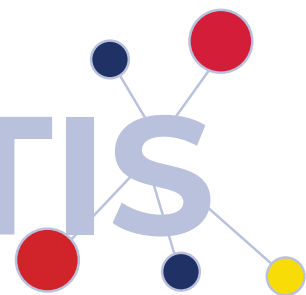


RESEARCH SUMMARY

ADVANCES IN

ENCEPHALITIS

2019



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EPIDEMIOLOGY

PATHOGENESIS

DIAGNOSIS

TREATMENT

OUTCOMES

RECOVERY

Welcome to the Encephalitis Society's Research Summary 2019

The Research Summary - Advances in Encephalitis 2019 presents a collection of research papers published during that same year.

An increase in the incidence and emergence of new endemic areas for viruses associated with encephalitis was reported in 2019. This growth has many implications for public health and potentially for the diagnosis of encephalitis cases of unknown cause.

The Australian Childhood Encephalitis study found that infectious encephalitis is the leading cause of paediatric encephalitis in Australia. In this study, only 17% of encephalitis patients had an unknown cause, which is much lower than other previous aetiology-focused studies. However, difficulties in the diagnosis of encephalitis still exist. The variety of presentations, reluctance to perform certain tests (e.g. lumbar puncture), lack of or poor resources, and insufficient medical training were all reported as barriers in diagnosing encephalitis. Clinicians are urged to consider encephalitis in differential diagnoses of patients with atypical clinical presentations such as, for example, older adults with rapid progressive cognitive decline, or female patients with concomitant mood and psychotic disorders. Diagnosis of travel-associated encephalitis is also complex and requires a good understanding of patients' travel history and travel-related pathogens. Travellers should be advised not only on the likelihood but also on the severity of the consequences of encephalitis if acquired.

Seizures are an important feature of autoimmune encephalitis. Studies showed not only the beneficial effect of immunotherapy on seizure management but also the rare likelihood of developing epilepsy after autoimmune encephalitis. Long-term anticonvulsant medication may not be justified in all autoimmune encephalitis types, which may have major implications on patients' quality of life.

There is a new "hot topic" in the autoimmune field which relates to MOG antibody and the spectrum of MOG antibody-associated disease. This is larger than previously thought and includes not only demyelinating diseases but also encephalitis other than ADEM.

The burden of encephalitis is still considerable. Mortality and morbidity remain high. Autoimmune encephalitis is associated with huge costs, four times higher hospitalisation costs than those of



Dr Ava Easton at the World Health Organization

herpes simplex encephalitis, and also great challenges in caring for these patients, often admitted to intensive care units.

The few studies on recovery and rehabilitation available showed that some patients can be left with long-term consequences and the impact on the whole family can be devastating. Multi-stage, person-centred and interdisciplinary rehabilitation is essential. Having reliable prognosis factors can help clinicians and professions allied to medicine in identifying those patients who need an additional input and monitoring, and in educating families on what to expect.

At the time of writing, the medical world is focused on managing the coronavirus pandemic. With evidence emerging around a link between neurology and COVID-19, we are launching a seed funding call exclusively for projects around COVID-19 and encephalitis (www.encephalitis.info/seedfund). However, we should not forget that research in encephalitis still needs to continue beyond the current pandemic. We are excited to announce the Encephalitis Conference 2020 keynote speakers - Prof Tom Solomon and Prof Carsten Finke - and we urge you to register to attend or submit your abstract. CPD points and prizes for best poster and oral presentation will be awarded (www.encephalitis.info/conference-2020).

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

Dr Ava Easton
CEO, Encephalitis Society

Disclaimer

This review has tried to provide a succinct summary of the original papers. References to the full papers 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 that you refer to the author's original paper before altering practice in any way.

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Epidemiology of encephalitis

“This severe disease continues to cause death in 1 in 20 affected children, and results in considerable neurological morbidity among survivors.”

(Britton et al., 2019)

Encephalitis in children: incidence and causes

Britton et al. (2019) reported the largest prospective cohort of all-cause childhood encephalitis in the world. Their study included 287 children aged ≤14-year-old with confirmed encephalitis between May 2013 and December 2016 at five paediatric hospitals in Australia. Fifty-six percent were male. Less than 5% of children had pre-existing neurological disease or immunocompromised status.

An infectious cause was identified in 57% of children. The most common infectious agents were: 10% enterovirus, 10% parechovirus, 8% bacterial meningoencephalitis (mostly *Streptococcus pneumoniae* and group B *Streptococcus*), 6% influenza, 6% herpes simplex virus (HSV), 6% *M. pneumoniae*. An immune-mediated cause was reported in 25% of children: 18% acute disseminated encephalomyelitis (ADEM), 6% anti-NMDAR encephalitis and 1% other immune-mediated causes. The remaining 17% of patients had an unknown cause. Infectious encephalitis was associated with younger age (median age 1.7 years) and immune-mediated encephalitis with older age (median age 7.1 years). Two patients with HSV encephalitis developed anti-NMDAR encephalitis less than four weeks after the initial illness. Many of the infectious causes were associated with defined epidemic periods.

Symptoms varied depending on the cause. No one symptom was present in all children. Nearly half of children (49%) were admitted to the intensive care unit (ICU), more frequently those with infectious and unknown causes than immune-mediated. Median length of hospitalisation was 11 days, however autoimmune cases had a prolonged hospital stay (>14 days).

Thirteen children died: 11 with infectious causes and two with no cause identified. Moderate to severe neurological difficulties on discharge were reported in 27% of children. Poor prognosis was associated with seizure with loss of consciousness, Glasgow coma score <13, abnormal electroencephalography and ICU admission. The authors concluded that viral agents predominated as causes of childhood encephalitis in Australia. Encephalitis still results in considerable mortality and morbidity.

Boesen et al. (2019) investigated the incidence of paediatric autoimmune encephalitis (AE) between 2011 and 2017 in Denmark. Overall, 375 children were tested for AE antibodies (median age 11.1 years; 54% girls) and 22% of them had a psychiatric hospital admission or ambulatory visit up to two months before their AE examination.

Only 5% of them tested positive for AE antibodies: cerebrospinal fluid (CSF) GAD65-IgG (3.1%), plasma NMDAR-IgG (2.8%), CSF NMDAR-IgG (1.8%), plasma GAD65-IgG (1.0%) and plasma CASPR2-IgG (0.4%). The conditions for probable/definite anti-NMDAR encephalitis were met in five children (four had positive CSF

and one only positive serum), an incidence rate of 0.07/100,000 person-year. Three children had low positive anti-NMDAR antibodies in serum but did not have encephalitis. The number of children tested for anti-NMDAR antibodies increased substantially during the study, however the proportion of children diagnosed with it did not change.

Nine children tested positive for anti-GAD65 in CSF, of which four met the criteria for anti-GAD65 encephalitis (incidence rate 0.055/100,000 person-year). Four children met the criteria for antibody-negative but probable autoimmune encephalitis pointing to an incidence of 0.055/100,000 person-year. In a subgroup of 25 children with demyelinating illness, ten children were diagnosed with ADEM. None of them had either anti-aquaporin-4 or anti-MOG antibodies.

The authors concluded that the diagnostic work-up should consider the low incidence of AE. But if the pre-test probability is higher, the antibody tests should be performed as treatment is very important for good outcomes. The authors also argued that there are no specific codes for AE in the ICD-9 or ICD-10. There should be a code for AE with subgroups for specific types.

Britton P.N., Dale R.C., Blyth C.C., et al. (2019) Causes and clinical features of childhood encephalitis: a multicentre, prospective cohort study. Clinical Infectious Diseases; XX (XX): 1–10.

Boesen M.S., Born A.P., Lydolph M.C., et al. (2019) Pediatric autoimmune encephalitis in Denmark during 2011–17: A nationwide multicentre population-based cohort study. European Journal of Paediatric Neurology; 23: 639–652.

Inpatient hospitalisation burden of autoimmune encephalitis (AE)

Cohen et al. (2019) assessed inpatient hospitalisation burden of AE and compared it with herpes simplex encephalitis (HSE) burden. The retrospective study included all adult patients (n=63) who met the criteria for probable or definite autoimmune encephalitis over 10 years at a tertiary care institution. The median age at admission was 50 years and 31 patients were antibody-positive. Nearly a quarter of patients were diagnosed with neoplasm before or during their hospital stay. The median duration from first symptom to admission was 75.5 days. Patients admitted to the intensive care unit (ICU) (n=27) were younger than those not admitted. Refractory seizures/status epilepticus (SE), respiratory failure, altered mental status requiring intubation, autonomic dysfunction, and agitation were the main reasons for admission to the ICU.

The median length of stay in hospital was 15 days. Factors contributing to an increased length of stay (> 10 days) were immune treatment (multiple plasma exchange), delay in establishing a diagnosis and lack of an early neurological response

to first-line treatments. Four patients died (all admitted to ICU), 30 were discharged home and 29 were discharged to another health care/rehabilitation inpatient facility.

The median hospital charges per patient with AE were more than \$70,000 with the charges for patients admitted to the ICU being \$173,000 per admission. Compared with HSE, both the median length stay and median hospital charges were substantially higher: three times and fourth times, respectively. The authors argued that care for patients with AE is associated with a substantial burden: prolonged hospitalisation, more extensive ICU use and high financial costs.

Cohen J., Sotoca J., Gandhi S., et al. (2019) Autoimmune encephalitis. A costly condition. *Neurology*; 92(9).

Tick-borne encephalitis (TBE): no longer an imported disease?

There has been an increase in the number of TBE cases which calls for a step up in monitoring, prevention and vaccination. A study conducted between 2007 and 2017 in Finland reported an increase of both overall incidence from 0.31 to 1.52/year/100,000 inhabitants, and locally acquired TBEV (Helsinki area) incidence from zero to 0.48/year/100,000 inhabitants (Smura et al. 2019). Kreuzsch et al. (2019) reported the first probable case of TBE in a three-month-old infant after a tick bite in Southern England. Holding et al. (2019) tested blood samples from deer culled in England and Scotland and collected and tested tick samples. Five ticks tested positive by LIV/TBEV real-time reverse transcription polymerase chain reaction, all from within the Thetford Forest area. Four percent of all deer samples were ELISA-positive for the TBEV. The highest seroprevalence (47.4%) was in south-western Norfolk and north-western Suffolk (Thetford Forest).

Makenov et al. (2019) reported the first confirmed autochthonous tick-borne encephalitis case in Moscow in 2016 and the detection of TBEV in five specimens of *Ixodes ricinus*. In the Netherlands, Dekker et al. (2019) reported a third autochthonous case of TBE in 2017, in the same geographical area of TBE virus positivity as previous cases. Geeraedts et al. (2019) reported the first paediatric case of TBE in the Netherlands in 2018 in a 12-year-old boy, contracted outside of the expected regions, suggesting TBEV may be more widespread.

The TBE burden also continued to rise in Mongolia, despite vaccination and information campaigns. A study of TBE cases between 2008 and 2017 in two regions showed that the case fatality rate was 28.6% in one of the regions and all fatalities were men with a median age of 45 ± 12.6 years (Baasandavga et al., 2019).

Steffen (2019) performed a systematic review of current data on TBE in children in Europe. Although the incidence in children is lower than that in adults, the author asks if this is because some cases in young children go underdiagnosed, and children have lower exposure or a reduced risk of developing manifest disease. Whilst most reports are inconclusive or report mild sequelae, some recent studies revealed long-term cognitive sequelae in children after TBE. The author suggested that vaccination recommendation should include one- to three-year-old children in countries with high endemicity.

Baasandavga U., Badrakh B., Burged N., et al. (2019) A case series of fatal meningoencephalitis in Mongolia: epidemiological and molecular characteristics of tick-borne encephalitis virus. *WPSAR*; 10 (1).

Dekker M., Laverman G.D., de Vries A., et al. (2019) Emergence of tick-borne encephalitis (TBE) in the Netherlands. *Ticks and Tick-borne Diseases*; 10: 176–179.

Geeraedts F., van der Kroft E., Reimerink J. (2019) First paediatric case of autochthonous tick-borne encephalitis in the Netherlands, 2018. *New Microbe and New Infect*; 32: 100603.

Holding M., Dowall S.D., Medlock J.M., et al. (2020) Tick-Borne encephalitis virus, United Kingdom. *Emerg Infect Dis*; 26(1): 90-96.

Kreusch T.M., Holding M., Hewson R., et al. (2019) A probable case of tick-borne encephalitis (TBE) acquired in England, July 2019. *Euro Surveill*; 24(47).

Makenov M., Karan L., Shashina N., et al. (2019) First detection of tick-borne encephalitis virus in *Ixodes ricinus* ticks and their rodent hosts in Moscow, Russia. *Ticks and Tick-borne Diseases*; 10: 101265.

Smura T., Tonteri E., Jääskeläinen A., et al. (2019) Recent establishment of tick-borne encephalitis foci with distinct viral lineages in the Helsinki area, Finland. *Emerging Microbes & Infections*; 8(1): 675–683.

Steffen R. (2019) Tick-borne encephalitis (TBE) in children in Europe: *Epidemiology, clinical outcome and comparison of vaccination recommendations*. *Ticks and Tick-borne Diseases*; 10: 100–110.

West Nile virus (WNV): an update

Papa et al. (2019) reported the presence of a novel WNV genetic variant belonging to the Eastern European subclade of lineage 2 in August 2018 in one patient from the north-eastern region of Greece. The year 2018 was characterised by an early start and a prolonged transmission season, with a record number of 316 cases and 47 deaths in Greece (Papa et al., 2019) and the largest outbreak of West Nile infections in Croatia with 54 patients with neuroinvasive illness (Vilibic-Cavlek et al., 2019). West Nile virus infection was also reported in France with 25 cases including 22 cases in the South East (Eldin et al., 2019). Parkash et al. (2019) reported two imported case of WNV infection: one severe encephalitis and one mild febrile illness in a couple in their 70s returning to the UK from a holiday in South Africa.

In 2018, 2,647 WNV infections were reported to the Centers for Disease Control and Prevention USA, which was 25% higher than previous years. Neuroinvasive infection was identified in 63% of cases and the mortality rate was 6% (Centers for Disease Control and Prevention USA, 2019). Philpott et al. (2019) investigated death records of individuals with WNV infection in Texas during 2002-2012. Of 4,142 individuals with WNV, 7% of cases died during the acute phase (<90 days after symptom onset) and 7% of the remaining individuals died in the convalescent phase. Of all deaths in the acute phase, 92% were cases of WNV neuroinvasive (WNVD) (median age 75 years) and 78% of the deaths in the convalescent stage were WNV neuroinvasive. Overall, when compared with the general population, people with WNVD had an increased rate of death due to renal and infectious causes.

