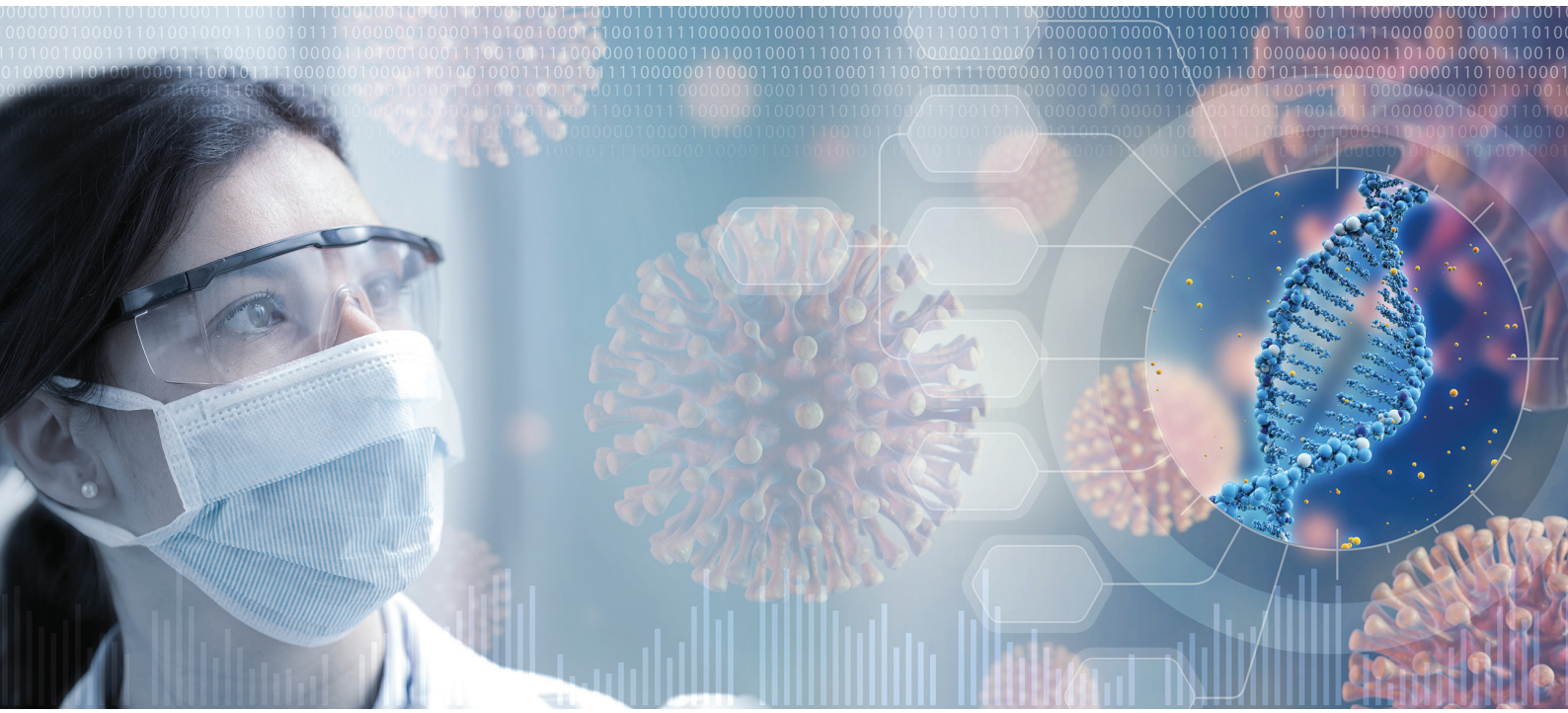
RESEARCH SUMMARY

ADVANCES IN ENCEPHALITIS

2020



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Welcome to the Encephalitis Society's Research Summary 2020

Dr Ava Easton at the World Health Organization

The Research Summary-Advances in Encephalitis 2020 presents a collection of research papers published during that same year.

Encephalitis in children, both infectious and autoimmune, was the topic of many research studies in 2020. These studies revealed that there is still a high percentage of cases without an established cause from 53% in Brazil to 31% in Sweden. There was a variation on the type of infectious agents causing encephalitis according to geographical location, the most common viruses being tick-borne encephalitis virus (Sweden), West Nile virus (USA), enterovirus (Brazil), herpes simplex virus (the Netherlands).

There are many challenges in establishing the exact cause of encephalitis and initial features do not show sufficient clues towards an etiological diagnosis. It is essential to follow current guidance especially it has been reported that only two-thirds of patients suspected of encephalitis in a study in the USA were given empirical acyclovir.

Autoimmune encephalitis rates are increasing which proves that more cases are diagnosed, but there is still more to do to improve and speed up the diagnosis. Clinicians are urged to have a better understanding of the antibody tests required for diagnosis and when to ask for them in order to avoid false positive results or being misled. Provisional paediatric autoimmune encephalitis classification criteria and an algorithm to facilitate early diagnosis have been developed (page 16).

Studies also looked at the consequences left by encephalitis. Sequelae were reported in more than a third of patients after tick-borne encephalitis, in nearly two thirds of patients after anti-NMDAR encephalitis andJapanese encephalitis. Studies on sleep disorders in autoimmune encephalitis showed that these persist after the initial illness and impact hugely on patient's quality of life. Adequate discharge planning and information regarding the illness, consequences and future care for patients and their family/carers are essential to improve the overall outcomes.

The year 2020 was taken over by the COVID-19 pandemic and many studies (single case reports and cohort studies) emerged, looking at neurological manifestations, including encephalitis, associated with COVID-19. However, there is still much to do to understand the various manifestations reported around neurology and COVID-19, especially the connection between the virus and the neurological manifestations.

