis, renal failure and metastatic cancer. Six patients had a mild or no disability, three had moderate cognitive disability and six had dementia. Despite the severity of the course of the illness in this cohort of patients, nearly a third of them had a very good recovery. The authors concluded that autoimmune illness needs to be considered when a patient is in ICU with subacute severe encephalopathy or encephalitis. Immunotherapy should be started before the antibody-testing results are confirmed and even if the patient does not present with the classical syndrome. However, the risk of infection is high.


**Voltage-gated potassium channel (VGKC) antibodies testing versus anti-leucine-rich glioma-inactivated protein 1 (LG1)/anti-contactin-associated protein-like (Caspr2) antibodies testing**

van Sonderen et al. (1) (2016) raised the question of clinical relevance of VGKC positivity and suggested that the term ‘VGKC complex antibody’ should be abolished. Patients with VGKC positive can be divided among three very distinctive subgroups: those with anti-LGI1 antibodies, mainly limbic encephalitis cases characterised by hyponatremia and faciobrachial dystonic seizures (FBDSs); those with Caspr2 antibodies which can cause a more variable syndrome of peripheral or central nervous system symptoms; and the third group—patients with VGKC antibodies, but without LGI1 or Caspr2 antibodies, with a wide variety of clinical syndromes.

In a study (van Sonderen et al. (2), 2016) of 50 VGKC positive patients, 25 had anti-LGI1 and Caspr2 antibodies and 25 lacked both antibodies. Only 28% of those without anti-LGI1 and anti-Caspr2 antibodies had evidence of autoimmunity (mainly patients with encephalitis/encephalomyelitis). In a VGKC negative patients control group, 18% had evidence of autoimmunity. Anti-LGI1 and anti-Caspr2 antibodies patients had higher VGKC titers, however, CASPR2 antibodies were also found in patients with low titers of VGKC.

Graus and Gorman (2016) also argued that the VGKC antibodies test should be replaced by the more specific LG1 and Caspr2 antibody tests in order to speed up and improve the accuracy of the diagnosis and treatment and avoid the unnecessary cancer screening and immunotherapy.


**Caspr2 antibody associated disease: clinical spectrum**

van Sonderen et al. (2016) conducted a large study of 38 patients with Caspr2 associated-disease to investigate the clinical spectrum of this condition. Thirty-four patients were male and the median age of the onset of the symptoms was 66 years. Patients presented with well-established spectrum of symptoms: cognitive disturbance (26%), seizures (24%), peripheral nerve hyperexcitability (21%) and neuropathic pain (21%). Other symptoms during the course of the disease included sleep disorder, pain, weight loss, autonomic dysfunction and cerebellar symptoms. The most common clinical phenotypes were limbic encephalitis in 16 patients and Morvan syndrome in 11 patients. Caspr2 antibodies were present in serum in all patients. Seven patients had a tumour: thymoma (four), adenocarcinoma of the lung (one), carcinoma in situ of sigmoid (one) and thoracic mass without pathologic diagnosis (one).

The clinical manifestations and the disease course were often less rapid than in other autoimmune encephalitis. Treatment included IVlg, steroids, plasma exchange or a combination of those and surgery or chemotherapy for those with tumours. In addition to this initial treatment, one patient had azathioprine and seven patients had cyclophosphamide or rituximab. Two patients were not treated (one died and one refused treatment). Of those treated, nine patients had a full recovery, 12 patients a partial recovery and two patients did not respond to immunotherapy. Four patients died, case fatality being 3% after initial treatment and 10% after two years.

Relapses occurred in 25% of patients up to seven years from the initial symptoms. In some cases, they presented with different symptoms than the initial illness. In almost half of the relapses, this was the time when the initial diagnosis was established. The authors concluded that recognition of the Caspr2 associated syndromes (which have recognisable features) is crucial for the management of these patients as the conditions are treatable with prompt immunotherapy and tumour therapy.

LGI1 antibody limbic encephalitis: clinical characterisation

Navarro et al. (2016) reviewed the clinical records of 34 patients with LGI1 antibody encephalitis. The antibody was present in serum and/or CSF. There were 19 males and 15 females with ages between 21 and 81 years. The time from symptom onset to diagnosis ranged from 0.2 to 13 months (4.4 median). In the first month of encephalitis three distinct clinical symptoms were reported: tonic-dystonic seizures (TDS) in 11 patients, a distinct pattern of epileptic seizures mainly involving temporal lobe in 13 patients and cognitive impairment in 19 patients. The authors suggest that the origin of these symptoms was cortical. Cortical regions involvement changed as the disease progressed. Over time, TDS occurred in 22/32 patients, temporal lobe epilepsy in 29/32 and cognitive impairment in 30/32 of patients. Other symptoms were sleep disturbances (12 patients), mood changes (15 patients) and autonomic system disturbances (two patients).

Hyponatremia was reported in 2/9 patients presented without major cognitive impairment and 18/20 of patients with cognitive impairment. Tumours (lung and kidney) were found in two patients. Magnetic resonance imaging (MRI) was abnormal initially in 21/31 (unilateral and bilateral hippocampal hypersignal). Subsequent MRIs showed abnormalities in 21/31 (unilateral hippocampal hypersignal, bilateral hippocampal hypersignal and hippocampal sclerosis). Electroencephalography (EEG) was abnormal in 24/32 patients showing focal or diffuse slowing (20) and seizure activity (17). The authors concluded that their study showed that, in LGI1 LE, the motor cortex is another target beside the temporal lobe. Firstly, the illness involves one area and then, in the absence of immunotherapy, it moves to the second area in days to months. Early recognition of TDS or the involvement of temporal lobe via temporal lobe seizures or specific cognitive deficit can facilitate an early diagnosis and initiation of immunotherapy.