Centers for Disease Control and Prevention US (2019) West Nile Virus and Other Domestic Nationally Notifiable Arboviral Diseases -- United States, 2018. *US Official News*; 8 Aug.

Eldin C., Mailhe M., Zandotti C., et al. (2019) West Nile virus outbreak in the South of France: Implications for travel medicine. *Travel Medicine and Infectious Disease*; 28: 100–101.

Papa A., Papadopoulou E., Chatzixanthouliou C., et al. (2019) Emergence of West Nile virus lineage 2 belonging to the Eastern European subclade, Greece. *Archives of Virology*; 164: 1673–1675.

Philpott D.C.E., Nolan M.S., Evert N., et al. (2019) Acute and delayed deaths after West Nile virus infection, Texas, USA, 2002–2012. *Emerging Infectious Diseases*; 25 (2).

Parkash V., Woods K., Kafetzopoulou L., et al. (2019) West Nile Virus Infection in travelers returning to United Kingdom from South Africa. *Emerging Infectious Diseases*; 25(2).

Vilibic-Cavlek T., Savic V., Sabadi D., et al. (2019) Prevalence and molecular epidemiology of West Nile and Usutu virus infections in Croatia in the 'One health' context, 2018. *Transbound Emerg Dis*; 66: 1946–1957.

Japanese encephalitis virus (JEV): changes in epidemiology and the effects of vaccination

Gao et al. (2019) reported changes in geographic distribution of JEV at global level. In Asia, JEV GI has replaced GIII as the dominant genotype and GIII has spread towards Europe and Africa and caused domestic JEV cases in Africa. GII and GV were present in Malaysia in the past but now GII has migrated southward towards northern Australia, while GV has emerged in China and Korea after decades of silence. Fang et al. (2019) investigated the presence of JEV in Shanghai, China where GI and GIII alternated between 2003 and 2008. Although the vaccination programme resulted in a substantial decrease in JEV cases in this area, the genotype GI has been detected recently. In Indonesia, where JEV is a public health threat (GII, GIII and GIV circulating), Garjito et al. (2019) reported the isolation of genotype I-a (GI-a) for the first time from a *Culex gelidus* mosquito in the Province of Jambi.

Turtle et al. (2019) investigated the efficacy of live attenuated JE vaccine SA14-14-2 used in Nepal. The neutralising antibody to JEV was found more frequently in districts which had been the subject of more vaccination campaigns, rather than in the most recently vaccinated districts. Previous infection with dengue virus (DENV) predisposed people to an immune response to JEV, though this effect was modest. However, a few participants had DENV IgM in their blood, but no history of travel to India, which may question the imported nature of DENV and point to a more established area within Nepal. A study conducted by Wang et al. (2019), regarding the SA14-14-2 vaccine level of protection after the vaccine booster, found that the highest seropositivity (82%) was observed in vaccinated children during the first 0.5–1.5 years after booster vaccination, after which it started to decline and remained low.

Fang Y., Zhang Y., Zhou Z-B., et al. (2019) New strains of Japanese encephalitis virus circulating in Shanghai, China after a ten year hiatus in local mosquito surveillance. *Parasites & Vectors*; 12:22.

Gao X., Liu H., Li X., et al. (2019) Changing geographic distribution of Japanese encephalitis virus genotypes, 1935–2017. *Vector-borne and zoonotic diseases*; 19(1).

Garjito T.A., Prihatin M.T., Susanti L., et al. (2019) First evidence of the presence of genotype-1 of Japanese encephalitis virus in *Culex gelidus* in Indonesia. *Parasites & Vectors*; 12:19.

Turtle L., Brindle H.E., Schluter W., et al. (2019) Low population Japanese encephalitis virus (JEV) seroprevalence in Udayapur district, Nepal, three years after a JE vaccination programme: A case for further catch up campaigns? *PLoS Negl Trop Dis*; 13(4).

Wang R., Xie L., Gao N., et al. (2019) Decreases in both the seroprevalence of serum antibodies and seroprotection against Japanese encephalitis virus among vaccinated Children. *Virologica Sinica*; 34: 243–252.

Sign alerts:

- Chatterjee (2019) drew attention to the death of almost 150 children in Bihar, Eastern India due to acute encephalitis syndrome (AES).
- Vasanthapuram et al. (2019) suggested that dengue virus (DENV) should be included in the routine testing for AES cases in India after a four-year surveillance study found that 5.2% patients with AES were positive for DENV.
- Ferreira et al. (2019) argued that detection of arboviruses (e.g. DENV, St Louis encephalitis virus) in the cerebrospinal fluid (CSF) of patients in Sao Paulo, Brazil is a reason for concern especially in regions where these viruses are endemic.
- Da Silva Mello et al. (2019) argued that DENV and chikungunya (CHIKV) can cause neurological infections in Brazil and their diagnosis can be improved by the use of a combination of molecular and immunologic tests on CSF and serum.
- Patel et al. (2019) reported 704 cases of measles in the USA between January and April 2019 occurring in 22 states: 71% in unvaccinated individuals, 11% in those who received at least one dose of vaccine and 18% with unknown status. Forty-four cases were imported, however 34 were USA residents travelling internationally, most not vaccinated. This is the highest number of measles cases following elimination in the USA in 2000.

Chatterjee P. (2019) No cause identified for death of children in Bihar, India. *The Lancet*; 393.

da Silva Mello C., Cabral-Castro M.J., de Faria L.C.S., et al. (2019) Dengue and chikungunya infection in neurologic disorders from endemic areas in Brazil. *Neurology: Clinical Practice*; 00(00): 1-6.

Ferreira J.E., Ferreira S.C., Almeida-Neto C., et al. (2019) Molecular characterization of viruses associated with encephalitis in São Paulo, Brazil. *PLoS ONE*; 14 (1).

Patel M., Lee A.D., Redd S.B., et al. (2019) Increase in measles cases — United States, January 1–April 26, 2019. *Morbidity and Mortality Weekly Report*; 68(17).

Vasanthapuram R., Hameed S.K.S., Desai A., et al. (2019) Dengue virus is an under-recognised causative agent of acute encephalitis syndrome (AES): Results from a four year AES surveillance study of Japanese encephalitis in selected states of India. *International Journal of Infectious Diseases*; 84S: S19–S24.

Pathogenesis of encephalitis

“Antibodies targeting LGI1 and CASPR2 are able to boost glutamatergic transmission and increase epileptic activity of CA1 pyramidal neurons.”

(Romoli et al. 2019)

Antibody specificity and neurons

Romoli et al. (2019) investigated the electrophysiological effects of cerebrospinal fluid (CSF) containing autoantibodies (LGI1, CASPR2, and GABA_BR) on intrinsic and extrinsic properties of hippocampal neurons. The study used whole CSF and *in vivo* inoculation of CSF antibodies for neurophysiological *ex vivo* studies. The authors concluded that neuronal hyperexcitability depends on the antibody specificity. Antibodies against LGI1 and CASPR2 are able to increase hippocampal CA1 neuron excitability, facilitating epileptiform activity. GABA_BR antibodies did not make any changes in the synaptic functioning.

Romoli M., Krashia P., Sen A., et al. (2019) *Hippocampal epileptogenesis in autoimmune encephalitis. Annals of Clinical and Translational Neurology*; 6(11): 2261–2269.

Microglia in Rasmussen’s encephalitis and viral encephalitis

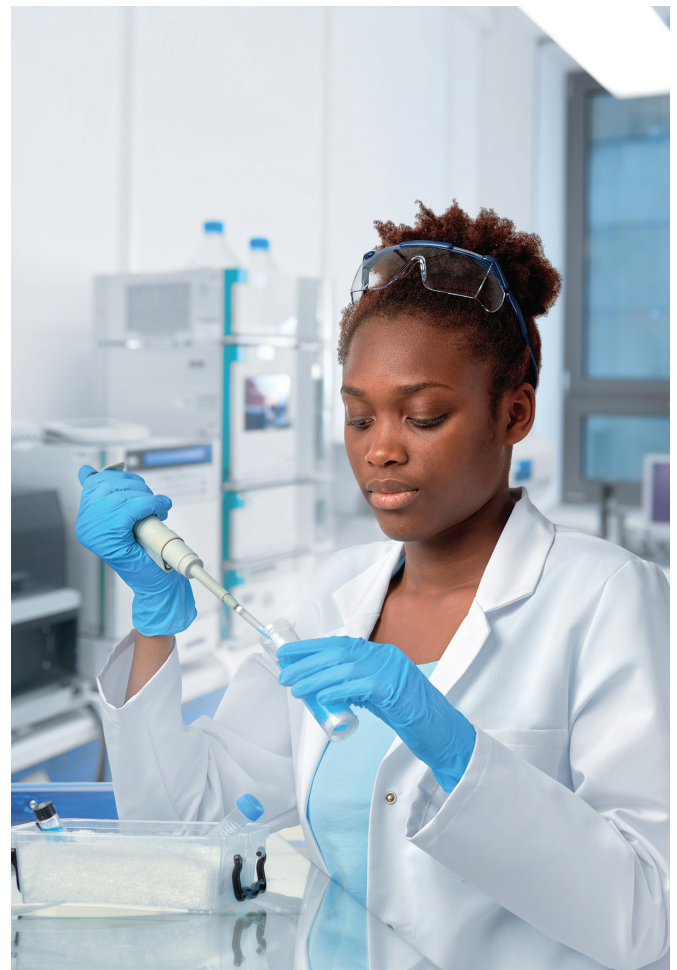
Tröscher et al. (2019) investigated the role of microglial nodule formation in Rasmussen’s encephalitis (RE) to test the hypothesis that, in RE, microglial nodules facilitate the initiation of the later dominating T-cell cytotoxicity. The study used 30 of 4% neutral buffered formalin-fixed and paraffin-embedded tissue blocks from 27 different patients (23 patients had RE and epilepsy surgery) staged according to the cortical pathology from early to acute stages. All patients were checked for neurodegeneration, microglia activation and CD3+ T-cell infiltrates.

In stage 0 of the disease, only small microglia nodules were present. In stage 1, local T-cell infiltrates and microglial nodules were identified. In stage 2, microglia activation and T-cell infiltrates were severe. Neurodegeneration, absent in stage 0, was focal in stage 1 and extensive in stage 2. Microglial activation preceded T-cell influx and was characterised by inflammasome activation. Furthermore, the study showed a positive correlation between the numbers of microglia and cytotoxic T lymphocytes (CTLs) within nodules and that CTLs influenced the inflammatory profile of the nodular microenvironments, which proves the role of T-cells in the secondary inflammatory response. Inflammatory response in RE could be induced upon TLR3 stimulation in neonatal microglial cell cultures. The authors concluded that their study shows two-stage inflammatory process: firstly, microglia are activated by TLR signalling and upregulating inflammasome genes, T cell- and monocyte attracting chemokines. Secondly, CD8+ T cells attack neurons and modulate the inflammatory milieu by IFN- γ secretion, thereby promoting inflammation. They suggested that these findings (the microglial microenvironment being an important step in T-cell cytotoxicity) could apply to other CTL-mediated diseases.

Chen et al. (2019) reviewed the role of microglia in viral encephalitis. Microglia serves important functions, from phagocytic activities in the brain and producing IFN-1 after recognition of the virus, to altering the hippocampal excitatory synapses - which can lead to cognitive disturbances, neuroinflammation and viral dissemination to the brain parenchyma causing neuronal death. The main points the authors made are the double role of microglia in viral encephalitis (anti-inflammatory role and pro-inflammatory role), the different roles of microglia depending on the type of viral infection, and the need for future research to concentrate on how to regulate activation of microglia (enhance or inhibit) in order to enhance its anti-inflammatory role and hence aid anti-viral treatments and reduce the consequences of encephalitis.

Chen Z., Zhong D., Li G. (2019) *The role of microglia in viral encephalitis: a review. Journal of Neuroinflammation*; 16: 76.8

Tröscher A.R., Wimmer I., Quemada-Garrido L., et al. (2019) *Microglial nodules provide the environment for pathogenic T cells in human encephalitis. Acta Neuropathologica*; 137(4): 619–635.



Infectious encephalitis

“Physicians should apply a high level of clinical suspicion and a low threshold to initiate life-saving acyclovir therapy.”

(Bewersdorf et al. 2019)

Herpes simplex encephalitis (HSE): atypical cases, outcomes and complications

Bewersdorf et al. (2019) discussed challenges in the diagnosis of atypical HSE. In a study of 18 consecutive patients, four patients had normal cerebrospinal fluid (CSF) work-up with only a slight elevation of protein, although they had a detectable HSV viral load in the CSF. Repeated tests showed pleocytosis in three patients. Eleven patients had normal computed tomography (CT) scans. All but one patient had an abnormal magnetic resonance imaging (MRI) with temporal lobe involvement, but the MRI findings also included atypical findings such as extensive global brain swelling and severe brainstem involvement in single patients. All patients received aciclovir and three patients additional foscarnet due to further deterioration. One patient required decompressive craniotomy. Eleven patients were admitted to intensive care unit (ICU). The outcomes were mostly unfavourable. One patient died and only 38.9% had a good clinical outcome at discharge. The authors noted that the patients with normocellular CSF spent more time on ICU than those with pleocytosis. The authors concluded by emphasizing the variety of clinical, laboratory and radiological features of HSE. Additional treatment with foscarnet should be added in case of deterioration under aciclovir.

Todokoro et al. (2019) investigated the likelihood of acute retinal necrosis (ARN) after HSE. Questionnaires sent to 792 neurology departments (response rate of 40.9%) and 986 ophthalmology departments (response rate of 54.3%) revealed 53 cases of HSE between 2011-2013, and 67 HSV-ARN cases between 2011-2016. Among the HSV-ARN cases, 16 cases had histories of prior HSE with nearly half developing ARN within two years after HSE. The authors concluded that neurologists and ophthalmologists should be aware that HSE survivors have a risk of developing HSV-ARN.

Hauer et al. (2019) systematically reviewed the cerebrovascular complication of HSE. Between 2000 and 2018, they identified 27 patients with intracerebral haemorrhage, 10 patients with ischaemic stroke and one patient with cerebral venous sinus thrombosis. In most patients with intracerebral haemorrhage, the initial presentation was encephalitis (93%). Haemorrhage happened at a median interval of 10 days after admission and initiation of aciclovir. The overall mortality was 21%. HSV-1 was a major cause of haemorrhagic complications. In patients with ischaemic stroke, clinical presentation included encephalitis (50%), meningitis (20%) and stroke (30%). There was evidence of cerebral vasculitis in 63%. Infarction was frequently multifocal, and at times preceded by haemorrhage (20%). It was associated with HSV-2. Unfavourable outcomes, but no death, were reported for 40% of the patients. The patient with venous sinus thrombosis was initially treated with aciclovir for six days, when he developed bilateral limb weakness, ataxia and bilateral headache. An MRI revealed features



of encephalitis in the left temporal lobe and a superior sagittal sinus thrombosis. The authors proposed that HSV-related cerebral haemorrhage and infarction are distinct manifestations of central nervous system HSV infection.