Despite the pandemic year, the Encephalitis Society has continued its aim of contributing to, and funding research on encephalitis. We have launched our third year of seed funding which is aimed at projects in low-to-middle income countries. Deadline is 31st August 2021. To apply please visit our website (www.encephalitis.info/seedfund). Plans for our annual conference - Encephalitis 2021 are under way. After the 2020 virtual conference saw a record number of participants (257 delegates from 34 countries) we are delighted to adopt a new conference format - a hybrid with both face-to-face (Royal College of Physicians, London) and virtual attendance on 7th December 2021. We urge you to submit an abstract and register for the Conference (www.encephalitis.info/conference).

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

Thank you to Oliver Milner (Student, Department of Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London) for his help with producing this Summary.

Contents

Epidemiology of encephalitis

"Since treatment options for infectious encephalitis are scarce, measures to prevent viral infections known to cause severe illness in children should be made and considered when designing immunization programs."
(Fowler et al., 2020)

Paediatric encephalitis: Sweden, USA, the Netherlands and Brazil

Fowler et al. (2020) performed a prospective study on paediatric acute encephalitis at a primary and tertiary hospital in Sweden between 2011 and 2016. Eighty-nine children, 52% female with a mean age of 53 months were included. A cause was established in 69% of patients (n=62) (confirmed in 29, probable in four and possible in 29 children), most common being tick-borne encephalitis (TBE) virus, enterovirus (EV) and rotavirus. A third of cases were caused by a vaccine-preventable virus. Immune-mediated encephalitis was diagnosed in 8% of children. An abnormal electroencephalogram (EEG) was reported in 90% of children, an abnormal magnetic resonance imaging (MRI) in 27% of children and seizures in 43% of children. Nearly half of the children were left with consequences. The authors concluded that encephalitis in children is a serious condition with many children needing admission in the intensive care unit (ICU).

Erickson et al. (2020) reported on 231 paediatric patients diagnosed with encephalitis between 2010 and 2017 in Houston. Fifty-five percent were male, the mean age was 8.1 years, and mean Glasgow Coma Scale (GCS) on admission was 12.3. Fifty-eight percent of patients had a cause identified: 55% infectious (of which 70% viral, 14% bacterial, 16% fungal and parasites) and 45% immune mediated. No cause could be identified in 42% of patients.

The most common infectious agents were human herpersvirus (herpes simplex virus 1, herpes simplex virus 2, human herpesvirus 6, varicella zoster virus, Epstein-Barr virus) (27%), arborvirus (18%), respiratory virus (13%) and EV (9%). West Nile virus (WNV) was the most common infectious cause of encephalitis. The most common immune-mediated types were anti-NMDAR encephalitis (52%), acute disseminated encephalomyelitis (ADEM) (30%) and Hashimoto's encephalitis (7%). Herpes simplex virus (HSV) and EV were diagnosed at a median of two days from presentation, whereas autoimmune and zoonotic causes were identified at a median of six days. Those with rarer autoimmune antibodies had a median time to diagnosis of 32.5 days. Patients with infectious encephalitis were more likely to be immunocompromised and have an abnormal MRI when compared with those with autoimmune encephalitis. Nine children died, the majority of whom had unknown causes despite extensive testing. The authors suggested that increased testing for WNV, Bartonella, and immune-mediated causes would likely result in more identified causes, earlier treatments and improved outcomes.

De Blauw et al. (2020) reported on encephalitis in children admitted to eight paediatric intensive care units (PICU) in the Netherlands between 2003 and 2013. A total of 121 children were included, of which 47.1% were males. The median ages at the time of admission to a PICU was 4.6 years with 20.7% patients <1 year of age. In 32.5% of cases, the illness course was complicated by co-infections. Comorbidity was reported in 23.5% children; the most frequent were: 4.2% malignancy, 3.4% immune deficiency and 2.5% prematurity. In 55.4% of patients, a cause was identified: 33.1% viral, 10.7% immune-mediated, 9.9% bacterial and 1.7% parasitic (malaria falciparum) and fungal encephalitis (aspergillosis). The most frequent viral causes identified were: 13.2% HSV, 5.0% EV and 4.1% HHV-6. Streptococcus pneumoniae was the most frequently identified bacterial pathogen (5.8%). ADEM was the most frequent cause of immune-mediated encephalitis (5.0%). HSV encephalitis was more common in children <5 years and immune-mediated encephalitis in older children. The authors concluded that an age of ≥5 years at initial presentation was associated with lower mortality, and the detection of a bacterial or viral pathogen was associated with a higher mortality.

Do Valle et al. (2020) conducted a cross-sectional study that included 270 children with a median age of two years diagnosed with viral meningoencephalitis at Hospital Pequeno Principe, Brazil, between 2013 and 2017. There was a male predominance in children with encephalitis younger than three years. A cause was identified in 47% of children: definite cause in 23.3% and probable cause in 24.1%. The most common definite causes were EV (18.1%), cytomegalovirus (CMV) (2.2%) and HSV (1.5%). The most probable causes were varicella-zoster virus (VZV) (5.9%), Epstein-Barr virus (EBV) (6%) and CMV (4.8%). Clinical manifestations included fever (81%), vomiting (50%), focal neurologic findings (46%), seizures (31%), and headache (30%). Full resolution of symptoms on discharge from the hospital was reported in 87% of children. Consequences were mainly observed in patients with focal neurologic symptoms, seizures, and EEG abnormalities. The authors concluded that, in southern Brazil, EV was the major cause of encephalitis in children. However, due to its changing spectrum, there is a need to continue to monitor viral encephalitis.

De Blauw D., Bruning, A.H.L., Busch C.B.E. et al. (2020) Epidemiology and etiology of severe childhood encephalitis in The Netherlands. The Paediatric Infectious Disease Journal. 30(4): 267-272.