Gao et al. (2016) retrospectively investigated the characteristics of LGI1 autoimmune encephalitis in 10 patients. Their age was between 27 and 75 years, and there were more males than females (7/3). Initial clinical manifestations included memory impairment (seven), generalised tonic-clonic seizures (two) and visual hallucinations with mental and behavioural changes (one). There was a high rate of misdiagnosis; the time from the initial symptoms to correct diagnosis was one to eight months. All patients had brief faciobrachial dystonic seizures (FBDS) whose frequency was very high in half of the patients, but only rare in the other half. The FBDS developed after the onset of memory impairment. Eight patients had hyponatremia (intractable in three patients). No tumours were detected in any of the patients. Anti-LGI1 antibody was found in serum of all patients and CSF of nine patients. EEG was abnormal in all patients (generalised background slowing, associated sometimes with slow wave and temporal sharp wave). MRI showed abnormalities in the hippocampal or medial temporal lobes in eight patients. Single-photon emission computed tomography (SPECT) performed in three patients showed abnormal glucose metabolism in basal ganglia.

Seizures in patients with frequent FBDS did not respond well to anti-epileptic drugs (AED) until immunotherapy was commenced. One patient was treated with corticosteroids and in the other nine patients corticosteroids were associated with IVIg. In all patients symptoms improved after immunotherapy. At the follow-up (10 months), one patient died and the other patients had mRS scores of 0–2 (mRS scores on first day of hospital were ≥3). The authors concluded by stressing the importance of an early diagnosis and immunotherapy.

Li et al. (2016) conducted a study of 10 patients with anti-LGI1 LE. In all their patients the initial symptom was epileptic seizures. At onset, four patients had very frequent FBDSs, four patients had complex partial seizures and four had generalised tonic-clonic seizures. Three patients developed FBDSs in the course of disease progression. Memory impairment developed in four patients 0.5 to six months after seizure onset. Lung cancer was found in one patient.

MRI was abnormal in four patients: T2/ fluid-attenuated inversion recovery (FLAIR) hyperintensity and evidence of edema in the right medial temporal lobe (one), left hippocampal atrophy (one), hyperintensities in the bilateral medial temporal lobes (one), and hyperintensities in the basal ganglia and
frontal cortex (one). Inter-ictal VEEG showed normal patterns, focal slowing, or sharp waves in the temporal or frontotemporal lobes. Ictal VEEG in three patients revealed diffuse voltage depression preceding FBDS, a left frontal/temporal origin, and a bilateral temporal origin. CSF was positive for anti-LGI1 antibodies in seven patients and serum in all. Hyponatremia was reported in five patients.

All patients received AEDs with poor responses. Nine patients were treated with IVIg followed by prednisone in eight patients. One patient was treated only with prednisone. Immunotherapy administered between 0.5 to 1.5 months from seizure onset resulted in good improvement regarding seizures management and cognitive deficits. The authors concluded by suggesting that this diagnosis should be considered in adults with sudden mesial temporal origin, unexplained, and drug-resistant seizures with or without cognitive deficits.


Imaging in anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis

Lagarde et al. (2016) reported cerebral FluoroDeoxy-Glucose Positron Emission Tomography (FDG-PET) findings in six children with anti-NMDAR encephalitis. The FDG-PET performed during the acute phase showed brain metabolism alteration in all six patients with extensive, symmetric cortical hypometabolism especially in posterior areas; asymmetric anterior focus of hypermetabolism; and basal ganglia hypermetabolism. The FDG-PET performed at follow-up, after the end of first-line of treatment, showed metabolism improvement in five patients (who also showed clinical improvement) and worsening in one patient (who also showed clinical worsening) suggesting a relation between clinical severity and the degree of brain metabolism alteration. The authors noted the inherent risk of ionising radiation when using FDG-PET in children.

A correlation between brain metabolism changes, clinical course and level of antibody in patients with anti-NMDAR encephalitis was the conclusion of a study by Yuan et al. (2016). Their study of eight patients analysed 18 serial positron emission tomography (PET) scans taken in various stages of the illness: acute and subacute; early recovery; recovery and relapse. In the acute and subacute stage, a severe hypometabolism in bilateral occipital lobes and relatively mild hypermetabolism in the partial frontal and basal ganglia was correlated with the high level of antibody. In the early recovery phase extensive cortical hypometabolism was associated with a partial improvement of the symptoms and a low level of antibody. In the recovery phase there were no obvious neurological and psychiatric symptoms, PET images were nearly normal, and the antibodies tests were all negative. Finally, the relapsing stage in three patients was characterised by heterogeneous brain metabolic abnormalities.

Foff et al. (2016) aimed to determine if electroencephalographic (EEG) characteristics, beta:delta power ratio (BDPR) were a marker for anti-NMDAR encephalitis. They compared 10 patients with anti-NMDAR encephalitis with five patients without anti-NMDAR encephalitis. The anti-NMDAR encephalitis group had a higher median log BDPR than the non-encephalitis group. The authors argued that these findings may suggest that BDPR could be a marker of this condition, however, further studies are needed to investigate this theory.

Chanson et al. (2016) reported a case of anti-NMDAR encephalitis who presented with generalised rhythmic delta activity (GRDA) and extreme delta brush (EDB) on EEG and clinically subtle paroxysmal and intermittent myoclonic and tonic movements. She was intubated due to severe autonomic dysfunction and disturbed consciousness. Non-convulsive status epilepticus (NCSE) was suspected. However, the intracranial pressure was not raised and the anti-epileptic drugs had no effect. This prompted the decision to stop the sedation and awake the patient. EEG rhythmic activities disappeared and the patient started to improve. The authors performed a literature review and found 11 similar cases of NCSE. Five of these cases had the diagnosed dismissed. The authors concluded that, sometimes, the incidence of NCSE in anti-NMDAR encephalitis cases may be overrated. Video EEG and other more invasive techniques may be necessary for an accurate diagnosis.


Novel types of antibodies: anti-glutamic-acid-decarboxylase 65 (anti-GAD65) and neurexin-3α

Although limbic encephalitis is a well-established type of encephalitis, limbic encephalitis (LE) associated with GAD65 antibodies is newly recognised. Gagnon and Savard (2016) reviewed the published articles on LE associated with anti-GAD65 antibodies aiming to provide an overview of this condition. Thirty-one articles described 58 cases. There were 37 adults and 21 children. Overall, females were predominant (59%), however, among the children, there were more boys than girls (12/9). Systemic autoimmune disorders were frequent (48%) and included diabetes, psoriasis, common variable immune deficiency, celiac disease and autoimmune thyroiditis. Cancer was found in six patients (all men) and included small-cell lung carcinoma and malignant thymoma. Half of these patients had concurrent antibodies.