Bewersdorf J.P., Koedel U., Patzig M., et al. (2019) Challenges in HSV encephalitis: normocellular CSF, unremarkable CCT, and atypical MRI findings. Infection; 47: 267–273.

Hauer L., Pikija S., Schulte E.C., et al. (2019) Cerebrovascular manifestations of herpes simplex virus infection of the central nervous system: a systematic review. Journal of Neuroinflammation; 16:19.

Todokoro D., Kamei S., Goto H., et al. (2019) Acute retinal necrosis following herpes simplex encephalitis: a nationwide survey in Japan. Japanese Journal of Ophthalmology; 63: 304–309.

Cytomegalovirus (CMV) in immunocompetent children

CMV is endemic in most areas worldwide. Although CMV encephalitis affects mainly immunocompromised individuals, a few cases have been reported in immunocompetent children. Guo and Jiang (2019) investigated the clinical characteristics of 18 immunocompetent children with CMV encephalitis diagnosed in a single medical centre in southwest China over 15 years. The median age of patients was 5.1 months. Clinical symptoms were acute or subacute and included seizures (94.4%) as the earliest and most common neurological symptom, fever (77.8%), poor feeding (77.8%), alteration of consciousness (44.4%) and vomiting (22.2%). Laboratory tests showed elevated cerebrospinal fluid

(CSF) protein and CMV polymerase chain reaction of CSF positive in all patients, while anti-CMV IgM was positive in 77.8% of patients. Measurement of the CMV load in CSF and urine was useful for evaluating the response to treatment. Brain scans showed brain lesions in six patients and electroencephalography was abnormal in 88.9% of patients. Treatment included two-stage ganciclovir in 11 patients. All treated patients showed a steady clinical improvement. At follow-up (up to 36 months), nine patients had a complete recovery, three continued to experience seizures and hearing loss and two presented delayed psychomotor development. The authors concluded that CMV encephalitis in children has different clinical manifestations than in adults. Although rare, clinicians should be alerted to the possibility of CMV encephalitis in immunocompetent children, especially in those younger than six months.

Guo Y., Jiang L. (2019) *Cytomegalovirus encephalitis in immunocompetent infants: A 15-year retrospective study at a single centre. International Journal of Infectious Diseases* 82; 106–110.

Mycoplasma pneumoniae encephalitis (MPE)

Feng et al. (2019) reported four children (three boys and one girl with ages between three and eight years) with MPE with status epilepticus. All children had an acute onset with high fever, two had respiratory symptoms and three disturbance of consciousness. Status epilepticus' presentation varied: myoclonus secondary to tonic-clonic seizures (one), generalised tonic-clonic (one), complex partial seizures (one), generalised tonic-clonic combined with subclinical electronic discharges (one). Cerebrospinal fluid was positive for *M pneumoniae* RNA. Magnetic resonance imaging (MRI) was abnormal in three patients: long T1 and T2 signals in the hippocampus (two) and demyelination of the paraventricular white matter (one). Electroencephalography (EEG) showed slow wave background rhythm in all patients. Treatment included azithromycin for two weeks (n=4), dexamethasone (n=3) and immunoglobulin (n=2). After treatment, two children were seizure-free and two had seizure reduction. All children were on antiepileptic drugs. A follow-up EEG showed slow waves in all children, but no epileptiform discharges. MRI revealed varied degrees of brain atrophy in all children. The authors emphasised the need to diagnose and treat this entity as soon as possible. Cunha and Cunha (2019) reviewed the antibiotic therapy for MPE. They suggested that, although there is insufficient evidence, the duration of therapy should be between two and three weeks. Antibiotics most likely to be efficient for MPE are macrolides (azithromycin), quinolones (levofloxacin or minofloxacin) or second-generation tetracyclines (high-dose doxycycline or minocycline).

Cunha B.A., Cunha C.B. (2019) *Pharmacokinetic considerations in selecting optimal antibiotic therapy for Mycoplasma pneumoniae encephalitis. European Journal of Clinical Microbiology & Infectious Diseases*; 38: 631–635.

Feng S., Chen J-X., Zheng P., et al. (2019) *Status epilepticus associated with Mycoplasma pneumoniae encephalitis in children: good prognosis following early diagnosis and treatment. Chinese Medical Journal*; 132(12).

Rabies

Mani et al. (2019) reported clinical and radiological findings of eight patients from India with laboratory-confirmed rabies who survived the illness. Five patients were male and seven were between three and 13 years old. All patients met the World Health Organization (WHO) criteria for category III exposures through dog bites. In seven cases, wound management and anti-rabies vaccination with at least three doses were initiated on the day of exposure and, in one case, 12 days after the dog bite. Only three patients received rabies immunoglobulin within 12 hours, 24 hours and 20 days after the bite. After a 15- to 90-day incubation period, most patients had an atypical clinical presentation which did not fit the classic forms of rabies (encephalitic and paralytic). All patients required admission to intensive care unit needing correction of fluid and electrolyte imbalance, management of autonomic dysfunction and anticonvulsants. Three patients died due to severe neurological sequelae (average survival of 6.3 months). Five patients survived (follow-up between six and 13 months): two patients in a vegetative state, two with moderate neurological sequelae and one with mild neurological sequelae. However, all patients had poor cognitive function. The authors argued that although these cases show a greater awareness of rabies and access to better critical care facilities in rabies-endemic countries, there is still much to do on the prevention of rabies.

Mani R.S., Damodar T., Divyashree S., et al. (2019) *Case report: survival from rabies: case series from India. Am. J. Trop. Med. Hyg.*; 100(1): 165–169.

Enterovirus A71

During 2016, an outbreak of enterovirus with neurological involvement occurred in Spain. Taravilla et al. (2019) reported clinical manifestations and management of 30 children with neurological presentations (meningitis, brainstem encephalitis, encephalitis, encephalomyelitis with or without autonomic dysfunction and acute flaccid paralysis) of confirmed enterovirus infection at a hospital in Madrid during 2016. There were 18 males and the median age was 23 months. Neurological symptoms included: lethargy or drowsiness (n=24), ataxia (n=17), tremor (n=7), myoclonic jerks (n=4), tetraparesis (n=1), paresis isolated to right arm (n=1). Cardiorespiratory failure (cardiogenic shock and neurogenic pulmonary oedema) was reported in three patients and cardiac arrest in one. Magnetic resonance imaging was abnormal in 21/26 patients: alteration of the signal of the white matter in the rhomboencephalic region (n=16), leptomeningeal enhancement (n=5), and cervical myelopathy (n=3). Real-time polymerase chain reaction detected enterovirus in the nasopharyngeal aspirate (n=17), cerebrospinal fluid (CSF) (n=8), and anal swab (n=5). Enterovirus A71 was the most common serotype (21/25) and the only serotype detected in patients with brainstem encephalitis or encephalomyelitis. Median hospital stay was 10 days and 14 patients were admitted to the intensive care unit. Treatment consisted of immunoglobulin (n=21), corticosteroids (n=17), fluoxetine (n=11). The outcomes were mostly favourable at discharge: 20 children recovered completely, seven had cerebellar



dysfunction, one paresis, one peripheral facial paralysis and one needing tracheostomy and nasogastric tube for feeding. Elevated leukocytes at admission was associated with the severity of the disease. The authors concluded by suggesting that clinicians should test (not only in CSF) for enteroviruses in children with brainstem encephalitis or encephalomyelitis.

Taravilla C.N., Pérez-Sebastián I., Salido A.G., et al. (2019) Enterovirus A71 infection and neurologic disease, Madrid, Spain, 2016. Emerging Infectious Diseases; 25:1.

Norovirus-associated encephalitis/encephalopathy (NoVE)

Norovirus is a cause of outbreaks of gastrointestinal infections worldwide, predominantly in winter. Shima et al. (2019) investigated all NoVE in children in Japan between 2011 and 2016. There were 29 children aged between four months and 12 years, 10 boys and 19 girls. Pre-existing neurological disorders were present in five children. Initial symptoms included pyrexia (n=20), diarrhoea (n=20) and vomiting (n=19). Twelve children developed shock. The median time from initial symptoms to the initiation of neurological symptoms was 1.5 days. The neurological symptoms included: impaired consciousness (n=29), seizures (n=23), status epilepticus (n=10), delirious behaviour (n=3). Treatments consisted of steroid pulse therapy (n=22) and intravenous immunoglobulin (n=11). The outcomes included: death (n=4), good recovery (n=13), poor outcome (n=11) and unknown (n=1). Poor outcome was associated with shock, status epilepticus, shorter interval (0.6 days) between initial symptoms and onset of encephalitis/encephalopathy, elevated serum creatinine level and abnormal blood glucose level. Treatment did not influence the outcomes.

Shima T., Okumura A., Kurahashi H., et al. (2019) A nationwide survey of norovirus-associated encephalitis/encephalopathy in Japan. Brain & Development; 41: 263-270.

Varicella zoster virus encephalitis (VZE) in solid organ transplant (SOT) recipients

Kang and Aslam (2019) reported the clinical features of VZE in SOT recipients by presenting two case studies and reviewing 10 cases already reported in the literature. Primary VZV infection is rare, however herpes zoster (HZ) is frequent in SOT recipients. In 75% of cases reported here, VZE developed in the first four years after transplant. Risk factors are unknown, although known risk factors for HZ are old age, African American ethnicity, heart transplant and cytomegalovirus infection. Most cases in this review were renal recipients. Rash (mostly prior to neurological infection, but also concurrently or after) was present in 67% of cases. Cerebrospinal fluid showed lymphocytic pleocytosis. Treatment consisted of reducing immunosuppressant and antivirals (aciclovir, aciclovir followed by valacyclovir, ganciclovir, famcyclovir, vidarabine). One patient received steroids in addition to aciclovir and one patient received immunoglobulin. Outcomes varied from recovery to death (mortality rate 42%), factors affecting the outcomes being presenting symptoms, timing of antiviral treatment and the degree of immunosuppression. The authors concluded that prompt diagnosis is essential as without treatment it can disseminate rapidly.

Kang M., Aslam S. (2019) Varicella zoster virus encephalitis in solid organ transplant recipients: Case series and review of literature. Transpl Infect Dis; 21.

Other viral encephalitis: Alongshan virus, pseudorabies virus and Madariaga virus

Wang et al. (2019) reported a newly discovered segmented RNA virus called Alongshan virus (ALV) in the family *Flaviviridae*, associated with a febrile illness in north-eastern China. The infection was confirmed by reverse-transcriptase-polymerase-chain-reaction assay in 86 patients who presented with fever, headache and a history of tick bites. Yang et al. (2019) reported five patients with encephalitis caused by pseudorabies virus and drew attention to this cause of encephalitis, especially in patients who have had recent contact with pigs. Four patients had a history of a hand injury from dealing with pigs. Lednicky et al. (2019) reported the emergence of Madariaga virus (MADV) in Haiti, after identifying MADV in cultures of plasma of eight children with acute febrile illness between 2015 and 2016.

Lednicky J.A., White S.K., Mavian C.N., et al. (2019) Emergence of Madariaga virus as a cause of acute febrile illness in children, Haiti, 2015-2016. PLoS Negl Trop Dis; 13(1).

Wang Z-D., Wang B., Wei F., et al. (2019) A new segmented virus associated with human febrile illness in China. N Engl J Med; 380: 22.

Yang X., Guan H., Li C., et al. (2019) Characteristics of human encephalitis caused by pseudorabies virus: A case series study. International Journal of Infectious Diseases; 87: 92-99.

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

“Although the clinical advances have been remarkable, a pressing need exists to maintain rigorous clinical and immunological criteria for the diagnosis of the disease.”
(Dalmau et al., 2019)

An update and clues to diagnosis

Dalmau et al. (2019) presented an overview of anti-NMDAR encephalitis highlighting some of the challenges in its management. Recognising this illness still poses difficulties. Whilst seizures, abnormal movements, insomnia, irritability and speech disorder are more frequently identified in children, psychosis, abnormal behaviour, memory impairment and hypoventilation are more common in adults. Some patients have neurological symptoms initially, while others develop them within a few days. Many patients initially present with complex psychiatric manifestations and differential diagnosis from a psychiatric illness is very important. Some patients develop neuroleptic malignant syndrome in response to intolerance to neuroleptics, which is challenging to differentiate from symptoms of anti-NMDAR encephalitis. Movement disorders are present in 75% of adults and 95% of young children. Facial dyskinesia and various abnormal movements affecting the trunk and limbs are important clues to this entity. No specific phenotype exists for either psychiatric symptoms or movement disorders. Seizures are a common manifestation (75%), however, most patients become seizure-free after the acute illness. A gradual withdrawal of antiepileptic drugs post-acute is suggested. Many patients (70%) are admitted to the intensive care unit and their management is complex. Treatment involves first-line and/or second-line immunotherapy. If these fail, third-line therapy (bortezomib or tocilizumab) is suggested. Treatments with azathioprine, mycophenolate mofetil and methotrexate have been tried, however larger cohorts are needed to confirm their efficacy. Electroconvulsive therapy has been reported in patients with catatonia, however sometimes, it may exacerbate the symptoms caused by anti-NMDAR encephalitis. In a small number of patients, anti-NMDAR antibodies coexist with antibodies against aquarin-4 or myelin oligodendrocyte glycoprotein. About 80% of patients improve with immunotherapy and, if needed, tumour removal, but the recovery is slow. Delay in treatment and admission to ICU are considered factors for unfavourable prognosis.

The authors suggested a diagnostic clues acrostic: S (sleep dysfunction), E (excitability, disinhibition or manic behaviour alternating with depressive behaviour), A (agitation or aggression), R (rapid onset), C (children and young people predominance), H (history of psychiatric disease absent), F (fluctuating catatonia), N (negative and positive symptoms at presentation), M (memory

deficit), D (decrease of verbal output or mutism), A (antipsychotic intolerance), R (rule out neuroleptic malignant syndrome), A (antibodies and additional paraclinical tests).

Dalmau J., Armangue T., Planaguma J. et al. (2019) An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models. The Lancet Neurology; 18(11): 1045-1057.