Do Valle, D.A., Schmitz Ferreira Santos M.L., Garcia Giamberardino H.I. et al. (2020) Acute Childhood Viral Encephalitis in Southern Brazil. The Pediatric Infectious Disease Journal; 39(10): 894-898.

Erickson E.T., Muscal E., Munoz F.M., et al. (2020) Infectious and autoimmune causes of encephalitis in children. Paediatrics; 145(6): e20192543.

Fowler A., Ygberg S., Svensson E., et al. (2020) Prospective evaluation of childhood encephalitis: predisposing factors, prevention and outcome. The Pediatric Infectious Disease Journal; 39(12).

Autoimmune encephalitis (AE) and paraneoplastic neurological syndromes (PNSs)

Hébert et al. (2020) investigated the incidence of AE and PNSs in the Rhône-Ain- Isère region, France. Of 13,442 cases referred at the French National Reference Centre, Lyon, between 2016 and 2018, 5.1% had a diagnosis of definite PNS or AE. The most identified antibodies were anti-NMDAR, anti-LGI1 and anti-Hu.

Age distribution of cases showed one peak at ages 15-19 years, predominantly female patients with AE, and a second higher peak at ages 65-69 years, predominantly males with PNS. There were more females positive for Yo-, NMDAR, and GAD antibodies and more males positive for LGI1, Ma2, and CASPR2. Within the antibody-positive AE subgroup, the sex distribution differed according to age: a female predominance was noted in patients younger than 50 years, and males over 50 years were more commonly diagnosed. Among the patients with definite PNS or AE diagnosis, 38.4% had an associated diagnosis of cancer.

Of the 317 patients diagnosed with PNS, 195 met the criteria for classical PNS, 82 had atypical/negative testing for antibodies with associated cancers, and 40 were diagnosed with paraneoplastic AE. Of the 40 patients with paraneoplastic AE, there were 11 with GABABB receptor, 11 with anti-LGI1, and nine with CASPR2 antibodies.

The observed incidence rate of definite PNS and AE in France was 3.2 per million person-years compared with an expected incidence rate of 7.1 per million person-years. The national observed incidence rate for antibody-positive AE increased from 1.4 per million person-years in 2016 to 2.1 per million person-years in 2018, a substantially higher rate than the incidence rate of classical PNS (1.2 per million person-years) in 2018. The authors concluded that there is an increase in the incidence of diagnoses regis tered with the Reference Centre for all subgroups of PNS and AE studied. The national observed incidence rate is likely underestimated due to underdiagnosis and underreporting, with the authors highlighting the need for uniform diagnostic procedures on a national scale.

Hébert, J., Riche, B., Vogrig, A. et al. (2020) Epidemiology of paraneoplastic neurologic syndromes and autoimmune encephalitides in France. Neurol Neuroimmunol Neuroinflam; 26:7. OPEN ACCESS https://creativecommons.org/licenses/by/4.0/

Mortality and morbidity of patients in intensive care units (ICU) in Pakistan

Andleeb et al. (2020) performed a retrospective study of patients admitted to the ICU at the Aziz Fatimah College and Hospital, Faisalabad, between 2013 and 2018. Of a total 3,921 patients admitted to ICU, 75 had a confirmed diagnosis of encephalitis: an incidence rate of 1.9%. The mean age of encephalitis patients was 29.77 ± 12.45 years, and 45.3% were female. The estimated Glasgow Coma Score (GCS) at time of presentation was 8.35 ± 3.49. The most common clinical presentations in patients diagnosed with encephalitis were: 64% seizures, 53% headache, 29.3% irritability and 26.7% hemiparesis. Of all, 58.7% patients needed invasive ventilation, and 9.3% required non-invasive ventilation. The mortality rate of encephalitis was 37.3%, and only 6.7% of patients improved without any complications. The authors concluded that mortality and morbidity rates of patients with encephalitis remain high despite advancements in technology. They highlighted the need for health care facilities to pay special attention to monitoring and to properly allocate resources.

Andleeb, S., Bari, M.Y., Gill, I., et al. (2020) Incidence of encephalitis in the intensive care unit, a tertiary care hospital, Pakistan: a 5 year retrospective study. Turkish Journal of Anaesthesiology & Reanimation; 48:4; 288-293. OPEN ACCESS https:// creativecommons.org/licenses/by/4.0/

Clues to aetiology of encephalitis

Le Maréchal et al. (2020) sought to identify trends in encephalitis of unknown cause and to what extent initial presentation may be predictive of aetiology in patients with encephalitis, especially herpes simplex virus (HSV) and varicella zoster virus (VZV) encephalitis. Data from 349 patients enrolled in the National Cohort of Infectious Encephalitis in France (ENCEIF) from January 2016 to August 2018 were analysed. The most frequently identified causes were: 25% HSV, 11% VZV, 6% tick-borne encephalitis virus, 5% Listeria monocytogenes and 3% influenza virus. An unknown cause was reported in 34% of patients. The authors used a factor analysis of mixed data (FAMD) to describe the data and highlight correlated variables among the initial presentation of the patient (clinical, blood, cerebrospinal fluid-CSF, neuroimaging, and electroencephalogram data) and the etiologic pathogen. FAMD demonstrated no specific patterns

of variables related to encephalitis of unknown cause. The only patterns associated with HSV and VZV were haemorrhagic lesions, temporal lesions and a high rate of lymphocytes in the CSF. The authors concluded that initial presentation was not associated with any etiological pattern despite the recent advances in the diagnosis of encephalitis. They reiterated the importance of early treatment with acyclovir and amoxicillin being maintained until an aetiological pathogen can be identified.