Clinical manifestations included seizures (97%) with status epilepticus (generally refractory) in 24%, cognitive impairment (memory, language, orientation, executive function, attention/concentration, praxia and confabulation) (66%), psychiatric symptoms (depression, changes in behaviour and personality, psychomotor agitation, perception disorder and anxiety) (28%), fever (14%), dysautonomia (12%), cerebellar manifestations (7%) and headache (5%). Radiologically, magnetic resonance imaging (MRI) was abnormal in 78% of patients and electroencephalography (EEG) in 72/35 cases, both, usually with temporal involvement. Multifocal abnormalities were also reported on MRI (16%) and EEG (7%). Lumbar puncture...
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Gresa-Arribas et al. (2016) report a new type of autoimmune encephalitis associated with antibodies against neurexin-3a which is a cell adhesion molecule with an essential role in synapse development and function. They describe five patients (four female and one male) aged 23–50 years. They presented with fever, headache, nausea or diarrhoea which progressed rapidly (days) to confusion, decreased level of consciousness and seizures. Myoclonic jerks were present in one patient and mild orofacial dyskinesias reported in two patients. Four patients had a history or findings of systemic autoimmunity. Moderate pleocytosis was found in four patients and elevated immunoglobulin G index found in one patient. MRI was normal in four patients and one patient had increased fluid-attenuated inversion recovery T2 signal in the medial temporal lobes.

Treatment consisted in steroids in all patients and additional IVlg in one patient and cyclophosphamide in one patient. Two patients died, the other three had partial recovery at follow-up (two, 24 and 26 months). There were no signs of CNS infection identified at autopsy: brain edema but no inflammatory cells (one patient), subarachnoid haemorrhage (second patient who died of sepsis). Antibodies that reacted with the neuropil of rat brain were found in the blood and CSF in all patients. Immunoprecipitation, and mass spectrometry and cell based assay confirmed that the target was neurexin-3a. Following more investigations, the authors found that the patients’ antibodies caused a reduction of neurexin-3a which decreased the total number of synapses in neurons undergoing development. The authors conclude by emphasising the necessity of further studies of more patients with this new clinical entity (which mimics anti-NMDAR encephalitis), but nevertheless the findings of this study are the first steps in understanding this condition.


Hashimoto's encephalopathy (HE)

“Clinicians should be aware of the possibility of HE in all patients with history or evidence of thyroid dysfunction and concurrent neuro-psychiatric manifestations poorly responsive to standard psychotropic treatment.”

(Vivek et al., 2016)

Different presentations and outcomes of treatment

Hashimoto’s encephalopathy is a poorly-understood disorder whose symptoms can mimic other conditions. It is often associated with increased anti-thyroperoxidase antibodies (TPOAb) in serum and sometimes in cerebrospinal fluid (CSF). Montagna et al. (2016) performed a literature research on this condition and presented an overview of this condition. HE is more frequent in females than in males (4/1). One fifth of the reported cases are children, but it can present at any age. Generally, it is a relapsing and remitting condition. According to clinical manifestations, two types were described: a vasculitic type with repetitive stroke-like episodes (hemiparesis, aphasia, ataxia) and an indolent progressive type with insidious onset of dementia, seizures, hallucinations, psychotic episodes or altered consciousness. Both types can also present with seizures, stupor, tremor and myoclonus. Systemic symptoms (malaise, fever and fatigue) and peripheral nervous system symptoms (polynueuropathy, ganglionopathy, chronic inflammatory demyelinating polyneuropathy and myelopathy) have also been reported. HE can sometimes manifest with psychiatric symptoms as initial symptoms. However, the clinical manifestation most specific to HE is the non-specific encephalopathy with alteration of mental status and consciousness.

Regarding the pathogenesis of HE, various hypotheses have been proposed with an autoimmune aetiology predominance and a role of a marker of autoimmunity, rather than being the cause of the disease for antithyroid antibodies. Usually, the patients have thyroid dysfunction or have a history of a thyroid disease. TPOAbs are normally found in blood (86–100% of cases). Cerebrospinal fluid (CSF) analysis may show elevated protein concentration, anti-thyroid antibodies, lymphocytic pleocytosis, oligoclonal bands or elevated Ig synthesis. Electroencephalography (EEG) shows mild to severe generalised slowing in 85–98% cases. Magnetic resonance imaging (MRI) may be normal or can show various abnormalities such as focal or confluent white matter lesions, bitemporal symmetrical hippocampal lesions with focal edema (in patients with seizures), focal hypertensity or volume depletion of the nucleus accumbens, frontal white matter changes, cerebellar atrophy and hippocampal and periventricular lesions (in children). HE is a diagnosis of exclusion from a wide range of conditions such as central nervous system (CNS) infections, metabolic encephalopathy, structural lesions, CNS vasculitis, toxins, acute disseminated encephalomyelitis (ADEM), autoimmune encephalopathies and neurodegenerative disorders.

Treatment includes steroids and oral prednisone to taper off slowly, either as monotherapy or together (intravenous followed by oral), treatment for dysthyroidism and anti-epileptic drugs. Other immunomodulator drugs have been used when prednisolone treatment failed or reduction of dose was required such as azathioprine, methrotrexate, cyclophosphamide or rituximab. Second-line treatments with intravenous immunoglobulin (IVlg) and plasmapheresis were also reported.

The long-term prognosis is good if the condition is treated. Studies showed that up to 91 % of patients have improved. Younger adults were found to have a good response to steroids and a marked improvement, whilst older patients were more prone to have a progressive form of the disease with a poor response to steroids.

The authors argued that HE should be suspected:

- in patients with rapidly progressing dementia
- in patients with psychiatric symptoms with an atypical presentation associated with a thyroid disorder and/or a response to treatment.

The authors concluded that the triad of encephalopathy, electroencephalographic slowing and increased protein content in CSF should prompt testing for anti-thyroid antibodies in blood and CSF, regardless of thyroid function.