Anti-NMDAR encephalitis in Chinese patients

Xu et al. (2019) undertook a single-centre prospective study of patients with anti-NMDAR encephalitis in China. Two hundred and twenty patients were enrolled between 2011 and 2017. Most patients presented with psychosis (82.7%) and seizures (80.9%). All patients tested antibody-positive in cerebrospinal fluid (CSF) and 71.4% had antibody-positive serum. Other symptoms were fever (57.3%), decreased level of consciousness (53.2%), memory deficits (48.2%), speech disturbance (45.5%), movement disorder (42.7%) and sleep disorder (42.3). Abnormal EEG findings were reported in 51.4% of patients and abnormal MRI in 35.9%. Four patients also had AQP4 antibodies, and five patients MOG antibodies. An interesting finding of the study is the misdiagnosis rate. In 2011, the misdiagnosis rate was 75% (mostly viral encephalitis) and in 2017 the rate was 15.4% (viral encephalitis, schizophrenia, epilepsy, cerebral angiitis, cerebral vascular events and tuberculosis).

A fifth of the patients had an underlying neoplasm. First-line therapy was administered in 99.5% of patients, second-line in 7.3%, and long-term therapy with mycophenolate mofetil or azathioprine >1 year in 53.2% of patients. At 12-month follow-up, five patients died and 92.7% of patients had favourable clinical outcomes (modified Rankin Scale score ≤2). Overall, 36.4% of the patients relapsed and 26.3% experienced more than one relapse. Most relapses happened in the first 24 months, but there were also relapses reported six years later. During relapses, 88.2% patients had antibody-positive CSF. The delay in treatment initiation was associated with a high risk of relapse, however the tumour status or treatment regimen did not have an influence.

Xu X., Lu Q., Huang Y., et al. (2020) Anti-NMDAR encephalitis. A single-centre, longitudinal study in China. Neurol Neuroimmunol Neuroinflamm; 7.

Psychopathological and psychiatric profile

Al-Diwani et al. (2019) analysed the psychopathological, demographic and aetiological data of adult patients with definite anti-NMDAR encephalitis reported in the literature between 2005 and 2017. According to their psychopathological features, the patients were grouped into five categories: behaviour (68%), psychosis (67%), mood (47%), catatonia (30%) and sleep disturbance (21%). These five features overlapped in 74% of patients with the most common overlaps being combinations of moods, psychosis and behavioural features, often with catatonia.

The study revealed that a cluster of features across catatonia, mood, behaviour and psychosis domains – agitation, aggression, hallucinations, delusions, mutism, irritability or mood instability and depressed mood—characterise the psychopathology of patients with anti-NMDAR encephalitis. The authors concluded that overall, patients with anti-NMDAR encephalitis do not present with manifestations that fit the traditional psychiatric classifications, but exhibit a complex presentation in which core aspects of mood and psychotic disorders coexist. This complex profile associated with a predominantly young, female demographic can help distinguish patients with anti-NMDAR encephalitis from patients with new onset mental illness and justify the need for lumbar puncture, and consequently immunotherapy.

Gibson et al. (2019) also investigated the psychiatric phenotype of anti-NMDAR encephalitis. In their observational retrospective study of 22 patients older than 18 years, they found that patients with anti-NMDAR encephalitis present with a distinct cluster of psychiatric symptoms not commonly seen in functional psychoses. Compared with first episodes of psychosis and schizophrenia, thought disorder and behaviour disorder were more prominent than delusions and hallucinations in patients with anti-NMDAR encephalitis. These patients present with characteristics features: severe cognitive disturbances, negative symptoms (prominent avolition and distractibility) and excitability.

Gurrera (2019) reviewed all published reports of antibody-confirmed anti-NMDAR encephalitis associated with psychiatric symptoms in patients <19 years old, in order to establish the psychiatric presentations and thus improve early recognition of this entity. The conclusion was that clinicians should suspect anti-NMDAR encephalitis if a patient presents with new behavioural symptoms following a recent viral prodrome associated with seizures, unexplained fever, dyskinesia or insomnia, or when these psychiatric symptoms are unusual (non-verbal hallucinations).

Al-Diwani A., Handel A., Townsend L., et al. (2019) *The psychopathology of NMDAR-antibody encephalitis in adults: a systematic review and phenotypic analysis of individual patient data. Lancet Psychiatry*; 6: 235–46.

Gibson L.L., Pollack T.A., Blackman G., et al. (2019) *The psychiatric phenotype of anti-NMDA receptor encephalitis. J Neuropsychiatry Clin Neurosci*; 31(1): 70-79.

Gurrera R.J. (2019) *Recognizing psychiatric presentations of anti-NMDA receptor encephalitis in children and adolescents: A synthesis of published reports. Psychiatry and Clinical Neurosciences* 73: 262–268.

Treatment updates

Nosadini et al. (2019) investigated the use of mycophenolate mofetil (MMF), azathioprine (AZA) and methotrexate (MTX) in paediatric anti-NMDAR encephalitis. Their study (literature review) included 87 patients: 100% of these patients received steroids, 83% intravenous immunoglobulin, 45% plasma exchange and 50% received second-line treatments (rituximab/cyclophosphamide). Of all, 46% had a relapsing course with a total number of median events of 2.5/patient. Treatment included MMF (52%), AZA (27%), MTX (15%), and a combination of MMF/AZA/MTX (6%) for a period of one to 48 months. The median time to initiation of MMF/AZA/MTX was 8.2 months from the disease onset (>6 months from onset in 51%, and only after relapse in 40%). Seven percent of patients relapsed on MMF/AZA/MTX. These relapsing patients had a low rate of second-line treatments before MMF/AZA/MTX, a long median time between onset and MMF/AZA/MTX usage, and were frequently started on MMF/AZA/MTX only after relapse. More people relapsed on MMF and AZA than on MTX. Two patients experienced adverse effects: cytomegalovirus colitis and respiratory infection. The authors concluded that although large cohorts are needed, these studies show that MMF/AZA/MTX may reduce risk of relapse.

Zhang et al. (2019) investigated the effects of therapeutic plasma exchange (TPE) in patients with severe refractory anti-NMDAR (no improvement after steroids and/or intravenous immunoglobulin treatment for at least 10 days). The study included 19 patients treated with TPE and compared the outcomes with a group of 21 non-TPE patients. NMDA receptor antibody titres in the cerebrospinal fluid (CSF) and/or plasma decreased or were negative after the last TPE procedure in 18 patients. Great clinical improvement was observed in the TPE group at one and two months, compared with the non-TPE group. However, follow-up at three, six and twelve months showed no significant differences in the outcomes between the TPE group and non-TPE group. The authors conclude that TPE should be considered as a first-line treatment as it can rapidly improve the clinical manifestations in patients with severe refractory anti-NMDA receptor encephalitis: relieve symptoms, improve consciousness and reduce the dosage of drugs for epilepsy.

Coffey and Cooper (2019) investigated the use of electroconvulsive therapy (ECT) in anti-NMDAR encephalitis to treat neuropsychiatric symptoms. A literature review identified six studies describing the use of ECT in treating catatonia (either as a symptom of encephalitis or effect of dopamine-blocking medications), four of which referred to patients ≤ 18 years. All patients were severely ill, however ECT was administered safely; there were no reports of adverse effects. The authors remarked that in most cases, the ECT was administered before the diagnosis of anti-NMDAR. Moreover, in all six studies the ECT was successful in treating symptoms of catatonia. Some patients improved after ECT but before immunotherapy; some patients who did not improve after immunotherapy, improved after ECT; and one patient improved with ECT and did not require immunotherapy. Although the reported studies lacked complete information about the technical parameters of ECT delivered to each patient, the authors suggested that clinicians should consider ECT early if the patient presents with neuropsychiatric illness suggestive of anti-NMDAR encephalitis.

Deng et al. (2019) reported the efficacy and safety of reduced dosage rituximab (600mg) in anti-NMDAR encephalitis. Ten patients (seven male and three female) were included in this study. None of the patients had a tumour. The median modified Rankin Scale (mRS) was 5 at the worst disease status. Seven patients were admitted to the intensive care unit. Rituximab was given after first-line treatment failure in five patients, and after a relapse in the other five. Eight patients received only one cycle of rituximab. Two patients received a second cycle: one after a relapse with serum antibody-positive at nine months and the other patient after having serum antibody-positive at 12 months but with no relapse symptoms. Only one patient had a mild infusion reaction during the first day. All patients had a good outcome – mRS being between 0 and 2. The proportion of total B cells in lymphocytes was depleted from one day after treatment. B cells started to regenerate at three months. At 12 months after treatment, the proportion of regulatory B cells in reconstituted B cells was significantly higher than that before treatment ($15.3 \pm 12.1\%$ vs. $0.5 \pm 0.6\%$, $p=0.006$), while the proportion of memory B cells was significantly lower than baseline level. The authors conclude that reduced dosage rituximab is safe and effective in anti-NMDAR encephalitis.

Coffey M.J., Cooper J.J., et al. (2019) *Electroconvulsive Therapy in Anti-N-Methyl-D-Aspartate Receptor Encephalitis. A Case Report and Review of the Literature. Journal of ECT; 32(4).*

Deng B., Yua H., Liu X., et al. (2019) *Reduced dosage rituximab in the treatment of anti-N-methyl-D-aspartate receptor encephalitis: An observation study in Chinese patients. Journal of Neuroimmunology; 330: 81–86.*

Nosadini M., Mohammad S.S., Toldo I., et al. (2019) *Mycophenolate mofetil, azathioprine and methotrexate usage in paediatric anti-NMDAR encephalitis: A systematic literature review. European Journal of Paediatric Neurology; 23: 7-18.*

Zhang Y., Liu G., Jiang M., et al. (2019) *Efficacy of therapeutic plasma exchange in patients with severe refractory anti-NMDA receptor encephalitis. Neurotherapeutics; 16: 828–837.*

Relapses in anti-NMDAR

Nosadini et al. (2019) undertook a retrospective study of 62 children to identify the factors that are associated and may predict the risk of relapses in anti-NMDAR encephalitis. There were 39 females and the age ranged between 1.2–18 years. Most children (88.7%) had a definite diagnosis of anti-NMDAR, whilst the other 11.3 % had a probable diagnosis, being only serum-antibody tested. Four patients had a tumour, two of which had a tumour at relapse stage. All patients but two received immunotherapy at onset. Nearly half of them received second-line immunotherapy and 41% received long-term immunomodulation (\geq five months). At follow-up, one child died at initial illness and two children were left with seizures. The median mRS was 1.

Overall, 21% of children relapsed (median two total events per patient) at a median time of 31.5 months (range of 7–89 months). Relapses were less severe than the initial episode (mRS=3 compared with mRS=5 and less admission to ICU). Treatment consisted of immunotherapy in most patients (10/11), and second-line therapy

in three patients (none of these patients had a second relapse). The patients who did not relapse had received three or more different immune therapies at first disease event. At follow-up, both groups of patients had similar outcomes. However, the duration of follow-up was longer for those who relapsed. The authors concluded that aggressive immunotherapy at onset may reduce the risk of relapse.

Nosadini M., Granata T., Matricardi S. (2019) *Relapse risk factors in anti-N-methyl-D-aspartate receptor encephalitis. Developmental Medicine and Child Neurology; 61: 1101-1107.*

Nursing care in patients with anti-NMDAR encephalitis

Yang et al. (2019) reported their experience of providing nursing care for 45 patients (aged between 11 and 58 years) with anti-NMDAR encephalitis. The average hospital stay was 25.2 days. Thirty-four patients exhibited behavioural and psychiatric manifestations (agitation, shouting, anxiety, irritability, tension, insomnia, and auditory and visual hallucinations, delusion, aggression). Nine patients had urinary and faecal dysfunction. Five patients had tachycardia. Eleven patients had an ovarian teratoma with one having bilateral teratoma. Eleven patients had tracheal intubation or tracheotomy and ventilation.

Firstly, nursing care applied to those who needed surgical removal of ovarian teratoma: pre-operative care which included routine pre-operative care and examinations, informing patients regarding personal hygiene and surgical procedure, preparation of the patient for the surgery, and early post-operative care. Secondly, nursing care referred to administering the medication – immunotherapy, looking for adverse reactions and monitoring patients functions: heart, breathing, temperature, imbalances in water, electrolytes, carbohydrates, proteins and lipids, blood sugar, endocrine disorders, osteoporosis, ulcers. Thirdly, medical personnel had to manage various symptoms. Seizures required nursing input via medication, and supporting the patient during seizures. Mental and behavioural symptoms required extra nursing support to keep the patients safe and administer treatment. Additionally, nursing care was also concerned with managing hypoventilation, tracheostomy and autonomic dysfunction (hyperthermia, urinary and faecal incontinence, hypertension, severe cardiac dysrhythmia, clinically significant cardiac pauses, hypersexuality and hypersalivation). The authors concluded that the nursing care of those patients is challenging but essential in order to maintain the safety of patients and improve outcomes.

Yang L., Jiang Q., Guan H., Bo H. (2019) *Nursing care in anti-N-methyl-D-aspartate receptor encephalitis A case series. Medicine; 98: 46.*

The importance of electroencephalography (EEG) in anti-NMDAR

Gillinder et al. (2019) investigated EEG characteristics and their relationship with outcomes in patients with anti-NMDAR encephalitis. Of 446 patients with anti-NMDAR encephalitis and EEG findings reported so far, 83.6% of patients had an abnormal EEG (diffuse encephalopathy). One hundred and one patients

presented delta range abnormalities, and 18.4% reported focal abnormalities distributed throughout the brain. The most common regions with abnormalities were the temporal, frontal and frontotemporal regions. Although 65.9% of patients had seizures, only 39 patients had electrographic seizures and 67 patients had epileptiform discharges. Electrographic seizures correlated strongly with clinical seizures, but not with intensive care unit (ICU) admission or poor outcome. The EEG abnormalities (especially severe generalised slowing or EDB) were correlated with ICU admission and time to recovery. The authors emphasized the importance of performing EEG in all suspected cases (in this study in the preliminary screening, 30% of the patients did not have EEG findings reported) for the clinical management and prognosis of patients with anti-NMDAR encephalitis.

Miao et al. (2019) investigated the relationship between electroclinical characteristics and cerebrospinal fluid (CSF) antibody titres in 51 patients with anti-NMDAR. High CSF antibody titres were observed in 75.9% (22/29) of female patients and 70% (14/20) of male patients. Seizures were reported in 60% of male and 65.5% of female patients. CSF antibody titre was correlated with clinical symptoms. Behavioural symptoms were more common in females with high antibody titre, more clinical symptoms were more common in females, and overall in those with high antibody titre. Also, high antibody titre was correlated with worse background activity (BA) in EEG recordings and high modified Rankin scale scores. The BA during peak stage was worse in female patients than in male patients, and higher in patients with high CSF antibody titres than in those with low CSF antibody titres. Brush patterns and constant chewing (seven patients) were observed primarily in female patients with high CSF antibody titres. The authors concluded with the association between the electroclinical features of patients with anti-NMDAR encephalitis, gender and CSF antibody titres.