Le Maréchal, M., Mailles, A., Seigneurin, A., et al. (2020) A prospective cohort study to identify clinical, biological, and imaging features that predict the etiology of acute encephalitis. Clinical Infectious Diseases; 20. ciaa598

West Nile virus (WNV) in the USA and Europe

Snyder et al. (2020) reported on WNV surveillance data across California, US, since WNV was first detected in 2003 in southern California. From 2003 to 2018, 6,909 human cases of WNV disease were identified, including 326 deaths. An additional 730 asymptomatic WNV infections were identified through screening of blood and organ donors. More than a half of cases (59%) were reported as WN neuroinvasive disease. Vlaskamp et al. (2020) reported on the first autochthonous WNV neuroinvasive disease, diagnosed in October 2020 in the Netherlands. Pietsch et al. (2020) reported on nine autochthonous cases of WN fever and WN neuroinvasive disease in eastern Germany, which included one fatality.

Vlaskamp, D.R.M., Thijsen, S.F.T., Reimerink, J., et al. (2020) First autochonous human West Nile virus infections in the Netherlands, July to August 2020. Euro Surveill. 25(46):pii=2001904.

Pietsch, C. Michalski, D., Münch J, et al. (2020) Autochthonous West Nile virus infection outbreak in human, Leipzig, Germany, August to September 2020. Euro Surveill. 25(46):pii=2001786.

Snyder, R.E., Feiszil, T., Foss, L., et al. (2020) West Nile virus in California, 2003–2018: A persistent threat. Neglected Tropical Diseases. 14(11): e0008841.

Pathogenesis of encephalitis

"We demonstrate highly active intrathecal B-cell activity in LGI1 antibody patients and show that B-cell repertoires, particularly from postgerminal center B cells on both sides of the BBB, may actively mutate and mature in patients with LGI1 antibody encephalitis."
(Lehmann-Horn et al., 2020)

Intrathecal B-cell activation in LGI1 antibody encephalitis

Lehmann-Horn et al. (2020) studied intrathecal B-cell activity in LGI1 antibody encephalitis. "Paired cerebrospinal fluid (CSF) and peripheral blood (PB) mononuclear cells were collected from six patients with LGI1 antibody encephalitis and two patients with other neurologic diseases. Deep B-cell immune repertoire sequencing was performed on immunoglobulin heavy chain transcripts from CSF B cells and sorted PB B-cell subsets. In addition, LGI1 antibody levels were determined in CSF and PB. Serum LGI1 antibody titers were on average 127-fold higher than CSF LGI1 antibody titers. Yet, deep B-cell repertoire analysis demonstrated a restricted CSF repertoire with frequent extensive clusters of clonally related B cells connected to mature PB B cells. These clusters showed intensive mutational activity of CSF B cells, providing strong evidence for an independent CNS-based antigen-driven response in patients with LGI1 antibody encephalitis but not in controls. Our results demonstrate that intrathecal immunoglobulin repertoire expansion is a feature of LGI1 antibody encephalitis and suggests a need for CNS-penetrant therapies." (Abstract from https://nn.neurology.org/content/7/2/e669.long)

Lehmann-Horn K., Irani S.R., Wang S., et al. (2020) Intrathecal B-cell activation in LGI1 antibody encephalitis. Neurol Neuroimmunol Neuroinflamm 2020;7: e669. OPEN ACCESS https://creativecommons.org/licenses/by/4.0.

Human monoclonal LGI1 autoantibodies

Ramberger et al. (2020) generated patient-derived monoclonal antibodies (mAbs) against LGI1 and explored their sequences and binding characteristics, plus their pathogenic potential using transfected HEK293T cells, rodent neuronal preparations, and behavioural and electrophysiological assessments in vivo after mAb injections into the rodent hippocampus. "In live cell-based assays, LGI1 epitope recognition was examined with patient sera (n = 31), CSFs (n = 11), longitudinal serum samples (n = 15), and using mAbs (n = 14) generated from peripheral B cells of two patients. All sera and 9/11 CSFs bound both the leucine-rich repeat (LRR) and the epitempin repeat (EPTP) domains of LGI1, with stable ratios of LRR: EPTP antibody levels over time. By contrast, the mAbs derived from both patients recognized either the LRR or EPTP domain. mAbs against both domain specificities showed varied binding strengths, and marked genetic heterogeneity, with high mutation frequencies. LRR-specific mAbs recognized LGI1 docked to its interaction partners, ADAM22 and ADAM23, bound to rodent brain sections, and induced internalization of the LGI1-ADAM22/23 complex in both HEK293T cells and live hippocampal neurons. By contrast, few EPTP-specific mAbs bound to rodent brain sections or ADAM22/23-docked LGI1, but all inhibited the docking of LGI1 to ADAM22/23. After intrahippocampal injection, and by contrast to the LRR-directed mAbs, the EPTP-directed mAbs showed far less avid binding to brain tissue and were consistently detected in the serum. Post-injection, both domain-specific mAbs abrogated

long-term potentiation induction, and LRR-directed antibodies with higher binding strengths induced memory impairment. Taken together, two largely dichotomous populations of LGI1 mAbs with distinct domain binding characteristics exist in the affinity matured peripheral autoantigen-specific memory pools of individuals, both of which have pathogenic potential. In human autoantibody-mediated diseases, the detailed characterization of patient mAbs provides a valuable method to dissect the molecular mechanisms within polyclonal populations." (Abstract from https://academic.oup.com/brain/article/143/6/1731/5841730)

Ramberger M., Berretta A., Tan J.M.M., et al. (2020) Distinctive binding properties of human monoclonal LGI1 autoantibodies determine pathogenic mechanisms, Brain; 143 (6): 1731–1745. OPEN ACCESS https://creativecommons.org/licenses/by/4.0

Anti-LGI1 and anti-CASPR2 antibodies: unfolding immunopathogenesis

Körtvelyessy et al. (2020) analysed serum and CSF cytokine levels of seven patients with antibodies against LGI1 and nine patients with antibodies against CASPR2 recruited from two tertiary AE centres in Germany. The results showed distinct cytokine differences in CSF but not in IgG subclasses between patients with LGI1 and CASPR2. Screening of CSF samples revealed three candidate parameters (CCL2, CXCL10 and sICAM1), which showed elevated levels, but no biomarker properties; the levels of most candidate parameters were higher in the CSF of patients with CASPR2 than of LGI1 and controls; there were no significant changes of cytokine concentrations before and after initiating treatment; CXCL13 points at a B cell-mediated neuroinflammation and sICAM1 at a T cell-mediated neuroinflammation. The authors argue that although anti-CASPR antibodies may play a more important role than anti-LGI1 antibodies, none of the examined parameters could be a biomarker for the disease stage. CASPR2 and LGI1 antibody encephalitis have different immunological mechanisms.