Rasmussen's encephalitis (RE)

"Hemispherotomy achieves good seizure control with cognitive improvement and ambulatory status post-operatively."
(Hoffman et al., 2016)

Treatment and neuronal antibodies

Hoffman et al. (2016) conducted a retrospective chart review of 13 consecutive children diagnosed with RE over a period of 30 years. There were six boys and seven girls with a median age of 10.6 years. Three children had simple partial seizures and 10 children had complex partial seizures. Immunotherapy (intravenous immunoglobulin-IVIg, rituximab, prednisone or plasma exchange) was administered in nine patients. The immunotherapy did not have any sustained benefit regarding seizure control, but two patients experienced treatment-related morbidity. Further on, six of the patients had functional hemispherotomy (FH), one had biopsy only, one vagal nerve stimulator and one had amygdalohippocampectomy (AHC) followed by FH three years later. The patients who did not receive immunotherapy had FH (three) and AHC (one). Two patients who did not qualify for surgery were young adults (aged 18 and 16) with minimal cognitive decline and non-progressive or infrequent seizures.

The patients who underwent surgery were followed-up for a median of 5.6 years. Seven patients became seizure-free and four had a significant seizure reduction; 10 patients improved their cognitive functioning and one remained stable. All patients were ambulatory and none of the patients in the non-dominant group experienced language deficits post-surgery. In the dominant group (six patients), five patients improved their language and the patient with normal language before surgery remained normal. Magnetoencephalography (MEG) proved to be useful in assessing the suitability for surgery, contributing to a decrease of latency to treatment. The authors argued that their study proved that hemispherotomy is beneficial for patients with RE by reducing seizures and improving cognitive decline and language dysfunction, even if performed late. They recommended early hemispherotomy to prevent further functional and cognitive decline.

Nibber et al. (2016) investigated if patients with RE have antibodies to neuronal antigens. Samples serum from 52 patients with RE were tested by cell-based assays for antibodies to AMPAR GluA1/2/3, NMDA receptor, GABA_A_R and GABA_B_R receptors, potassium channels complex protein and for binding to live cortical and hippocampal neuronal cultures. In two patients, they identified Abs to AMPAR, bound only when GluA2 and GluA3 were co-expressed together. These two patients had a typical course of the disease. In eight other patients, including one patient with low level of VGKC-complex Abs, sera bound to hippocampal neurons in culture, but only one to cortical neurons. The authors suggested that these antibodies may not play a primary role in the disease, rather a marker of a neuronal damage influencing disease activity and progression. However, there is a need for further studies to investigate this role.


Viral encephalitis and autoimmunity

“More cases of anti-NMDAR encephalitis may be associated with HSV type 1 than currently recognised using CSF PCR only.”

(Ellul et al., 2016)

Herpes simplex encephalitis (HSE) and anti-N-methyl-D-aspartate receptor (NMDAR) antibodies

Westman et al. (2016) investigated the proportion of HSE patients who developed anti-NMDAR antibodies in the first three months of the disease and also how their positivity correlated with their cognitive performance at onset and during a 24-month follow-up. Forty-nine patients with HSE from a valacyclovir study were included. The patients were ≥12 year-old with clinical signs of encephalitis and evidence of HSV in cerebrospinal fluid (CSF). They had been treated with acyclovir for 14-21 days followed by oral valacyclovir or placebo for three months. In the initial stage of disease none of the CSF (31 samples) or serum samples (35 samples) tested positive for anti-NMDAR antibodies. During the study, 12 patients (24.5%) developed anti-NMDAR IgG: two CSF samples were positive after acyclovir treatment and 11 CSF samples and two serum samples were positive at three months’ follow-up.

The cognitive performance was significantly less improved from baseline in the antibody-positive group than the negative group. However, at the end of follow-up (24 months), there was no difference between the two groups as regarding the Mattis Dementia Rating Scale (MDS) and Mini–Mental State Examination (MMSE) total score. The authors argued that the NMDAR autoimmunisation is a part of the inflammation and develops during the course of HSE. It may also contribute to the long-lasting, persisting neurocognitive symptoms after HSE. This needs to be considered in the future treatment approaches as CNS autoimmunity responds well to immunotherapy.

Single case studies

• Phan et al. (2016) reported the presence of a new densovirus called human CSF-associated virus (HuCSFDV1) in the CSF of a six-year-old girl with a second episode of encephalitis. The girl presented with altered mental status, aphasia, facial droop and hemiplegia. CSF was positive for anti-NMDAR antibodies. Treatment with high-dose steroids and rituximab followed by seven weeks inpatient rehabilitation resulted in improvement. Twenty months later the girl had the third episode of encephalitis with seizures, pleocytosis and MRI changes after which she returned to baseline without treatment. The replication, pathogenicity and alternative explanations for the detection of this virus DNA in CSF are discussed, however its role and cellular origin remain unknown.

• Niehusmann et al. (2016) report a 25-year-old man with new-onset epilepsy and psychotic syndrome who had anti-GAD antibodies in serum and CSF and a positive serum and CSF-polymerase chain reaction (PCR) for human herpes virus (HHV) 6B. They raise the possibility for HHV-6B infection to be a trigger for nonparaneoplastic form of limbic encephalitis.

• Ellul et al. (2016) report a case of a three-year-old child with anti-NMDAR encephalitis and evidence of HSV-1 infection on brain biopsy. The authors believe that the boy had mild HSV1 encephalitis four weeks prior to admission although he did not have the features of severe clinical HSE. At admission, he had a secondary anti-NMDAR encephalitis syndrome. They argued that this case suggested that some patients with anti-NMDAR encephalitis may have a preceding subtle HSV1 infection which may be the trigger for the autoimmune process.


Improving the management of encephalitis

Cooper et al. (2016) conducted 30 narrative interviews with people who have been diagnosed with herpes simplex virus (HSV) encephalitis and their relatives regarding their experience and views on the diagnosing and hospital care in the acute stage of their illness. Half of the participants (55%) reported that, at the onset of the illness they knew that was something seriously wrong for the individual affected, something that was outside their ‘normal’ character or behaviour. However, when they tried to get help from various professionals (e.g. GP, NHS helpline, walk-in centres, emergency departments), some of the participants (31%) had their symptoms attributed to most common and non-urgent conditions, such as flu, rather than to a serious condition such as encephalitis. This made people think that they were not heard or taken seriously by the professionals. It resulted in them having to try to persuade doctors by making multiple phone calls, hospitals visits, demanding investigations, refusing to leave until investigations were done or, sometimes, to directly suggesting to health professionals the possibility of being HSV.