Jeannin-Mayer et al. (2019) investigated EEG patterns and epileptic features in patients with anti-NMDAR encephalitis. Their retrospective study included 24 consecutive patients of which seven were children and 21 were female. Seizures were recorded in 75% of patients. In 21% of patients, electrographic seizures were recorded without any clinical manifestations. The authors described three EEG abnormal patterns which appeared consecutively through the course of the disease: Excessive Beta Activity range 14–20 Hz (EBA) in 71% of patients (median 10 days), Extreme Delta Brush (EDB) in 58% (median 16.5 days) and Generalized Rhythmic Delta Activity (GRDA) in 50% (median 21.5 days). The presence of GRDA was strongly associated with concomitant abnormal movements and higher mRS score. EBA was strongly associated with EDB. None of these features were associated with seizures or with an mRS score <3 at 6, 12, and 18 months follow-up. The authors concluded by emphasizing that EDB and GRDA are important features of EEG patterns, which can help an early diagnosis and thus frequent EEG monitoring is recommended. GRDA should be distinguished from seizure or status epilepticus.

Gillinder L., Warren N., Hartel G., et al. (2019) EEG findings in NMDA encephalitis – A systematic review. *Seizure: European Journal of Epilepsy*; 65: 20–24.

Jeannin-Mayer S., André-Obadia N., Rosenberg S. (2019) EEG analysis in anti-NMDA receptor encephalitis: Description of typical patterns. *Clinical Neurophysiology*; 130: 289–296.

Miao A., Du M., Wang L., et al. (2019) Analysis of relation between electroclinical features and cerebrospinal fluid antibody titers in patients with anti-NMDAR encephalitis. *Clinical EEG and Neuroscience*; 50(1): 56–62.

Case reports:

- Li et al. (2019) reported a patient with anti-NMDAR encephalitis induced by bilateral ovarian teratoma with distinct histopathological types: one an immature teratoma and one a mature teratoma.
- Hou et al. (2019) reported three children with anti-NMDAR encephalitis associated with reactivated EBV infection. All patients had both anti-NMDAR antibody and EBV-EA-IgG antibody in the CSF. They were all treated with immunoglobulin, corticosteroids and ganciclovir which resulted in substantial recoveries.
- Garg et al. (2019) reported a child with anti-NMDAR encephalitis following a prior diagnosis of typhoid fever. The authors suggested a potential triggering effect of typhoid fever for anti-NMDAR encephalitis.
- Gastaldi et al. (2019) reported a case of anti-NMDAR encephalitis presenting as akinesia in a patient with Parkinson's disease (PD) whose diagnosis was very challenging as her symptoms were interpreted as a deterioration of PD for some months.
- Savage et al. (2019) reported a case of anti-NMDAR encephalitis presenting as transient epileptic amnesia in a 47-year-old male. The authors suggested considering an autoimmune origin in cases where features are atypical for alternative diagnosis.
- Do Valle et al. (2019) reported six/nine children with anti-NMDAR encephalitis in Brazil with unilateral symptoms (two patients with hemichorea, one patient with hemidystonia and three patients with spastic hemiplegia).

do Valle D.A., Galeazzi J.S.P., de Rezende Machado M., et al. (2019) Clinical variability of children with anti-N-methyl-D-aspartate receptor encephalitis in southern Brazil: a cases series and review of the literature. *Neurological Sciences*; 40: 351–356.

Gastaldi M., Arbasino C., Dalocchio C., et al. (2019) NMDAR encephalitis presenting as akinesia in a patient with Parkinson disease. *Journal of Neuroimmunology*; 328: 35–37.

Garg M., Mittal J., Gupta P. (2019) Association of typhoid fever with anti-NMDAR encephalitis in a young child. *Journal of Neuroimmunology*; 328: 76–77.

Li W., Jia D., Tong L., et al. (2019) Anti-N-methyl-D-aspartate receptor encephalitis induced by bilateral ovarian teratomas with distinct histopathologic types. A case report and brief literature review. *Medicine*; 98: 48.

Hou R., Wu J., He D., et al. (2019) Anti-N-methyl-D-aspartate receptor encephalitis associated with reactivated Epstein–Barr virus infection in pediatric patients. Three case reports. *Medicine*; 98: 20.

Savage S.A., Irani S.R., M. Leite M.I., Zeman A.Z. (2019) NMDA receptor antibody encephalitis presenting as transient epileptic amnesia. *Journal of Neuroimmunology*; 327: 41–41.

Myelin oligodendrocyte glycoprotein (MOG) antibody

“Most anti-MOG antibody-positive children experience a monophasic disease, with clinical relapses occurring more commonly, although not exclusively, in children with persistent seropositivity.” (Waters et al., 2019)

MOG-associated disease

A condition associated with MOG antibodies which is distinct from multiple sclerosis (MS) and aquaporin-4 (AQP4) antibody neuromyelitis optica spectrum disorders (NMOSD) is described by Jureńczyk et al. (2019). The manifestations of this disease can range from classical neuromyelitis optica (NO) to acute demyelinating encephalomyelitis (ADEM) and cortical encephalitis. It can affect both children and adults and it can be monophasic or relapsing. Most relapses happen within the first two to three years. The risk of relapse is lower in patients treated with prednisolone for longer periods of time. It is not a progressing disease and its prognosis is better than AQP4 antibody NMOSD, with which clinical features can overlap. ADEM presentation is more common in children. Over half of children with ADEM have MOG antibodies and all patients with multiphasic ADEM have MOG antibodies. Although rare, encephalitis-type presentation includes seizures, abnormal behavioural and focal symptoms.

Jureńczyk M., Jacob A., Fujihara K., Palace J. (2019) Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease: practical considerations. Pract Neurol; 19: 187–195.

MOG antibody and acquired demyelinating syndromes

Waters et al. (2019) reported antibody status (MOG and AQP4 antibodies), imaging features and outcomes of 274 children with acquired demyelinating syndromes (ADSs) selected from the Canadian Paediatric Demyelinating Disease Study. Almost a third of participants (30.7%) had MOG antibodies and AQP4 antibodies were detected in one participant, who was negative for MOG antibodies.

Overall, 96% of patients presented with optic neuritis (ON), transverse myelitis (TM), acute disseminated encephalomyelitis (ADEM), or a combination of these. Patients with MOG antibody were younger than patients without it. On MRI, patients younger than 11 years with MOG antibody had a high number of lesions ill-defined and/or distributed in a diffuse bilateral pattern, with frequent thalamic and juxtacortical involvement and more often presented with ADEM. Patients older than 11 years had normal brain MRI findings or fewer focal lesions at onset and were more likely to present with ON.

At one-year follow-up, 98.6% of MOG antibodies-negative patients remained negative in all subsequent examinations. Of those MOG antibodies-positive, 24 remained positive, five fluctuated between positive and negative status and 38 became negative. Characteristic for patients persistently positive were older age at presentation and more monofocal ON. Overall, more than 80% of patients had a monophasic course and a favourable outcome.

In antibody-positive children, an older age at presentation was associated with a higher probability of relapse. Those children who relapsed benefitted from treatment with immunoglobulin, anti-CD20, or more general immunosuppressive therapies. The authors suggested a careful examination of children with MOG antibody and meeting multiple sclerosis (MS) criteria, as these children may have an evolution atypical of MS which suggests that the presence of MOG antibodies equals non-MS diagnosis. The authors concluded that no anti-MOG antibody can be a reassurance for a monophasic disease, and an anti-MOG antibody a reassurance for a non-MS disease course. Clinical relapses happen more often in persistently positive children.

Zhou et al. (2019) reported the clinical characteristics of 23 Chinese children with relapsing MOG-IgG-associated demyelination. The patients' median age at disease onset was 5.38 years. Initial clinical presentation and relapsing episodes included ADEM most frequently. In most relapses, MRI showed new lesions and the most common location was the juxtacortical white matter. Anti-NMDA receptor antibodies were detected in two patients, one of which presented with anti-NMDAR encephalitis-associated symptoms. Treatment such as rituximab, mycophenolate mofetil, azathioprine



administered for a longer time (> 6 months) resulted in a decrease of relapse rates from 1.71 before treatment to 0.44 during treatment. The neurological sequelae included visual dysfunction (most common), cognitive dysfunction and epilepsy.

Zhou J., Lu X., Zhang Y., et al. (2019) Follow-up study on Chinese children with relapsing MOG-IgG-associated central nervous system demyelination. *Multiple Sclerosis and Related Disorders*; 28: 4–10.

Waters P., Fadda G., Woodhall M., et al. (2019) Serial anti-myelin oligodendrocyte glycoprotein antibody analyses and outcomes in children with demyelinating syndromes. *JAMA Neurol*; 77(1).

MOG antibody and encephalitis

Wang et al. (2019) investigated how many patients with MOG antibodies have encephalitis which is distinctive from demyelinating syndromes. A total of 690 patients were included in this study: 87 were MOG-ab-positive and 140 were AQP4-ab-positive. Typical presentation of encephalitis was found in 18 MOG-ab-positive patients. Sixteen of these patients fulfilled criteria for definite autoimmune encephalitis and five patients overlapped with anti-NMDAR encephalitis. Regarding AQP4-ab-

positive patients, only 3.6% had encephalitis and none overlapped with anti-NMDAR encephalitis. Rojc et al. (2019) and Sarigecili et al. (2019) reported the association of MOG antibody and NMDAR antibody in a 47-year-old male and six-year-old child respectively. The first patient had a history of recurrent bilateral optic neuritis, and the second patient had a clinical presentation suggestive of anti-NMDAR encephalitis.

Rojc B., Podnar B., Graus F. (2019) A case of recurrent MOG antibody positive bilateral optic neuritis and anti-NMDAR encephalitis: Different biological evolution of the two associated antibodies. *Journal of Neuroimmunology*; 328: 86–88.

Sarigecili E., Cobanogullari M.D., Komur M., Okuyaz C. (2019) A rare concurrence: Antibodies against Myelin Oligodendrocyte Glycoprotein and N-methyl-D-aspartate receptor in a child. *Multiple Sclerosis and Related Disorders*; 28: 101–103.

Wang L., Zhang Bao J., Zhou L., et al. (2019) Encephalitis is an important clinical component of myelin oligodendrocyte glycoprotein antibody associated demyelination: a single-center cohort study in Shanghai, China. *European Journal of Neurology*; 26: 168–174.

Other autoimmune encephalitis

“Our case highlights the importance of differential diagnosis and ongoing follow-up of patients with rapidly progressive dementia.”

(Li et al., 2019)

Autoimmune encephalitis in patients with new onset cognitive decline

New onset of cognitive decline is primarily a characteristic for degenerative illnesses with a poor prognosis. However, some patients with cognitive decline are diagnosed with autoimmune encephalitis and can benefit substantially from early treatment. Chandra et al. (2019) aimed to identify features that distinguish the two entities based on bedside observations. They analysed the Panic score, Epworth sleepiness score, catatonic symptoms and history of seizures in 23 patients with anti-NMDAR encephalitis and 11 patients with anti-VGKC antibody-associated encephalitis and compared them with 20 patients with probable behavioural variant of frontotemporal dementia (bvFTD) and 20 patients with probable Alzheimer’s disease. The authors found that all four parameters were highly significant in the immune-mediated syndromes. They argued that in patients with cognitive decline, the triad of panic, sleepiness with either catatonia or seizures should prompt antibody testing. The authors acknowledged the small size of their sample. Li et al. (2019) drew attention to anti-LGI1 antibody encephalitis manifesting with a rapid progressive dementia and hyponatraemia whose early diagnosis is very important for a good prognosis. Their patient was a 56-year-old man who presented with

fever for three weeks and memory decline (deficits in anterograde amnesia) for two weeks. He was treated with immunotherapy which resulted in complete remission of symptoms at 30 days follow-up.

Chandra S.R., Ray S., Isaac T., et al. (2019) A clinical TRIAD for early suspicion of autoimmune encephalitis as a possibility in patients presenting with progressive cognitive decline. *Asian Journal of Psychiatry*; 41: 5-12.

Li X., Yuan J., Liu L., Hu W. (2019) Antibody-LGI 1 autoimmune encephalitis manifesting as rapidly progressive dementia and hyponatremia: a case report and literature review. *BMC Neurology*; 19:19

Sleep disturbances in autoimmune encephalitis (AE)

Blattner et al. (2019) investigated the prevalence of sleep disturbances in patients with AE and how these related to specific AE autoantibodies. Twenty-six patients with median age of 53 years with AE were included in this study. Twenty-three percent of patients had antibodies against intracellular antigens (including Ma, Yo, CRMP5 and Hu autoantibodies) and the remaining 77%

of patients had antibodies against cell-surface neuronal antigens (including NMDAR, LGI1, AMPAR and GABAR). Sleep disturbances (new or worsening) were reported in 73% of patients and these included gasping or snoring (47%), dream enactment behaviour (32%), insomnia (29%), hypersomnia (21%), other parasomnias (21%) and dream-wake confusional states (11%). Polysomnography in 12 patients showed reduced total sleep time, stage 3 and rapid eye movement sleep and prominent sleep fragmentation. With regard to the type of antibody, the authors reported that a characteristic for patients with anti-LGI1 antibodies was dream enactment behaviours (57% of patients) and narcolepsy was reported only in one patient with Ma1/Ma2 antibodies. No association was made between the sleep disturbances and age or gender. Different antibodies may have an increased risk of specific sleep disturbances. Sleep disturbances completely resolved in 71% of the surviving patients. In 29% of patients, sleep disturbances of varying intensity persisted. The authors concluded that sleep disturbances are common in AE. Screening, prompt recognition and treatment of these disturbances may improve patients' outcomes.

Blattner M.S., de Bruin G.S., Bucelli R.C., Day G.S. (2019) Sleep disturbances are common in patients with autoimmune encephalitis. Journal of Neurology; 266: 1007–1015.

GABA_BR antibody encephalitis

Maureille et al. (2019) described clinical features and long-term outcomes of 22 newly diagnosed patients with GABA_BR antibody encephalitis. Male patients of older age (55-85 years) were predominant. According to clinical manifestations there were two groups: one group of patients (77%) who had isolated recurrent seizures as the first symptom for a median of 10 days. The second group (23%) initially manifested with cognitive disturbances. Over time, all patients developed confusion and 81% of patients developed status epilepticus (SE). Dysautonomic episodes (bradycardia and central apnoea) were present in 36% of patients. Cerebrospinal fluid (CSF) was antibody-positive in all patients and in all patients but one it was abnormal. Magnetic resonance imaging (MRI) was abnormal in 73% of patients showing temporal FLAIR hypersignal. Cancer was found in all patients: 20 with small-cell lung cancer, one malignant thymoma and one uncharacterised lung mass. In one patient, the cancer was diagnosed 18 weeks before encephalitis and in another patient the cancer was diagnosed eight months after encephalitis.