Muñiz-Castrillo et al. (2020) investigated whether the diseases described with the anti-CASPR2 antibodies – acquired neurotomya, limbic encephalitis (LE) and Morvan syndrome (MS) – are three distinct entities with different pathogenesis or one spectrum of diseases with same immunopathology. The study included 56 patients with CASPR2 antibody, looking at their symptoms, immunological features and the association with human leucocyte antigen (HLA). Patients with LE were divided in two groups: those with isolated limbic features and those with combined extra limbic features; however, both groups shared similar immunogenetic characteristics. Compared with the other patients, those with LE were more frequently carriers of HLA-DRB1*11:01 and had higher serum and CSF titres. The authors argued that these are different clinical phenotypes with no overlap between LE and MS.

Körtvelyessy P., Goihl A., Guttek K., et al. (2020) Serum and CSF cytokine levels mirror different neuroimmunological mechanisms in patients with LGI1 and Caspr2 encephalitis. Cytokine; 135: 155226.

Muñiz-Castrillo S., Joubert B., Elsensohn M.-¬H., et al. (2020) Anti-CASPR2 clinical phenotypes correlate with HLA and immunological feature. J Neurol Neurosurg Psychiatry; 91:1076–1084.

Infectious encephalitis

"Clinicians and public health officials need to be aware of the wide spectrum of neurological diseases linked to arboviruses and appreciate that dual infection is common and might affect disease pattern and severity."
(Brito Ferreira et al., 2020)

Neurological disease in adults with Zika and chikungunya virus infection in Northeast Brazil

Brito Ferreira et al. (2020) undertook a prospective observational study during epidemics of Zika and chikungunya viruses in a dengue-endemic area in Brazil. Of 1,410 patients admitted to hospital, 201 adult patients with suspected acute neurological disease and a history of suspected arboviral infection were included in this study. Evidence of Zika, chikungunya or dengue infection by viral RNA or specific IgM antibodies in serum or cerebrospinal fluid (CSF) was identified in 74% of patients: 49% of them had a single viral infection (27% had chikungunya, 20% had Zika, and 1% had dengue infection) and 25% had evidence of dual infection, mostly with Zika and chikungunya viruses.

Neurological syndromes seen more frequently included: encephalitis in 16, myelitis in 22, ADEM in eight and Guillain-Barré syndrome in 47. The patients with chikungunya infection were more often associated with central nervous system (CNS) disease, and the patients with Zika infection were more often associated with peripheral nervous system disease. The risk of stroke or transient ischaemic attack was also higher for those with dual infection (17%) than for those with mono infection (6%). All patients with encephalitis presented with fever, rash, or both, followed by neurological disease at a median interval of five days for patients with Zika mono-infection and nine days for those with chikungunya infection. Most patients (14) had altered behaviour or reduced consciousness, seven patients had seizures and one presented with meningism. At discharge, ten patients had motor or cognitive deficits and one had ongoing seizures.

The authors concluded that patients with arboviral infection (Zika and chikungunya) present with a wide and overlapping range of neurological manifestations. Dual infection may have an increased risk of acute cerebrovascular disease.

Brito Ferreira M.L., Militão de Albuquerque M.F.P., de Brito C.A.A., et al. (2020) Neurological disease in adults with Zika and chikungunya virus infection in Northeast Brazil: a prospective observational study. Lancet Neurol; 19(10):826-839.

Tick-borne encephalitis (TBE): a comparison and overview

Krawczuk et al. (2020) compared the course of TBE in children and adults, following a retrospective analysis of the medical records of 669 patients (68 children and 601 adults) in Poland. Firstly, TBE in children differed from the TBE in adults regarding presentation: symptoms in children were milder compared with those in adults.

In total, 97% of children presented with meningitis and 49.26% of adult patients presented with meningoencephalitis and meningo-encephalomyelitis. Nausea and vomiting were more frequent in children, while neurological manifestations were more frequent in adults. There were no differences in CSF pleocytosis at the onset of disease, but there were differences at the follow-up examination. The CSF protein concentration at both times was higher in adults. Children treated with corticosteroids over seven days had higher pleocytosis than pleocytosis at the onset of disease compared with adults, which suggests that corticosteroid use prolongs the disease duration. However, it did not influence the outcomes. Children had more favourable outcomes than adult patients (27% of children and 42.1% of adults developed sequelae).