Whilst in hospital, 66% of participants admitted that the care received was not suitable to their needs: inappropriate care environments (people were treated on general wards with non-specialist staff), communication gaps (no information about encephalitis, treatment or outcomes); care deficiencies (treatment with acyclovir was stopped without explanation, tests results were delayed or mixed up, medical complications unnoticed or untreated). This resulted in family needing to get involved in the care of their relative by (e.g. searching the internet, reading books) and about their relative (patient medical notes) that she felt she was taken seriously, her family (three full pages of handwritten examination of the patient and consulted one doctor undertook a thorough examination of the patient and consulted her family (three full pages of handwritten notes) that she felt she was taken seriously, which led to her being diagnosed with anti-NMDAR encephalitis.

Some of the types of encephalitis have established treatment protocols with good outcomes, so it is essential to recognise the signs, symptoms, laboratory and radiological findings for a prompt and accurate diagnosis. Piquet and Cho (2016) reviewed the clinical approach (diagnosis and treatment) to managing several types of encephalitis: encephalitis caused by viruses (herpes viruses, arboviruses, enteroviruses) encephalitis caused by bacteria (listeria, tuberculosis, Mycoplasma) and encephalitis caused by autoimmune diseases (acute disseminated encephalomyelitis and autoimmune encephalitis mediated by specific autoantibodies). Although more diagnosis advances are required, the clinical approaches described in this study may help identify these types of encephalitis.


The role of imaging in the early management of encephalitis

Granero et al. (2016) investigated the role of imaging in the early management of encephalitis. They examined 85 computerised tomography (CT) from 68 patients and 101 magnetic resonance imaging (MRI) scans of 80 patients. The examiners (three neuroradiologists) were blinded to patient and clinical details. The patients represented suspected encephalitis cases enrolled in the Prospective Aetiological Study of Encephalitis conducted by the Health Protection Agency (now Public Health England). The sensitivity was high in cases of herpes simplex virus (HSV) encephalitis (especially in adults) for both MRI and CT (80%). The sensitivity for the MRI scan 3–10 days after the onset of the symptoms was 100% in HSV encephalitis cases. In acute disseminated encephalomyelitis (ADEM) cases, the sensitivity was low (20% for MRI). The level of agreement among examiners was measured using kappa statistic. Agreement among examiners was high for HSE and poor for ADEM and good for CT, but moderate for MRI. In patients with suspected encephalitis or encephalitis of unknown cause, the
agreement was also poor. High agreement was noted when observing abnormalities in temporal and frontal lobes (corresponding with the high agreement in diagnosing HSV encephalitis).

The authors concluded that there was a subjective component to scan interpretation which may need to be considered by clinicians when managing encephalitis patients. The diagnosis of encephalitis is complex and needs to include clinical manifestations, radiological findings and laboratory test results for each patient.


Improving the speed and accuracy of diagnosis of encephalitis

Guan et al. (2016) used next-generation sequencing (NGS) to detect viral infections in cerebrospinal fluid (CSF) of four patients with suspected viral meningoencephalitis. They detected herpes simplex virus-1 (HSV-1) in the CSF of two patients, HSV-2 in one patient and human herpes virus-3 (HHV-3) in the other patient. The number of unique reads of the identified viral genes ranged from 144 to 44,205 and the coverage of identified viral genes ranged from 12% to 98%. They validated the NGS results by using polymerase chain reaction (PCR) analysis in three cases (there was no CSF sample available after NGS for the fourth patient). The authors concluded by highlighting the importance and feasibility of using NGS in diagnosis CNS viral infection.

Wong et al. (2016) aimed to speed up the diagnosis of CNS viral infection using HSV and varicella zoster (VZV) and increase the sensitivity and specificity for detection of HSV/VZV by replacing DFA/culture with a multiplex realtime PCR. The multiplex assay showed increased specificity and sensitivity than the culturing techniques. It was more rapid and involved lower costs than two single plex real-time PCR for the detection of common pathogens found in lesion swab and CSF. Another value was that it was more accurate at genotyping. Also, a smaller volume of CSF was needed. One interesting finding of a study of a large data set of samples taken over 18 months was that HSV-1 was nearly as often found in the genital lesion samples as HSV-2. The authors argued that these findings provided evidence for the value of a multiplex assay in diagnosing the presence of viruses which may not be presumed according to clinical manifestations. Rapid diagnosis means early treatment and, furthermore, better outcomes.

Shi et al. (2016) developed a multiplex PCR Mag-Array (MPMA) system which integrated three strategies: chimeric primer design, temperature switch PCR and MagPlex-TAG techniques. Fragments of the specific genes from 13 selected viruses were used. One hundred and seventy-seven CSF samples were analysed. The results were confirmed using the new multiplex system. The positive rate of MPMA detection for all 177 CSF samples was validated using sequencing and Elisa detection. The overall concordance between the MPMA system and DNA sequencing was 96.05% (170/177) with 100% sensitivity and 98.78% specificity for HSV-1, 100% and 98.22% for HSV-2, and 100% and 99.43% for CMV, VZV, and EB, respectively. However, there was a discordance when compared to ELISA results, the sensitivity of the MPMA system being 14.2% for HSV-1, 30% for HSV-2, and only 20% for EB. The authors concluded that the new MPMA system provided high specificity, throughput and rapid detection in detecting 13 associated-meningoencephalitis cases and also for pathogen screening and routine surveillance of CNS infection.

The FilmArray Meningitis and Encephalitis Panel (MEP, BioFire Diagnostics/Biomerieux, Salt Lake City, UT) was developed to allow rapid, simultaneous, PCR-based detection in CSF of 14 targets (six bacteria, seven viruses, and a yeast) capable of causing CNS infections. Messacar et al. (2016) compared MEP retrospectively with conventional diagnostic methods to assess its performance, looking at diagnostic yield, time to diagnosis and potential clinical impact. CSF samples of 138 children with suspected or confirmed CNS infection were used. There was an agreement for 100% target by MEP. Out of negative samples tested, there was an agreement for 100%.

Graf E.H, Farquharson M.V., Cárdenas A.M. Comparative evaluation of the Film Array meningitis/encephalitis molecular panel in a pediatric population. Diagnostic Microbiology and Infectious Disease 2017; 87: 92–94.