Of all patients, 64% had to be admitted to intensive care unit (ICU). Treatment with first-line immunotherapy was administered at a median delay of 26 days from disease onset. The outcome was poor: 12 patients died (three patients of dysautonomic episodes and nine of cancer). All surviving patients were left with massive anterograde amnesia. At 24 months follow-up, all patients were seizure-free, 17% reported behavioural disorders and 66% depression. Unfortunately, none of the patients returned to their previous cognitive status and occupation. The authors suggested that, in this condition, immunotherapy may be too weak and too late, after the onset of a substantial neuronal injury. Earlier diagnosis and treatment are essential.

Different clinical manifestations and outcomes were reported by McKay et al. (2019) in a systematic review of published cases. They identified 94 patients with GABA_BR, with a male predominance. Seizures were also predominant (84%), however only 9.6% had SE. Symptoms included confusion, disorientation, behavioural changes but also gait ataxia and gait instability. Only 14.9% required ICU admission. The rate of tumour was smaller, with less than a half (49.5%) having a neoplasm, predominantly small cell lung cancer. In this review, 86.3% of patients had a partial or complete recovery.

Good recovery was also experienced by five patients with GABA_BR reported by Si et al. (2019). There were three males and two females with ages between 22 and 77 years. The patients had an acute or subacute onset with epileptic seizures, mental disorder, confusion and memory impairment. All patients had GABA_BR antibodies in blood and CSF, but normal leukocyte count and protein level. MRI was abnormal in two patients with abnormal signals at the median temporal lobe and/or hippocampus. The EEG showed a slow wave rhythm in all five patients. After treatment with methylprednisolone pulse therapy, all patients had a substantial recovery.

Maureille A., Fenouil T., Joubert B. et al. (2019) Isolated seizures are a common early feature of paraneoplastic anti-GABAB receptor encephalitis. Journal of Neurology; 266: 195–206.

McKay J.H., Dimberg E.L., Chiriboga A.S.L. (2019) A systematic review of gamma-aminobutyric acid receptor type B autoimmunity. Polish Journal of Neurology and Neurosurgery; 53(1): 1–7.

Si Z., Wang A., Liu J., et al. (2019) Typical clinical and imaging manifestations of encephalitis with anti-γ-aminobutyric acid B receptor antibodies: clinical experience and a literature review. Neurological Sciences; 40: 769–777.

Antibody specific for kelch-like protein 11 (KLHL11)

Mandel-Brehm et al. (2019) reported the identification of an autoantibody specific for kelch-like protein 11 (KLHL11) in 13 men with similar neurological features: brainstem and cerebellar symptoms (ataxia, vertigo, tinnitus hearing loss) and testicular disease (11 patients with seminoma and two patients with testicular microlithiasis and fibrosis). The autoantibody specific for kelch-like protein 11 (KLHL11) was identified with the use of programmable phage display. In nine patients, encephalitis appeared before the emergence of cancer. The median age of patients was 41 years. Cerebrospinal fluid testing showed elevated protein concentration, pleocytosis, oligoclonal bands, or an elevated IgG index. All patients received immunotherapy and cancer treatment.

Mandel-Brehm C., Dubey D., Kryzer T.J., et al. (2019) Kelch-like protein 11 antibodies in seminoma-associated paraneoplastic encephalitis. N Engl J Med; 381:1.

Acute disseminated encephalomyelitis (ADEM) presenting with psychosis

Neeki et al. (2019) reported an adolescent with ADEM presenting initially with acute psychosis. The 14-year-old girl had a history of mycoplasma encephalitis (nine years of age) which she recovered from with minor personality changes. The current illness started with depression, self-mutilation and suicide attempt followed by dramatic personality change with anger, belligerence and paranoia. This resulted in the girl being detained for serious charges. The patient subsequently developed neurological symptoms (headache, facial drop, slurred speech, persistent episodes of emesis, and hemiplegia) and was transferred to hospital where she continued to deteriorate. Laboratory, imaging and clinical symptoms pointed to ADEM. Magnetic resonance imaging (MRI) revealed a large T2 hyperintense right fronto-parietal lesion with extension into the corpus callosum, deep white matter tracts, and brainstem. Treatment with steroids and plasmapheresis resulted in improvement. Following rehabilitation, the patient fully recovered at two-month follow-up.

Neeki, M.M., Au C., Richard A., et al. (2019) Acute disseminated encephalomyelitis in an incarcerated adolescent presents as acute psychosis. Case report and literature review. Pediatric Emergency Care; 35 (2).

Rasmussen's encephalitis: 11-year follow-up

Foster et al. (2019) reported a seven-year-old child with medically refractory epilepsy secondary to Rasmussen's encephalitis who, after a complete right-sided anatomical hemispherectomy had a substantial recovery, being seizure-free, independently mobile (spasticity of upper limbs) and of normal intellect at 11-year follow-up. A functional MRI revealed that left-sided motor control had relocated from the excised right hemisphere to an anatomically comparable area within the left hemisphere. The authors concluded that their case study showed a good example of effective neuroplasticity of the young brain.

Foster M.T., Das K., May P. (2019) Motor cortex relocation after complete anatomical hemispherectomy for intractable epilepsy secondary to Rasmussen's encephalitis. British Journal of Neurosurgery; 33(2): 234-236.

Seizures

"After immunotherapy, the development of epilepsy after resolved encephalitis is rare in our cohort of AIE patients treated with immunotherapy."

(De Bruijn et al., 2019)

Seizures in autoimmune encephalitis (AE)

De Bruijn et al. (2019) investigated the difference in efficacy between immunotherapy and antiepileptic drugs (AEDs) in patients with anti-LGI1, anti-NMDAR and anti-GABA_BR encephalitis. In this study of 153 patients, 110 of patients manifested with epileptic seizures.

Immunotherapy was administered in 101 patients and AEDs in 100 patients in combination with immunotherapy and in nine patients alone. Most seizures were refractory to AEDs even after changing dosage or treatment regimen. In some patients, the use of AEDs was followed by serious manifestations: behavioural changes, psychosis and suicidal thoughts induced by levetiracetam, and rash after using carbamazepine. Being on AEDs did not prevent relapses, which were resolved with immunotherapy within days or weeks. Immunotherapy resulted in seizure freedom faster (28 days from the start of the treatment) than AEDs (59 days from the start of the treatment) and also more often (53% of patients) than AEDs (14% of patients). Patients treated earlier on in disease course with immunotherapy were seizure-free quicker.

Overall, 89% of all patients with seizures became seizure-free. Only one patient developed epilepsy after the acute stage of encephalitis. Most patients stopped using AEDs successfully after resolution of encephalitis. The authors suggested that the development of epilepsy after autoimmune encephalitis treated with immunotherapy is rare and long-term AED use does not appear to be necessary in most patients with autoimmune encephalitis.

Given the importance of early immunotherapy, the authors emphasized the need to consider autoimmune encephalitis as a cause of drug-resistant seizures, especially when patients do not present with other symptoms specific to AE syndromes. Immunotherapy is very important in AE. AEDs should be given as an addition to immunotherapy and not as primary treatment. The authors suggested using AEDs (like carbamazepine or potentially oxcarbazepine) as first add-on next to immunotherapy in the symptomatic treatment of patients with anti-LGI1 encephalitis and seizures. However, caution is needed on rapid dosage increase due to side effects (rash).

Yao et al. (2019) evaluated seizure characteristics, treatment outcomes and prognosis factors of 103 patients with seizure secondary to autoimmune encephalitis (AE): anti-GABA_BR encephalitis (n=11), anti-LGI1 encephalitis (n=16), anti-NMDAR encephalitis (n=73) and anti-Caspr2 encephalitis (n=3). Overall, 83 patients had seizures and 36% of them had multiple types of seizures: tonic-clonic (68.7%), focal (61.4%), status epilepticus (21.7%). Thirty-nine patients had daily seizures. Five patients had faciobrachial dystonic seizures. All patients underwent both immunotherapy and antiepileptic drugs (AEDs). Overall, 93% of patients achieved effective seizure control and 81% seizure freedom. All patients with anti-LGI1 encephalitis and anti-Caspr2 encephalitis and 83% of patients with anti-NMDAR encephalitis achieved seizure control within two years. Nearly half of patients with anti-GABA_BR encephalitis (45%) had limited seizure control at follow-up. Eleven patients relapsed, although with less severe symptoms. Grand Total Electroencephalography (EEG) Score (GTE) used to evaluate EEG abnormalities was significantly different between the group with seizure reduction and the group with seizure remission. The authors concluded that seizures represent a large burden for patients with autoimmune encephalitis. With the exception of anti-GABA_BR encephalitis, patients with other types of AE may not necessarily need long-term AEDs. The GTE Score may be a predictor of seizure outcomes.

In a study by Casciato et al. (2019) of 33 patients with limbic encephalitis (LE) (12 antibody-positive and 21 antibody-negative), 13 patients developed chronic epilepsy (median 19-month follow-up). The authors found that delay in diagnosis, low seizure frequency at onset, absence of amnesic syndrome, and absence/rarity of inter-ictal epileptic discharges on EEG were important factors to developing chronic epilepsy. They concluded that mild forms of LE, rather than LE presenting with definite and severe limbic syndrome, seemed to be associated with chronic epilepsy. They suggest this is explained by the delay in diagnosis due to atypical/mild clinical presentation at onset.

Casciato S., Morano A., Fattouch J., et al. (2019) Factors underlying the development of chronic temporal lobe epilepsy in autoimmune encephalitis. *Journal of the Neurological Sciences*; 396: 102–107.

De Bruijn M.A.A.M., van Sonderen A., van Coevorden-Hameete M.H., et al. (2019) Evaluation of seizure treatment in anti-LGI1, anti-NMDAR, and anti-GABA_BR encephalitis. *Neurology*; 92: e2185-e2196

Yao L., Yue W., Xunyi W., et al. (2019) Clinical features and long-term outcomes of seizures associated with autoimmune encephalitis: a follow-up study in East China. *Journal of Clinical Neuroscience*; 68: 73–79.



Epilepsy surgery after viral encephalitis (VE)

Liu et al. (2019) investigated the outcomes of patients who underwent surgery after VE. Epilepsy after VE is usually difficult to control, however surgery is rare due to the difficulties in finding the precise location of the epilepsy. This study used stereoelectroencephalography (SEEG) to define the epileptogenic area after VE. SEEG allows sampling from deep cortical tissues and regions beyond the reach of subdural electrodes and also provides direct intralésional recordings. All ten patients in the study had recurrent seizures requiring long-term antiepileptic drugs for more than 12 months after the acute episode of encephalitis. Twelve months after the surgery, three patients became seizure-free. One patient had a selective amygdalohippocampectomy and two patients had lobectomies. Five patients achieved a reduction in the frequency of seizures. Two patients did not get an improvement. In patients with significant improvement or seizure cessation, the seizure onset was located either in the antero-mesial temporal structures or focal gyrus. In the other patients, the seizure started from multiple brain lobes. The authors concluded that some patients do benefit from having tailored surgery after VE. SEEG technology makes localising the epileptogenic area possible.

Liu Y-O., Zhou W-J., Hong B., et al. (2019) Surgical outcomes in patients with epilepsy after viral encephalitis: contribution of SEEG study. *BMC Neurology*; 19: 165.

Diagnosis, management and outcomes of encephalitis

“It is essential to narrow the differential diagnosis, since starting treatment promptly can improve outcome and avoid unnecessary testing and treatments.”
(Toledano and Davies, 2019)

Challenges in diagnosing encephalitis

Toledano and Davies (2019) presented an overview of infectious encephalitis with an emphasis on the challenges in the diagnosis. Infectious encephalitis usually manifests with acute onset of fever, altered mental status, focal neurological deficits and generalised or focal seizures. However, the authors argued that, in some instances, infectious encephalitis can also present sub-acutely and without fever, making it more difficult to recognise. When assessing a suspected case of encephalitis, they suggest that age, environment, season, immunocompetent status and psychosocial factors should be taken into consideration. In addition, all patients with suspected encephalitis should be tested for human immunodeficiency virus (HIV). Radiological investigations could provide clues as to the cause of encephalitis (e.g. HSV 1 has a predilection for the mesial temporal lobes, flaviviruses such as Japanese encephalitis and West Nile virus for deep grey matter, and brainstem involvement is seen in infections with arthropod-borne viruses, enteroviruses, listeriosis, brucellosis and tuberculosis). All patients with suspected encephalitis should have a lumbar puncture (LP), if there is no contraindication, to confirm the presence of inflammation and to distinguish between different infectious causes. The authors described the main neurological conditions that mimic infectious encephalitis, focusing on the characteristics which distinguish them from encephalitis: para-infectious and post-infectious encephalopathies (acute disseminated encephalomyelitis and acute haemorrhagic encephalomyelitis, haemophagocytic lymphohistiocytosis syndrome, influenza-related encephalopathy/encephalitis, acute necrotising encephalopathy, cerebral malaria); non-infectious encephalitis (autoimmune encephalitis associated with paraneoplastic or neuronal surface antibodies, Bickerstaff's encephalitis, vasculitis, neuromyelitis optica spectrum disorder, systemic lupus erythematosus, neurosarcoidosis, syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis; toxic and metabolic encephalopathies (septic encephalopathy, toxic syndromes, posterior reversible encephalopathy syndrome); mitochondrial encephalomyopathies; neoplasia (temporal lobe tumours, intravascular large cell lymphoma, stroke-like migraine attacks after cranial radiation). Unusual presentations of infectious encephalitis are also reviewed: paralytic rabies and viral acute flaccid paralysis, symptomatic cerebrospinal fluid HIV viral escape, immune reconstitution inflammatory syndrome and varicella zoster virus vasculopathy. The authors concluded that clinicians should consider a broad differential diagnosis for a patient presenting with possible encephalitis.

Kenfak et al. (2019) discussed the challenges in diagnosing encephalitis and meningoencephalitis acquired outside Europe in returning travellers. The initial diagnostic work-up of a returning traveller should include assessment for the treatable causes (herpes simplex virus type 1, varicella zoster virus, human immunodeficiency virus 1 (HIV-1) and *Listeria monocytogenes*) and enteroviruses. The next step would be screening for life-threatening infections, as well as pathogens associated with epidemic potential. If the cause is not revealed, the emphasis should be on the identification of other travel-related aetiologies according to visited regions. The authors drew attention to the need to detail places of travel, nature of the trip (urban versus rural area, high comfort resorts versus backpacker trip, contact with animals, bathing in natural water sources), duration of the trip, timing and duration of symptoms, time since the return and minimal and maximal incubation period time and patient's immune status. The authors reviewed the viruses, bacteria, fungi and parasites that can cause encephalitis and their diagnosis methods. Microbiological tests should apply to a variety of samples: blood, CSF, throat or wound swabs and biopsies of accessible lesions. They concluded that finding the cause of encephalitis/meningoencephalitis is still challenging due to the variety of pathogens, but a detailed assessment of the patient can help in finding the cause.