Barp et al. (2020) reported clinical and laboratory findings resulting from a retrospective analysis of 148 TBEV infections in Italy from 2000 to 2019. There were 76% male and 24% female with ages between 13 and 84 years. Only half of the patients reported a tick bite and just three patients had a vaccination (one, two, or three doses, but no booster). A monophasic course was reported in 28% and included symptoms such as: fever, asthenia, arthromyalgia

and headache. The other 72% of patients had a biphasic course with the second phase manifested with fever, headache, ataxia, arthromialgia, vomiting and nausea. Laboratory findings included thrombocytopenia, neutropenia and leukocytosis (first phase) and monocytosis and lemphocytopenia (second phase). The study also reported patients having electrolyte disorders, high levels of transaminases, GGT, bilirubin, CPK, LDH, fibrinogen and amylase. Computed tomography was abnormal in 23% of those tested and magnetic resonance imaging in 44%: however, the abnormalities were not specific. More patients had an abnormal EEG at follow-up than had sequelae. Sequalae were reported in more than a third of patients at one month follow-up: neurological (tremor, limb palsy, ataxia, paresthesia) in 35% of patients, neurocognitive (anxious-depressive state, amnesia, concentration difficulties) in 7% and non-specific (asthenia, headache, arthromyalgia, nausea, abdominal pain) in 31%. Sequelae were more common in men. Parestesia and tremor were independently associated with sequalae.

Barp N., Trentini A., Di Nuzzo M., et al. (2020) Clinical and laboratory findings in tick-borne encephalitis virus infection. Parasite Epidemiology and Control; 10: e00160.

Krawczuk K., Czupryna P., Pancewicz S., et al. (2020) Comparison of tick-borne encephalitis between children and adults—analysis of 669 patients. Journal of NeuroVirology. 26: 565–571.

Bornavirus encephalitis

Niller et al. (2020) reported the presence of Borna disease virus 1 (BoDV1) infection in eight patients: two patients were immunocompromised after organ transplant and six were immunocompetent. All patients lived within the known endemic area in central Europe. Positive results were confirmed by deep sequencing antigen detection and BoDV1-reactive antibodies in serum and cerebrospinal fluid. Initial symptoms of headache and fever were followed by neurological signs, such as unsteady gait, confusion, memory deficits, seizures and progressive loss of consciousness. The patients progressed quickly into deep coma, loss of brainstem reflexes, and ultimately to death within 16–57 days after hospital admission. Electroencephalography revealed diffuse slowing in all individuals within 1–6 days of the disease. The authors concluded that BoDV-1 infection needs be considered as a severe and potentially lethal zoonosis. BoDV-1 virus should be considered a potential agent in severe encephalitis of unknown origin in endemic areas.

Finck et al. (2020) provided the first comprehensive description of the morphology of human BoDV-1 encephalitis, with histopathological verification of imaging abnormalities. “In an institutional review board-approved multicenter study, the authors carried out a retrospective analysis of 55 magnetic resonance imaging (MRI) examinations of 19 patients with confirmed BoDV-1 encephalitis. Fifty brain regions were analyzed systematically (T1w, T2w, T2*w, T1w + Gd, and DWI), in order to discern a specific pattern of inflammation. Histopathological analysis of 25 locations in one patient served as correlation for MRI abnormalities. Baseline imaging, acquired at a mean of 11± 10 days after symptom onset, in addition to follow-up scans of 16 patients, revealed characteristic T2 hyperintensities with a predilection for the head of the caudate nucleus, insula, and cortical spread to the limbic system, whereas the occipital lobes and cerebellar hemispheres were unaffected. This gradient was confirmed by histology. Nine patients (47.4%) developed T1 hyperintensities of the basal ganglia, corresponding to accumulated lipid phagocytes on histology and typical for late-stage necrosis. BoDV-1 encephalitis shows a distinct pattern of inflammation in both the early and late stages of the disease. Its appearance can mimic sporadic Creutzfeldt–Jakob disease on MRI and should be considered a differential diagnosis in the case of atypical clinical presentation. “(Abstract from https://onlinelibrary.wiley.com/doi/10.1002/ana.25873)

Finck T., Liesche-Starnecker, F., Probst M., et al. (2020) Bornavirus encephalitis shows a characteristic magnetic resonance phenotype in humans. ANN NEUROL; 88: 723–73. OPEN ACCESS. https://creativecommons.org/licenses/by-nc-nd/4.0/

Niller H.H., Angstwurm K., Rubbenstroth D., et al. (2020) Zoonotic spillover infections with Borna disease virus 1 leading to fatal human encephalitis, 1999–2019: an epidemiological investigation. The Lancet. Infectious Diseases; 20(4): 467-477.

Herpes simplex encephalitis (HSE) – challenging presentations

Hauw et al. (2020) described an 87-year-old patient with HSE who was in an intensive care unit due to respiratory failure following an exacerbation of myasthenia gravis. The authors drew attention to diagnostic pitfalls related to this type of HSE. In this case, HSE was not suspected based on initial symptoms (fever and confusion) and treatment was delayed. The patient died one week after the onset of neurological symptoms.

Niksefat et al. (2020) reported a patient with altered mental status whose first two polymerase chain reaction (PCR) results were negative, who was ultimately diagnosed with HSE following the third positive PCR. The authors emphasised that acyclovir should be administered when there is a high clinical suspicion of HSE (presentation, imaging and electroencephalography) despite initial negative PCRs.

Hauw F., Dinkelacker V., Jaquet P., et al. (2020) Herpes simplex encephalitis: A new type of “ICU-acquired infection”? Heliyon; 6: e03667.

Niksefat M., Guillen D., Moshayedi P., et al. (2020) Third time’s a charm: diagnosis of herpes simplex encephalitis after two negative polymerase chain reaction results. Heliyon; 6: e04247.

Covid-19 and encephalitis

Coronavirus, or COVID-19, has dominated world news since first reports of the respiratory disease in late 2019 and the World Health Organization, as of writing, currently reports there has been over 164 million confirmed COVID-19 cases worldwide. Besides the respiratory-related afflictions caused by COVID-19, there have been several case studies that report encephalitis, alongside other neurological disorders, to also be associated with COVID-19.