Post-encephalitis sequelae—what is the true extent?

Granerod et al. (2016) investigated the rates of the consequences of encephalitis in individuals attending primary care practices in the UK. Their retrospective study included 2,460 exposed individuals diagnosed with incident encephalitis in the Clinical Practice Research Datalink and 47,914 individuals without a history of encephalitis but matched by age, sex and GP to the ones with a history of encephalitis. This is the largest ever study to investigate the consequences of encephalitis and the first to compare rates of specific consequences between encephalitis patients and general population. The median length of follow-up was 3.5 years for the encephalitis group and 4.5 years for the non-encephalitis group. Most participants (60%) were 20–65 years old. There were slightly more females than males (53%/47%). Depressive disorders occurred in 15% of the encephalitis group (10% of the non-encephalitis), headache in 10% of the encephalitis group (7% of the non-encephalitis), anxiety disorders in 8% of the encephalitis group (7% of the non-encephalitis), epilepsy in 7% of the encephalitis group (0.2% of the non-encephalitis), cognitive problems in 5% of the encephalitis group (2% of the non-encephalitis group), dementia in 2% of the encephalitis group (1% of the non-encephalitis group), alcohol abuse in 1% of the encephalitis group (1% in the nonencephalitis), psychotic disorders in 1% of the encephalitis group (0.3% of the non-encephalitis) and bipolar affective disorder in 0.5% of the encephalitis group (0.1% of the non-encephalitis).

The authors explained that depression rates may be underestimated due to the difficulty in distinguishing mild depression from the unexpected reactive process to an illness such as encephalitis and/or the possible functional impairment. The study also showed that the risk of epilepsy in encephalitis patients was high, especially in the first year. An interesting finding was the high rates of psychiatric illness, such as psychotic and bipolar disorders—consequences not very often reported/assessed in patients after encephalitis. Regarding headache, the study showed an increased risk years after the illness rather than in the first year. The author explained this by the fact that people may minimise the importance of headache compared with other acute sequelae or they may consider it a pre-existent problem rather than a consequence of encephalitis.

The authors concluded by emphasising that encephalitis has sequelae, many of these treatable, especially in the first year but also years after. Follow-up of these patients is necessary to ensure these consequences of encephalitis are dealt with and the patients are leading the best quality life possible; not to underestimate the social/financial implications such as long-term care and returning to work after encephalitis.


Outcomes in children with anti-NMDAR encephalitis

Matricardi et al. (2016) looked at the cognitive and neurological evolution in 13 (10 prospective) consecutive children with anti-NMDAR encephalitis. There were eight females and five males with ages between 3 and 17 years. Median length of follow-up was 31 months after symptom onset. The time of the first cognitive evaluation varied in different patients from 1–12 months from the onset, depending on the severity of the initial symptoms. The findings of this evaluation showed deficits of various degree in all areas in five patients (median two months from the onset), normal intellectual abilities but deficits in verbal fluency, short-term verbal memory, sustained attention and processing speed in two patients (median two months from the onset); normal general intellect, but difficulties in short-term memory, planning, sustained attention, visual-motor integration, expressive language in two patients (six months after the onset); global cognitive functioning and reasoning in the lower normal range in one patient (12 months after the onset).

At the latest follow-up, seven patients presented no neurological disability, five patients had a significant improvement and one patient exhibited a behavioural disorder. Four patients reported difficulties with their academic performance and impaired social relationships regarding phonemic verbal fluency, naming skills, working memory, processing speed, planning abilities, sustained attention and short-term memory (verbal and visuo-spatial). The authors argued that patients with anti-NMDAR encephalitis experience severe global dysfunction during the course of the illness. At follow-up, all patients improved by various degrees. General intellectual abilities were within normal limits for most patients, but neuropsychological evaluation showed various deficits in more than half of patients. These difficulties were associated with frontal lobe and hippocampal dysfunctions. They impacted on social relationships and academic performance resulting in an altered quality of life. Personalised rehabilitation programmes, which need to consider the patient’s progress and the medical treatment, are necessary.


Tick-Borne encephalitis (TBE): significant impairments at follow-up

Veje et al. (2016) investigated the neurological sequelae of TBE after a follow-up of 2–15 years in Western Gotaland, Sweden. Ninety-two patients with TBE and 58 controls were included in the study. Medical records from the acute illness were consulted and phone-based interviews using the Encephalitis Support Group Questionnaire 2000 and the Functional Outcome of Sleep Questionnaire (FOSQ) (to assess sleep-related quality of life) were conducted. At follow-up, patients were aged 18–86 years. 63% of patients had moderate and severe course of the illness at acute stage. At follow-up, the main impairments were linked to cognitive skills such as concentration/attention, initiative/motivation, short-term and long-term memory and learning. Balance and coordination problems, tiredness/fatigue and problems with fine motor skills were also a significant outcome. There was no difference between the TBE patients and the control groups on the FOSQ questionnaire. The authors concluded that neurocognitive and motor symptoms are significant after TBE. The study conducted by Ullman et al. (2016) on the link between increased working memory and fMRI signal in children following TBE showed a prominent deficit in working memory capacity after a mean time of 3.8±1.4 years in patients with TBE. The authors emphasised that TBE can cause significant cognitive impairment.


Seizures and encephalitis

“Autoimmune encephalitis patients who presented with new-onset seizures exhibited dramatic seizure improvement after immunotherapy.”
(Byun et al., 2016)

Antibody-associated epilepsies: a summary

Bakpa et al. (2016) conducted a systematic literature review in order to present an overview of the antibody-associated epilepsies. They identified 537 studies (observational and case reports), but no controlled clinical trials. The authors summarised the clinical characteristics and treatment efficacy of the syndromes associated with LGI1, Caspr2, VGKC complex, NMDAR, GAD, GABAB receptors, and AMPAR antibodies. Facial ophthalmic dystonic seizures (FBDS) and antibodies in patients with chronic refractory epilepsy were also discussed. The authors concluded that the results supported the autoimmune origin of some of anti-epileptic drugs-resistant seizures when antibody-mediated encephalopathy is present. However, the treatment needs to be tailored according to the type of antibody. In addition, these studies provided evidence to support the role and safety of immunotherapies in patients with autoimmune epilepsies. The authors suggested that future possible research topics could investigate the pathogenic role of the antibodies and the ideal way to identify patients with epilepsy and autoantibodies.