Baumgartner et al. (2019) reviewed the initial diagnosis of 50 patients later diagnosed with autoimmune encephalitis (AE). Twenty-four patients had anti-NMDAR antibodies, seven had VGKC (no specificity for LGI1 or CASPR), 12 had anti-LGI1; five had CASPR2; one GABA_AR and one mGluR5. Of all patients, 80% had initial presentation consistent with AE, while 20% had atypical symptoms (isolated headache, cerebellar dysfunction, gait disorder, monocular visual loss, aphasia and hypaesthesia). In four patients, a tumour was the first manifestation of AE. Despite the typical presentation in most patients, only 32% have had an initial suspicion of encephalitis. In 68% of patients, other diagnoses considered were epilepsy, psychiatric diseases, transient ischaemic attack, dementia, meningitis, and cerebellitis. The authors concluded that AE presentations vary and the diagnosis can be missed. Due to the variety of unspecific symptoms and signs for AE, antibody testing should be extended to patients with rapidly progressive psychiatric diseases and neurological symptoms that are not in accordance with a common neurological disease.

Frackowiak et al. (2019) presented one medical student's experience of encephalitis, arguing that there is insufficient coverage of encephalitis during undergraduate training. This massively affects how they deal with encephalitis cases as junior doctors. At medical school, encephalitis is briefly described in the

context of meningitis, but omits the most important factors such as: the need for an early diagnosis including performing a lumbar puncture (LP) urgently, and prompt treatment in order to avoid or minimise death and disability. Students learn about herpes simplex virus as the cause of encephalitis, without giving more thought to the multitude of other possible aetiologies, from various viruses and other infectious agents to autoimmune causes. Students are left with an understanding that encephalitis is so rare they will probably never encounter an encephalitis case. The authors also emphasize another issue for a junior doctor and member of the accident and emergency team: the lack of time and confidence to perform an LP. Although there is knowledge of how to perform this procedure, there is no practical experience of doing so.

Imran et al. (2019) explored the difficulties in diagnosing CNS infection in Indonesia. Although most of the neurologist participants to the study questionnaire (93%) dealt with presumptive central nervous system (CNS) infections in the last three months, only 15% had performed an LP during the same time. Reluctance to perform an LP was because of unfavourable clinical presentation of the patient, lack of LP kits, concerns regarding possible blame from the family if complications would occur or fear of complications. Although computed tomography (CT) scan (81%) and routine CSF examinations (73%) were available in their local hospitals, the majority of neurologists did not have access to specific microbiological tests. Lack of drugs or costs not covered by patients' insurance were also frequently mentioned as barriers to diagnosis.

Baumgartner A., Rauer S., Hottenrott T., et al. (2019) Admission diagnoses of patients later diagnosed with autoimmune encephalitis. *Journal of Neurology*; 266: 124–132.

Frackowiak M., Easton A., Michael B.D. (2019) Encephalitis. *British Journal of Hospital Medicine*; 80(4).

Imran D., Satiti S., Sugianto P., et al. (2019) Barriers to diagnosis and management of CNS infections in Indonesia. *Neurology*; 92(2): 104-106.

Kenfak A., Eperon G., Schibler M., et al. (2019) Diagnostic approach to encephalitis and meningoencephalitis in adult returning travellers. *Clinical Microbiology and Infection*; 25: 415-421.

Toledano M., Davies N.W.S. *Infectious encephalitis: mimics and chameleons. Pract Neurol*; 19: 225–237.

Challenges in managing autoimmune encephalitis (AE) in the intensive care unit (ICU)

Günther et al. (2019) presented an overview of the challenges of managing AE in the ICU. Disturbances of consciousness, which can occur as first symptom or later in the disease course and can last from one day to more than one month, are one of the most common complications of people with AE, with consequences such as aspiration, ventilation and long-term immobility. Autonomic dysfunction, the second most common complication, can include hyperthermia (refractory fever), hypoventilation, hyperventilation, tachycardia, bradycardia, other cardiac arrhythmias, hypertension,

diarrhoea or hypersalivation. Status epilepticus and movement disorders can also occur very often. Sometimes, it is difficult to differentiate between hyperkinetic, myoclonic or subtle movement disorders and epileptic events. The need for ventilation and tracheostomy is also discussed. Other complications include severe sepsis and septic shock, thrombosis, surgical complication, pleural effusion, rhabdomyolysis, anaemia, electrolyte imbalances, pulmonary embolism, and suicide attempts. The authors noted that none of the patients with AE experienced brain oedema associated with herniation.

Whilst alteration of consciousness, autonomic dysfunction and the need for ventilation and tracheostomy can affect the short-term outcomes of patients in ICU, status epilepticus and movement disorder do not have an influence. The authors also discussed the ethical conflicts regarding changes in therapy goals, treatment limitations, treatment discontinuation and in case of anti-NMDAR encephalitis associations with teratoma the decision to perform an ovariectomy. The authors concluded that ICU admissions are still common for patients with AE and for some types of AE can have severe or even lethal consequences.

Günther A., Schubert J., Witte O.W., Bramer D. (2019) Intensive medical aspects of autoimmune encephalitis. *Medical Clinics-Intensive Care and Emergency Medicine*; 117(7): 620-627.

Cerebrospinal fluid (CSF) in autoimmune encephalitis (AE)

Blinder and Lewerenz (2019) investigated the basic CSF findings (CSF leukocyte count, total protein, and oligoclonal bands-OCB) in ten AE types with well-defined antibodies. The authors found that in NMDAR, GABA_BR and AMPAR and maybe DPPX antibodies-associated encephalitis, CSF frequently shows pleocytosis and positive OCB. AE types associated with LGI1, IgLON5, CASPR2, and GlyR antibodies rarely show positive OCB or pleocytosis. When pleocytosis is present, these types show a low cell count when compared with AE associated with NMDAR, GABA_BR and AMPAR antibodies. This means that inflammatory CSF changes in AE types with NMDAR, GABA_BR, AMPAR and DPPX antibodies can aid the diagnosis of AE before the antibody test is revealed. CSF of patients with GAD associated disease often showed positive OCB and very rare pleocytosis or elevated protein. Patients with IgLON5 showed very often high elevation of protein but no pleocytosis or OCB. In GABAAR patients, CSF showed pleocytosis in a minority of patients, however cell counts frequently exceed >20 cells/μl when elevated.

The authors concluded that different antibody-defined AE types are associated with characteristic CSF findings. Whilst anti-NMDAR antibodies are almost always associated with inflammatory CSF findings, LGI1 antibodies (which mostly affects elderly patients) are very rarely associated with inflammatory changes. Thus in elderly patients with delirium and rapid progressive dementia, a normal CSF should not dismiss a diagnosis of AE.

Blinder T. and Lewerenz J. (2019) Cerebrospinal fluid findings in patients with autoimmune encephalitis—a systematic analysis. *Front. Neurol.* 10: 804.

Next generation sequencing (NGS) of cerebrospinal fluid (CSF): usefulness in diagnosing neurological infections

Wilson et al. (2019) undertook a one-year prospective study to investigate the usefulness of NGS in diagnosing meningitis/encephalitis compared with conventional testing. The study included patients with encephalitis (n=130), meningitis (n=70) and myelitis (n=4) of all ages. Overall, the cause of infection was identified in 57 patients (58 infections). Thirteen of these did not get identified by conventional testing but by NGS: St. Louis encephalitis virus, hepatitis E virus, *Streptococcus agalactiae*, neisseria, *Nocardia farcinica*, *Candida tropicalis*, *Enterobacter aerogenes*, *S. mitis* and *Enterococcus faecalis*. In eight cases, the treating clinicians found that the NGF helped them establish the diagnosis. Nineteen infections were diagnosed by both conventional testing and NGS. NGS did not identify the infection in 26 cases which were diagnosed by serologic testing (n=11), tissue samples other than CSF (n=7), negative due to low titres of pathogens in CSF (n=8). The authors concluded that CSF NGS improved diagnosis of patients in this sample by identifying more potential pathogens than conventional direct-detection testing of CSF.

Xie et al. (2019) reported successfully using NGS on CSF of two infants to detect sequences of *A cantonensis* after finding hypereosinophils in patients' peripheral blood and CSF. The authors argued that ELISA and MRI are not accurate for the diagnosis of *Angiostrongylus eosinophilic meningoencephalitis* in infants, however NGS is very effective for an early and precise diagnosis.

Wilson M.R., Sample H.A., Zorn K.C., et al. (2019) *Clinical metagenomics sequencing for diagnosis of meningitis and encephalitis*. *N Engl J Med*; 380 (24): 2327-40.

Xie, M., Zhou Z., Guo S, et al. (2019) *Next-generation sequencing specifies *Angiostrongylus eosinophilic meningoencephalitis* in infants. Two case reports*. *Medicine*; 98:35.

Mycophenolate mofetil (MMF) in autoimmune encephalitis

Nosadini et al. (2019) investigated the safety and efficacy of mycophenolate mofetil (MMF) in paediatric autoimmune/immune-mediated central nervous system (CNS) conditions by doing a retrospective multicentre study of 44 children. Nineteen children had proven/suspected autoimmune encephalitis, 14 had inflammatory demyelinating CNS diseases and 11 had other autoimmune/immune-mediated CNS conditions. Prior to MMF treatment (median 9.5 months from onset), all children received first-line immune therapies, and 17 had second-line rituximab and/or cyclophosphamide. MMF was administered for a median of 18 months. In 22/40 patients, MMF was administered after relapses had occurred. During the MMF treatment, relapses were reported in eight patients. Factors associated with relapses were medication weaning/cessation, or suboptimal MMF dosage/duration. Also patients who were started on MMF early in the disease course or those who were on a higher rate of second-line treatments were less often associated with relapses. Moderate adverse effects

(gastrointestinal, movement disorder, tremor, rash) were reported in six patients and severe infections (influenza A pneumonia and herpes zoster) were reported in two patients. The median time to the initiation of these effects was one month since introduction of MMF.

Nosadini M., Gadian J., Lim M., et al. (2019) *Mycophenolate mofetil in paediatric autoimmune or immune-mediated diseases of the central nervous system: clinical experience and recommendations*. *Developmental medicine & child neurology*; 61: 458-468.

Predicting outcomes

Neutrophil-to-lymphocyte ratio (NLR) is a novel potential biomarker of inflammatory status in other inflammatory diseases. Zeng et al. (2019) investigated the use of NLR as a biomarker of autoimmune encephalitis (AE) progression. The levels of neutrophil-to-lymphocyte ratio (NLR) were measured from peripheral blood tests. The study, which included 34 newly diagnosed AE patients and 35 age- and sex-matched healthy controls, found that peripheral NLR level in AE patients was significantly higher than in healthy controls, and median NLR level in patients with severe impairments (modified Ranking Scale (mRS) >3) was significantly elevated when compared to patients with mild to moderate impairments (mRS ≤3). In addition, lymphocyte counts were negatively correlated with mRS score.

Broadley et al. (2019) performed a literature review (44 publications) in order to identify prognosis factors for patients with AE (n=2,823). They found that delay in immunotherapy was associated with worse outcomes in patients with various types of AE. Altered consciousness, intensive care unit (ICU) admission and no use of immunotherapy were associated with poor prognosis in anti-NMDAR encephalitis. Older age, sex, the presence of status epilepticus, cerebrospinal fluid (CSF) abnormalities and magnetic resonance imaging (MRI) changes did not influence the outcomes in these studies. The study did not find a clear association among the antibody titres, autonomic dysfunction, underlying malignancy and prognosis.

Balu et al. (2019) studied 382 patients with anti-NMDAR to ascertain the factors that may predict disease severity and neurological function at one year. Of all patients, 74% had good functional status and 26% had poor functional status at one year. Of those with poor functional status, 35% achieved good functional status at two years. The authors found that reduced level of consciousness, presence of an acute movement disorder, central hypoventilation, the need for ICU admission, time to first recorded clinical improvement after treatment initiation, and delay until treatment initiation for more than four weeks after symptom onset, were associated with poor one-year functional status. Abnormal MRI, elevated CSF white blood cell count and elevated CSF protein level were also associated with poor functional one-year status. The authors created the anti-NMDAR encephalitis one-year functional status (NEOS) score to predict patients functional outcome. The score included five variables: ICU admission, treatment delay >4 weeks, lack of clinical improvement within four weeks, abnormal MRI and CSF white blood cell count >20 cells/μL. Each variable was assigned one point and this score

was strongly associated with poor functional status at one year (3% for 0 or 1 point to 69% for 4 or 5 points). The authors highlighted the importance of this score for families and clinicians, enabling them to know what to expect and to identify those patients who may benefit from novel therapies in future clinical trials.

Loane et al. (2019) undertook a cross-sectional group study to look into structural and functional brain abnormalities and how these changes relate to the persistent memory impairment in patients with VGKCC antibody encephalitis. The study included 24 patients (20 males), 18 anti-LGI1 antibody-positive. A neuropsychological assessment revealed that patients were impaired on visual and verbal recall and verbal recognition memory measures. They also scored higher than the controls on the depression subscale of the Hospital Anxiety and Depression Scale, although not in the severe range. Structural brain imaging showed focal hippocampal atrophy within the medial temporal lobes, correlative atrophy in the mediodorsal thalamus, and additional volume reduction in the posteromedial cortex. The patients' hippocampal or thalamic volumes did not correlate with the memory disturbances or patients' premorbid Full Scale IQ (pFSIQ) or depression scores. A whole-brain seed-to-voxel Functional Connectivity (FC) analysis revealed reduced posteromedial cortico-hippocampal and interhippocampal FC. This did not correlate with pFSIQ or depression score, but with overall composite memory scores. The authors concluded that VGKCC antibody encephalitis causes focal amnesia with spared visual recognition memory. However, network dysfunction rather than focal atrophy predicts memory performance.

Loane C., Argyropoulos G.P.D., Roca Fernández A., et al. (2019) Hippocampal network abnormalities explain amnesia after VGKCC-Ab related autoimmune limbic encephalitis. *J Neurol Neurosurg Psychiatry*; 90: 965–974.

Balu R., McCracken, L., Lancaster E., et al. (2019) A score that predicts 1-year functional status in patients with anti-NMDA receptor encephalitis. *Neurology*; 92.