Pilotto et al. (2020) completed a multicentre study of encephalitis cases within healthcare centres of northern Italy between February and May of 2020. In total, 25 encephalitis cases (15 males and 10 females; mean age 65.9 ± 9.6 years, range 50-84) positive for COVID-19 infection via reverse transcription-polymerase chain reaction analysis were analysed. Magnetic resonance imaging (MRI) results classified the encephalitis cases as acute disseminated encephalomyelitis (ADEM) (n = 1), acute necrotizing encephalitis (ANE) (n = 2), limbic encephalitis (LE) (n = 2), encephalitis with normal imaging (n = 13) and encephalitis with MRI alterations (n = 7). Electroencephalography (EEG) was abnormal in all cases with most cases showing a generalised slowing deriving from the frontal lobe (64%), while focal epileptic alteration was observed in 24% of cases. Cerebrospinal fluid (CSF) analysis was abnormal in 68% of patients. Cases of ADEM and LE showed significantly delayed onset compared to other forms of encephalitis but were associated, alongside ANE, with greater severity of COVID-19 respiratory effects. Blood and CSF analyses also showed higher LDH levels within these subtypes of encephalitis. Common symptoms at the onset of encephalitis were delirium (64%), aphasia/dysarthria (24%) and seizures (24%). Headaches were reported at onset by 24% of patients, which increased to 40% of patients following disease progression. Spontaneous recovery was observed in 24% of patients. A positive response to methylprednisolone, was observed in one case of ADEM, one case of LE and three cases of encephalitis featuring MRI alterations. Four encephalitis cases resulted in death, three featuring MRI alterations and one featuring typical MRI. The authors proposed that, considering the 43,139 COVID-19 cases reported within the same period in this geographic region, the incidence of encephalitis following COVID-19 is 58 per 100,000 cases.

Varatharaj et al. (2020) investigated neurological and neuropsychiatric complications from COVID-19 via a multicentre analysis of the UK COVID-19 cases in April 2020. Case report platforms provided 153 (median age 71 years, range 23-94) unique cases of neurological impairments associated with COVID-19, of which 125 complete clinical datasets were available for analysis. Of the 125 cases, 31% presented with altered mental status, with 18% of these cases resulting in encephalitis diagnoses and 23% resulting in diagnoses of unspecified encephalopathy. Within the cases of altered mental status, 49% were younger than 60 years. All encephalitis cases were confirmed to have evidence of CNS inflammation that adequately met clinical definitions of encephalitis and confirmed to be positive for COVID-19 infection. Efficacy of treatment or clinical outcomes were not reported by the authors.

Koh et al. (2020) studied all confirmed cases of COVID-19 in Singapore that had been referred with a neurological complaint within three months of COVID-19 onset. Of 47,572 confirmed cases between March and July 2020, 90 cases (98.9% male, median age 38, range 22-75) were identified as featuring neurological disorders. Within these cases, four patients developed encephalitis (100% male, range 40-73 years). In terms of neurological deficit, Case 1 featured spastic quadriparesis and transient ocular flutter and Case 3 suffered two episodes of right and left hemiplegia. Cases 2 and 4 featured no focal neurological deficit. Case 1 displayed mild pleocytosis upon CSF analysis whilst Case 2's CSF analysis remained normal. Cases 3 and 4 did not undergo CSF examination. MRI scans showed that in Cases 1-3, there were multifocal abnormalities in the cerebral white matter with varying impact on grey matter, brainstem and spinal cord. MRI of Case 4 showed multifocal haemorrhagic lesions predominantly within white matter. Cases 1, 3 and 4 did not respond significantly to intravenous immunoglobulin and corticosteroids. Case 2 eventually recovered after three months with mild neuropsychiatric deficits in working memory, visuospatial perception and planning abilities following physical therapy. Case 3 died three months into illness. No outcomes were reported for Cases 1 and 4.

Rifino et al. (2020) conducted a retrospective analysis of all COVID-19 cases from February 23rd to April 30th that were referred for neurological assessment at the Papa Giovanni XIII hospital in Bergamo, Italy. Of 1,760 COVID-19 positive patients, 137 showed evidence of neurological impairments following COVID-19 onset, of which 49 (35.8%) displayed altered mental status. Following brain MRI and CSF analyses of the patients with altered mental state, five patients were diagnosed with encephalitis. Of these five (mean age 66), one case was reported to be HSV1-related encephalitis, one necrotising encephalitis and two confirmed to be encephalitis cases with positive COVID-19 infection following RT-PCR of CSF. Efficacy of treatment or clinical outcomes were not reported by the authors.

Meppiel et al. (2021) performed a study of COVID-19 cases with neurological manifestation from March-April 2020 through data from 46 hospitals in France. The study comprised 222 COVID-19 patients with neurological manifestations (61% male and 39% female, median age 65 years, range 53-72) with neurological manifestations confirmed by MRI and CSF examination, and COVID-19 infection confirmed via RT-PCR in most cases. COVID-19-associated encephalopathy was observed in 30.2% cases and diagnosed encephalitis was observed in 9.5% of cases. The authors reported that the onset of encephalitis typically occurred seven (range 5-10) days after the onset of COVID-19 symptoms. Brain MRI was abnormal in 14 of the 21 encephalitis cases and showed heterogeneous acute nonvascular lesions. EEG was also abnormal in 14 of the 15 encephalitis patients assessed this way. CSF examination showed pleocytosis in 14 of the 21 encephalitis patients. Concerning clinical outcomes, ten patients with encephalitis fully recovered, of which three received corticosteroids, and the mortality rate was 4.8%.