Wright and Vincent (2016) presented a summary of the current knowledge regarding neuronal antibodies in epilepsy-related syndromes. This summary is seen as a helpful tool aimed at clinicians who manage patients presenting with a combination of seizures and other symptoms such as neuropsychiatric, movement disorders, and autonomic symptoms. Anti-NMDAR antibody encephalitis, VGKC-complex antibodies associated limbic encephalitis, FBDS, AMPA and GABA receptor associated syndromes and new onset refractory status epilepticus are discussed. The key points of this review refer to the clinical presentation of the autoimmune epileptic encephalopathy (seizures, neuropsychiatric features, abnormal movements and cognitive decline), the presence of seizures in men with anti-NMDAR antibodies as a main feature, the characteristics of FBDS (association with LGI1 and basal ganglia T1 hyperintensity on MRI), the presence of extreme delta brush in anti-NMDAR antibody encephalitis and the clinical and diagnosis utility of the immunotherapy in patients with severe epilepsy without an identified antibody.


The characteristics and outcomes of seizures in autoimmune encephalitis (AE)

Byun et al. (2016) investigated the characteristics of seizures and the effects of immunotherapy on seizures in autoimmune encephalitis. Their prospective observational registry study included 41 adult patients with AE who presented with new onset seizures. There were 21 males and 20 females. The median age was 43 years. The time form the seizure onset to commencing immunotherapy was a median of 29 days. Seventeen patients (41.5%) were positive for anti-NMDAR antibodies, 17 patients (41.5%; 14 LGI1 and three Caspr2) were positive for anti-VGKC complex antibodies, three patients (7.1%) for anti-GABAb antibodies and four patients had onconeural antibodies. Initially, 12 (29.3%) patients had focal seizures without impaired awareness, 18 (43%) had focal seizures with impaire awareness, 21 (50%) had secondary bilateral convulsive seizures, and 11 (26.8%) had multiple seizure types. Facio-brachial dystonic seizures (FBDS) were reported in seven patients (17.1%), all with anti-LGI1 antibodies. Five patients (four with anti-NMDAR and one with anti-Ma2/Ta antibodies) had convulsive status epilepticus (SE). Apart from FBDS, which were present only in anti-LGI1 antibodies patients, the frequency and type of seizures did not differ between antibody groups.

Initially, patients received high dose steroids (19 patients), intravenous immunoglobulin (IVIg) (five patients) or a combination of both (17 patients). After two to four weeks, 51.2% of patients were seizure free. Ten patients (24.4%) experienced seizures reduction (six with anti-NMDAR, three with anti-VGKC, and one with anti-Yo antibodies). Ten patients (24.4%) had no change in their seizures (five with anti-NMDAR, two with anti-VGKC, one with anti-GABAb, one with anti-amphiphysin, and one with anti-Ma2/Ta antibodies). Second-line immunotherapy for the patients with seizures consisted in steroids or IVIg (with no effect) in four patients and/or rituximab in 12 patients. Eight of those who received rituximab were seizure free after the treatment and one reported seizure reduction. Overall, at six months follow-up, 73.2% of patients were seizure free. All patients with FBDS were seizure free. Poor seizure outcome was associated with the presence of onconeural antibodies and abnormal findings on MRI. The authors concluded by emphasising the importance of immunotherapy on seizure management in patients with antibody-positive autoimmune encephalitis. In patients with a partial response to initial immunotherapy, rituximab improved seizure outcome with only low level adverse effects.


Risk factors for developing status epilepticus (SE)

Sonneville et al. (2016) investigated the risk factors for developing early onset SE in patients with acute encephalitis in order to identify which patients may benefit from prophylactic anti-epileptic drugs. Out of 290 patients with acute encephalitis, 58 patients (20%) developed SE with 44 non-refractory SE (NRSE) and 14 refractory SE (RSE). The time from admission to hospital to SE onset was 48 hours, usually before the patient was transferred to the intensive care unit (ICU). The SE patients were...
Recovery and rehabilitation after encephalitis

“The training programme developed and evaluated within the Memory Aids Service provides a platform to allow people with acquired memory impairments to use these memory aids effectively to meet everyday functional goals.”

(Dewar et al., 2016)

Memory Aids Service for people with a non-progressive neurological disorder

Dewar et al. (2016) investigated the effects of systematic training in the use of compensatory memory aids on everyday memory functioning within a Memory Aids Service. Participants (128) in this controlled clinical trial had everyday memory problems following progressive or non-progressive neurological conditions. Participants were allocated to a treatment (88) or control group by the neuropsychologist. The outcomes of the treatment were measured by attainment of everyday memory goals. A cognitive profile of each patient was established by undertaking neuropsychological tests (premorbid function, intellectual function, memory, information processing and executive function). The participants in the treatment group took part in five sessions: baseline assessment, three training sessions across a six-week period and a follow-up assessment 18 weeks after baseline (12 weeks after the end of training). The participants in the control group had only neuropsychological assessment. The participants were involved in the selection of memory aids.

At the follow-up (18 months), the participants underwent a review interview, a neuropsychological assessment and administration of the Problem Solving Inventory (PSI). Sixty-three people in the treatment group and 24 in the control group completed the training. The treatment had a substantial effect on training on the goal attainment diary but only at 12 weeks follow-up. Participants with non-progressive neurological disorder improved attainment of everyday memory goals by using compensatory memory aids within a memory aids clinic. In participants with progressive neurological disorder, the treatment did not have the same outcomes. The Memory Aids Service was based on the following features: collaborative goal setting, task analysis of how to use and apply each memory aid, modelling of behaviour, use of error reduction techniques, opportunities for extended practice including compliance measures between sessions, and probes to determine retention of previously learnt information.

The authors concluded by affirming the utility of a Memory Aids Service for patients with a non-progressive neurological disorder.