Broadley J., Seneviratne U., Beech P., et al. (2019) Prognosticating autoimmune encephalitis: A systematic review. *Journal of Autoimmunity*; 96: 24–34.

Zeng Z., Wang C., Wang B., et al. (2019) Prediction of neutrophil-to-lymphocyte ratio in the diagnosis and progression of autoimmune encephalitis. *Neuroscience Letters*; 694: 129–135.



Recovery and rehabilitation

“An informed choice regarding vaccination must include an understanding of the potential consequences of acquiring JE, in addition to the likelihood.”

(Turtle et al., 2019)

“More than devastating” – Japanese encephalitis (JE) in returned travellers

Turtle et al. (2019) described the clinical details of three cases of JE in British travellers occurring between 2014 and 2015. They also described survivors and their families' personal experiences of life after JE. The interviews reveal how the illness changed the patients' lives and those of their families. The words and phrases the interviewees used are reflective of the impact JE has had on their lives: “strange”, “scary”, “devastating”, “shock”, “it is not anything you imagine”, “this is for life”.

All three cases had clear indications for vaccination, all experienced life-threatening illness, and all have been left with life-changing brain injuries. The patient interviews revealed they would have liked more information, particularly about the severity of the condition were they to have contracted it. The authors argued that travel health providers should be aware of the severity of JE as well as the likelihood, allowing travellers to make fully informed decisions on JE vaccination.

Parents' views on the impact of encephalitis

Lemon et al. (2019) investigated how parents experience and interpret outcomes in relation to their child who has been affected by encephalitis. In-depth, semi-structured interviews with 15 parents of 12 children and young people affected by encephalitis have been conducted. Parents reported an apparent full recovery for three children. The other nine children presented a range of ongoing difficulties. The authors interpreted the findings of their interviews by distinguishing among different stages of the illness. In the acute illness, the focus was on “the dysfunctional body”. Parents recollected the chaos that encephalitis had brought on their child's body and mind, disrupting their child's ability to function normally. At this stage of their child's illness, almost all parents reported an overwhelming fear that their child would die.

In the recovery and rehabilitation stage the focus was on outcomes beyond survival. Parents described the return of some element of their child's physical or mental functioning and their feelings of relief, which were followed by the distress at seeing their

children's increasing sufferings (e.g. headaches, the inability to control their own body, painful medical interventions). However, as improvements progressed, they also started to consider their child's reintegration back into their everyday life.

In the third stage of reintegrating into everyday life after encephalitis, parents reported challenges within the context of their everyday lives such as independence around the house, progress at school, participating in social life, and in their overall wellbeing and happiness. These outcomes were influenced by modifiable external factors, including availability of resources, adaptations, support and the attitudes of others. Parents' views of the outcomes were influenced by making comparisons to other children and reflecting on their child pre- and post-encephalitis.

The authors concluded that the outcomes of encephalitis in children need to be placed within the wider context of patient and family experience as well as the timeframe of recovery. The authors advised parents' participation in measuring outcomes and continuous assessment during recovery.

Lemon J., Cooper J., Defres S., et al. (2019) *Understanding parental perspectives on outcomes following paediatric encephalitis: A qualitative study. PLoS ONE 14(9): e0220042.*

Turtle L, Easton A., Defres S., et al. (2019) "More than devastating"—patient experiences and neurological sequelae of Japanese Encephalitis. *J Trav Med 2019; 26 (6).*

Multidisciplinary approach to rehabilitation

Perna et al. (2019) described three young adult males with non-paraneoplastic limbic encephalitis (NPLE) from the onset to rehabilitation and recovery. The patients (aged between 16 and 19) had an insidious onset of the disease with withdrawal and then became psychotic, and experienced delusions and hallucinations as initial symptoms. All patients were hospitalised and saw improvements only after treatment with immunoglobulin. A neuropsychological evaluation revealed cognitive sequelae such as short-term memory and executive functioning which fit the LE profile with limbic and frontal executive dysfunction. Two patients reported impairment on immediate and delayed recall of word lists, although language and simple focused attention were largely intact. Patients were distracted and had difficulty dual tasking. They also exhibited reduced self-regulation, monitoring and limited awareness of impairments. The authors reported a discrepancy between testing performance and behavioural presentation. Two patients returned gradually to school after home and/or online schooling initially. The authors argued that there is a need for ongoing neuropsychological input during recovery to better understand the recovery, as well as guide the treatment and reintegration into community. In this study, the authors continued the psychological intervention until emotional and behavioural difficulties were reduced and/or managed.

A multidisciplinary approach tailored to facilitate different stages of recovery is suggested by Han et al. (2019) in their report of a 15-year-old girl with severe anti-NMDAR encephalitis who spent one year in intensive care due to intractable seizures, dyskinesia, dysautonomia and severe encephalopathy. The patient received

intensive inpatient rehabilitation from a multidisciplinary team including a paediatric neurologist, a child psychiatrist, nurses, a physiotherapist, an occupational therapist, a speech therapist and a social worker. The challenges in her rehabilitation included altered consciousness, psychiatric disturbances and impaired cognition. She was also very often aggressive and required one-to-one nursing attention. Her family took part in the goals-setting process. After 20 months of intensive rehabilitation, she achieved substantial progress in all physical, cognitive, social, and communication aspects. She still required ongoing support with her residual neurocognitive deficits, visual perception and motor coordination difficulties, but her daily life has improved.

The authors suggested that using familiar therapists, sessions in less distracting environments, emotional memories to motivate, favourite music or activities, and allowing autonomy in choosing activities aided her rehabilitation process. A successful sleep-wake cycle was achieved by using melatonin, a clock and timetable, and cognitive orientation. The patient's food aversion was managed with a low dose of valproic acid and reintroduction of familiar scents and food she liked before her illness. Neurocognitive difficulties were targeted during activities such as cooking, bakery and grocery shopping. The authors concluded by emphasising the need for long-term rehabilitation in patients with severe sequelae after anti-NMDAR encephalitis.

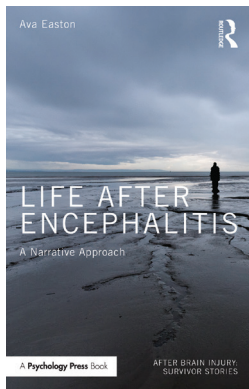
Zangrandi et al. (2019) presented the clinical and neuropsychological profile of a 74-year-old patient during nine years of monitoring which included 10 neuropsychological assessments. His illness started at 65 years, but he was diagnosed with VGKC antibody encephalitis only four years later and finally with anti-LGI1 encephalitis at 71 years. His neuropsychological profile varied according to the stage of the illness and type of treatment. His non-specific treatment before anti-VGKC encephalitis diagnosis did not impact on his neurocognitive profile or seizure control. Overall his difficulties included long-term memory impairment (verbal more than visual), executive function disturbances and language deficits. He maintained intact his attention and visual-spatial abilities. Anxiety and depression varied according to the treatment regimen and external events (e.g. family grievance). Depression scores were also correlated with his neuropsychological profile. The authors concluded with the great significance of specific treatments (immunoglobulin and corticosteroids) and continuity in their use on the neurocognitive profile of patients.

Han V.X., Lee M.W.X., Lin J.B. (2019) *Multistage neurorehabilitation of an adolescent with severe anti-N-methyl-D-aspartate receptor encephalitis: a case report. International Journal of Rehabilitation Research; 42: 89–91.*

Perna R., Harik L., Arenivas A. (2019) *Three case studies of nonparaneoplastic limbic encephalitis (NPLE) in young adult males: Onset, course, and recovery following rehabilitation services, Applied Neuropsychology: Child; 8:1, 93-99.*

Zangrandi A., Gasparini F., Marti A., et al. (2019) *A 9-year neuropsychological report of a patient with LGI1-associated limbic encephalitis, Journal of Clinical and Experimental Neuropsychology; 41(7): 749-759.*

Book review



Life After Encephalitis. A Narrative Approach by Dr Ava Easton

Life After Encephalitis provides a unique insight into the experiences of those affected by encephalitis, sharing the rich, perceptive, and often powerful, narratives of survivors and family members. It shows how listening to patient and family narratives can help us to understand how they make

sense of what has happened to them, and also help professionals better understand and engage with them in practice. The book will also be useful for considering narratives associated with brain injuries from other causes, for example traumatic brain injury.

Life After Encephalitis will appeal to a wide range of people: professionals working in neurology and rehabilitation, and also to survivors of encephalitis, their families, and carers.

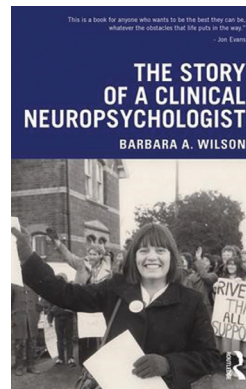
“Easton’s book makes you think about identity. If our brains hold our memories that largely determine our personality and effectively define us, what does it mean if part of our brain is destroyed? Personality creates relationships—so when someone you love changes, what happens to the relationship? Encephalitis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

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

Disability Experiences: Memoirs, Autobiographies, and Other Personal Narratives, 1st Edition By G. Thomas Couser, Hofstra University (Hempstead NY) and Susannah B. Mintz, Skidmore College (Albany NY)

This book presents essays on 200 narrative works written by persons with disabilities. The disabilities covered are mostly physical, but psychological/psychiatric conditions, developmental/intellectual impairments, and addiction are also included. It covers memoirs, autobiographies, family memoirs (e.g., written by spouse or sibling), and other forms of personal narratives, such as art, poetry, diary/journal entries, etc. The works date from as early as 1470 to as recent as 2018. Each essay provides an overview of the memoir/work, and discussion of historical and cultural context, themes, and critical response to the work. This book includes a review of Susannah Cahalan’s *Brain on Fire* by Dr Ava Easton, Encephalitis Society.

www.gale.com/ebooks/on-gvrl/disability-experiences

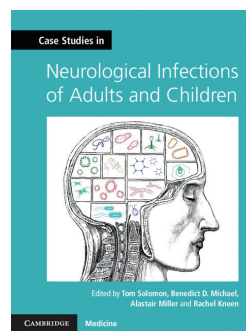


The Story of a Clinical Neuropsychologist by Prof Barbara Wilson OBE

From a disadvantaged childhood to becoming one of our best-loved clinical neuropsychologists, this exceptional book tells the life story of Barbara A. Wilson, who has changed the way we think about brain injury rehabilitation. Barbara’s story shows how it is possible to have a fulfilling career alongside

a successful family life, even when faced with the deepest of personal tragedies; the death of her adult daughter Sarah. Clinical and neuropsychologists will recognise Barbara’s influence on rehabilitation practice and her tireless aim to get what is best for people needing neuropsychological rehabilitation. It will inspire those with brain injury and their families who may struggle to make life meaningful, as well as encourage readers to stick to their beliefs and triumph in the face of obstacles.

Available from Routledge www.routledge.com



Case Studies in Neurological Infections of Adults and Children Edited by Prof. Tom Solomon, Dr Benedict Michael, Alastair Miller and Dr Rachel Kneen

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

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

www.cambridge.org

About the Encephalitis Society

How we help

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

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Support Line: +44(0)1653 699599
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- Producing high quality, evidence-based and peer-reviewed information about encephalitis.
www.encephalitis.info
- Raising awareness about encephalitis, its consequences and the need for improved services.
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www.worldencephalitisday.org
- Conducting and funding research and working in partnership with other researchers.

Professional membership

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

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

Some of the ways we support you and your work:

- We deliver the only accredited international Encephalitis Conference for health, social and educational professionals.
- We bring together and collaborate on research into the condition, and provide trusted support and information to the people in your care.
- We have an extensive database of over 10,000 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/professional-membership or contact us at mail@encephalitis.info or +44 (0)1653 692583.

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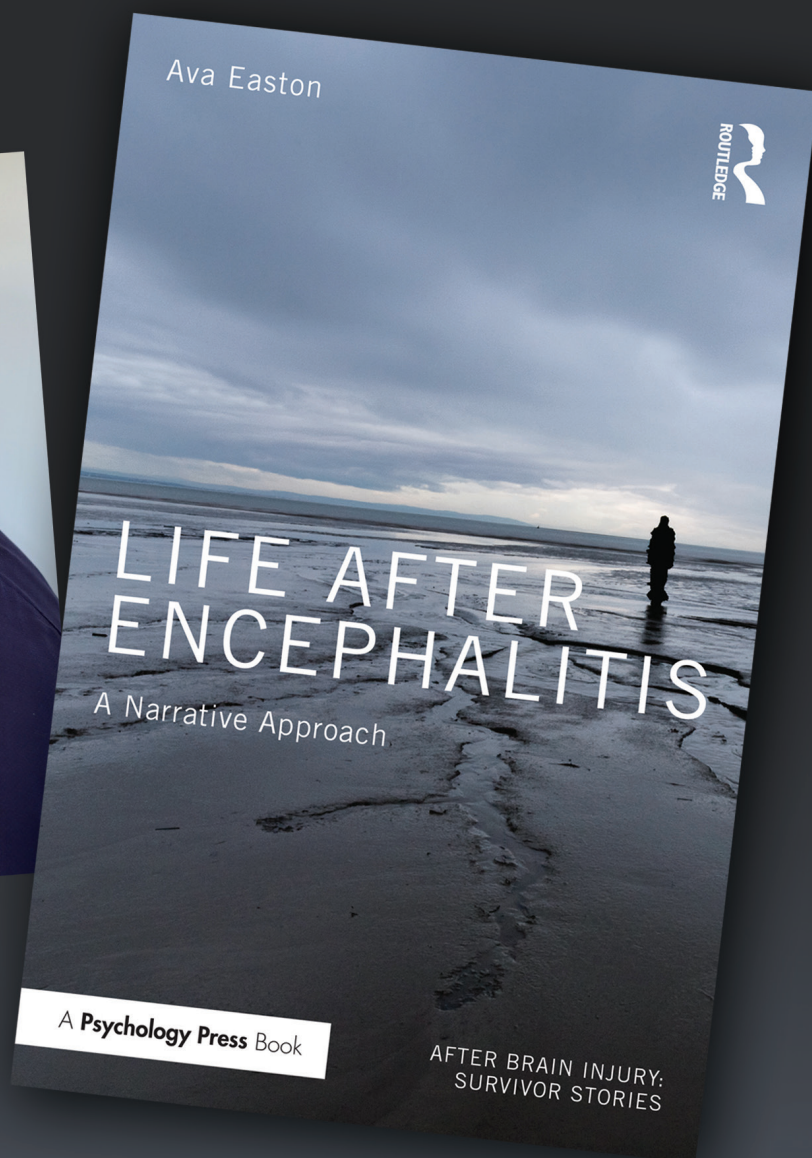
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