Anti-epileptic drugs in seizures prevention

Pandey et al. (2016) aimed to examine the efficacy and tolerability of anti-epileptic drugs for the primary and secondary prevention of seizures in viral encephalitis by reviewing randomised and quasi-randomised controlled trials in which patients were assigned to a treatment or control group. They did not find any clinical trials to fit the study criteria, therefore no data analysis took place. The authors concluded by highlighting the need for randomised controlled trials to assess the role of anti-epileptic drugs for the primary and secondary prevention as seizures in encephalitis are an important feature with high mortality and morbidity.


mostly patients with immune-mediated encephalitis (29%) and herpes simplex virus 1 (HSV 1) encephalitis (28%). The authors found that coma (on ICU admission), cortical involvement on imaging and non-neurologic organ failure were independent risk factors for SE in patients with acute encephalitis. Low risk of developing SE was for patients with a bacterial cause. Age, body temperature and blood sodium level were not related to the risk of developing SE. Electroencephalography (EEG) showed generalised slowing (44/51), focalisation (27/51), electric seizures (18/51), background activities (5/51), electric silence (4/51) and burst suppression pattern (1/51). Outcomes (measured at 90 days after ICU admission) were poor in 23% of SE patients overall, with RSE patients having the worst outcomes. Early onset RSE was an independent risk factor for 90-days’ mortality.

**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.

“This book is equally relevant to survivors, family members, carers, neurologists, psychiatrists, nurses, relatives and even disinterested readers. Ava Easton has brought the same demotic wisdom to this book that she exercises as the inspirational CEO of The Encephalitis Society. Over the years she has taken what was a deadly but obscure illness out to the world, and explained it simply and cogently to people who had no reason to have thought about it before, and to experts who had almost certainly never thought about it in those terms before. There is a useful explanation of the different forms of encephalitis, prevention measures, experts have their say, but at the heart of the book is a series of beautifully written, desperately moving first-hand accounts from those who have lived with the illness”.

Simon Hattenstone, *The Guardian*

“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](http://www.encephalitis.info/shop))

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**Neuropsychological Rehabilitation. The International Handbook**

Edited by Barbara A. Wilson, Jill Winegardner, Caroline M. van Heugten, Tamara Ownsworth

This outstanding new handbook offers unique coverage of all aspects of neuropsychological rehabilitation. Compiled by the world’s leading clinician-researchers, and written by an exceptional team of international contributors, the book is vast in scope, including chapters on the many and varied components of neuropsychological rehabilitation across the life span within one volume.

Divided into sections, the first part looks at general issues in neuropsychological rehabilitation including theories and models, assessment and goal setting. The book goes on to examine the different populations referred for neuropsychological rehabilitation and then focuses on the rehabilitation of first cognitive and then psychosocial disorders. New and emerging approaches such as brain training and social robotics are also considered, alongside an extensive section on rehabilitation around the world, particularly in under-resourced settings. The final section offers some general conclusions and an evaluation of the key issues in this important field.

This is a landmark publication for neuropsychological rehabilitation. It is the standalone reference text for the field as well as essential reading for all researchers, students and practitioners in clinical neuropsychology, clinical psychology, occupational therapy, and speech and language therapy. It will also be of great value to those in related professions such as neurologists, rehabilitation physicians, rehabilitation psychologists and medics.

Available from Routledge ([www.routledge.com](http://www.routledge.com))

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**Bed 12**
by Alison Murdoch

*Bed 12* is a survival guide to the world of acute medicine, and a poignant and darkly comic account of what it’s like to fight for someone’s life.

What do you do when the most important person in your life is about to die? Who can help you? How do you keep going?

When Alison Murdoch’s husband catches viral encephalitis and falls into a life-threatening coma, everything changes. Over the course of a summer, machines beep and clatter, medical staff come and go, and family and friends of varying beliefs offer well-intentioned advice. For someone unfamiliar with hospitals, death and dying, the insights of Buddhism assume a greater relevance than ever before. This book is an astute, profound and uplifting insight into how to cope with despair, heartache and the unknown.

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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 and their families. Our work involves:

• Supporting adults, children, families and carers of those affected by encephalitis.
• Producing high quality, evidence-based and peer-reviewed information about encephalitis accredited by the NHS England Information Standard.
• Raising awareness about encephalitis, its consequences and the need for improved services.
• Conducting research and working in partnership with other researchers.

Professional Membership

Professional membership with the Society is open to all professionals worldwide. Membership is free and it only takes two minutes to complete online.

Benefits of Professional Membership:

Free place at our Encephalitis Conference

Held once a year, the Conference presents current research advances and debates salient issues in the field of encephalitis. Professionals with various interests from epidemiology and virology, through clinical casework to rehabilitation and the social impact of the illness are taking part. CPD points awarded.

Free subscription to our Professional Newsletter

The Newsletter covers a range of topics including latest news about encephalitis and the Society’s work, book reviews, and other useful resources for those with an interest in this condition.

Research articles and books

The Society’s website www.encephalitis.info holds a database of research articles and books related to encephalitis and every year we produce a summary of the most important publications and research studies.

Support with collecting necessary data for research studies

The Society has an extensive database of over 5,000 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 or contact us at mail@encephalitis.info or on +44 (0)1653 692583.

We are now in a position to reveal our plans for World Encephalitis Day 2018!

We want supporters to let their feet do the talking by signing up and taking part in our digital #BrainWalk challenge in the run-up to February 22. By downloading the #BrainWalk app to your smartphone, you will be able to record your daily walking activity alongside others across the world.

We believe #BrainWalk will get people moving, get people thinking and, crucially, reduce the often overwhelming sense of isolation that can follow an acquired brain injury. It will also allow users to share with us how it feels to be part of #BrainWalk and how using the App improves their wellbeing.

So, we need you to download the #BrainWalk App when it goes live on January 17 and start walking and talking about encephalitis. You don’t have to go out of your way to run miles and miles either. The #BrainWalk App will work while you are doing the rounds at hospital, taking your dog for a walk or even enjoying a leisurely stroll to the pub.

We hope you will join us – every step takes us towards a world where encephalitis is as rare as it possibly can be.
Scientific Advisory Panel

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Consultant Neurologist
Chelsea and Westminster Hospital

Dr. Bonnie-Kate Dewar
Clinical Neuropsychologist
Neuropsychology Services

Dr. Julia Granerod
Epidemiologist
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LIFE AFTER ENCEPHALITIS:
A NARRATIVE APPROACH BY DR AVA EASTON

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