Cao et al. (2020) reported on five patients (range 37-77 years) with severe COVID-19-related encephalitis presenting with altered mental state and impaired consciousness. Brain MRIs showed punctiform and slightly diffuse bilateral hyperintense lesions in both deep and periventricular supratentorial white matter for Cases 1-3 and lesions in the pons for Cases 1-2. In Cases 4-5, these supratentorial lesions were diffuse and confluent. CSF examinations were reported to be unremarkable, besides in Case 3, which featured albuminocytologic dissociation, and in Case 4, which featured mild pleocytosis. EEGs showed unspecific slow-wave activity. All patients received immunotherapy combined with corticosteroids (methylprednisolone) for 5-10 days and therapeutic plasma exchanges with albumin for 5-10 sessions. Cases 1-3 showed neurological improvement and improvement to consciousness following this therapy. Cases 4-5, however, showed no signs of improvement and ultimately died. The authors proposed that differences in response to immunotherapy and therapeutic plasma exchange treatment was due to differences in lesion intensity, as shown by MRIs.

Cao A., Rohaut B., Le Guennec L., et al. (2020) Neurosciences study group. Severe COVID-19-related encephalitis can respond to immunotherapy. Brain;143(12):102.

Koh J. S., De Silva D. A., Quek A. M. L.,et al. (2020). Neurology of COVID-19 in Singapore. Journal of the Neurological Sciences; 418:117-118.

Meppiel E., Peiffer-Smadja N., Maury A., et al. (2021). Neurologic manifestations associated with COVID-19: a multicentre registry. Clinical Microbiology and Infection; 27(3): 458-466.

Pilotto A., Masciocchi, S., Volonghi I. et al. (2020). The clinical spectrum of encephalitis in COVID-19 disease: the ENCOVID multicentre study. Medrxiv.

Rifino N., Censori B., Agazzi E., et al. (2020). Neurologic manifestations in 1760 COVID-19 patients admitted to Papa Giovanni XXIII Hospital, Bergamo, Italy. Journal of neurology;1-8.

Varatharaj A., Thomas N., Ellul, M. A., et al. (2020). Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. The Lancet Psychiatry ; 7(10) : 875-882.

Anti-NMDAR antibody encephalitis

Diagnosing anti-NMDAR encephalitis

Singer et al. (2020) drew clinicians' attention to the importance of understanding the tests on screening for anti-NMDAR encephalitis in first episode psychosis. They urged them to consider the clinical features when undertaking diagnostics test in order to eliminate unnecessary testing. The authors argued that there is a limited understanding of the test accuracy measures, such as sensitivity and specificity, and so there is a high risk of false positive results.

Kerik-Rotenberg et al. (2020) conducted positron emission tomography (PET) with 2-deoxy-2-[fluorine-18]fluoro- D-glucose (18F-FDG) imaging examinations of 33 patients (18 men and 15 women; age between 17–55-years-old) with positive anti-NMDAR antibody encephalitis and compared them with a reference group of 14 brain 18F-FDG-PET scans from healthy volunteers using voxel-based statistical analysis. The study found that patients with anti-NMDAR encephalitis presented with mixed metabolic patterns: focal/bilateral hypermetabolism in the temporal lobe, insula, and cerebellum, associated with severe bilateral hypometabolism in the occipital and parietal lobes. The authors argued that 18F-FDG-PET should be included in the diagnosis work-up of suspected patients with anti-NMDAR antibody encephalitis.

Serra-Mestres et al. (2020) performed a systematic review of NMDAR antibody encephalitis case reports to ascertain the spectrum of catatonia associated with this condition. Overall, 139 articles describing 189 patients were included in the study. Patients presented with a variety of combinations of psychotic, mood and cognitive symptoms. At least two catatonia signs were present in 60% of these cases. The most common abnormalities were immobility/stupor (70%), mutism (67%), excitement (50%), posturing/catalepsy (34%), stereotypies (31%), rigidity (30%), withdrawal (27%) and negativism (20%). Immobility/stupor and excitement co-occurred in the same patient in 33% of cases. The authors argued that, overall, the phenomenological profile of catatonia for these patients was characterised by a preponderance of signs in the hypokinetic spectrum. However, in a third of patients, this presentation coexisted with excitement, which suggests that fluctuations in patients with anti-NMDAR encephalitis are frequent.

Guasp et al. (2020) undertook a retrospective assessment of serum antibody status and clinical features of 489 patients with anti-NMDAR encephalitis, defined by the presence of NMDAR antibodies in the CSF. In total, serum NMDAR antibodies was negative in 15% of the patients. Characteristics for this seronegative group included older age, more female and less tumour incidence. In multivariate analysis, older age at diagnosis, absence of tumour and less need for intensive care unit admission were independent variables associated with the absence of serum NMDAR antibodies. The authors concluded that a proportion of patients have anti-NMDAR negative serum; they may be older and have mild neurological symptoms.

Guasp M., Modena Y., Armangue T., et al. (2020) Clinical features of seronegative, but CSF antibody-positive, anti-NMDA receptor encephalitis. Neurol Neuroimmunol Neuroinflamm; 7:e659. OPEN ACCESS. https://creativecommons.org/licenses/by-nc-nd/4.0/

Kerik-Rotenberg N., Diaz-Meneses I., Hernandez-Ramirez R., et al. (2020) A metabolic brain pattern associated with anti-N-Methyl-D-Aspartate receptor encephalitis. Psychosomatics: 61:39–48.

Serra-Mestres J., Villagrasa-Blasco B., Thacker V., et al. (2020) Catatonia in N-methyl-D-aspartate receptor antibody encephalitis: Phenomenological characteristics from a systematic review of case reports. General Hospital Psychiatry; 64: 9-16.

Singer J., Sachdev P., Mohan A. (2020) Understanding the tests that we order: screening for anti-NMDA receptor encephalitis in first episode psychosis. Australasian Psychiatry; 28(2): 199–201.

Prognosis and outcomes

In a retrospective study of 60 patients with anti-NMDAR encephalitis (Mo et al. 2020), 38.3% of the patients had a good prognosis and 61.7% of the patients had a poor prognosis at discharge. One patient died during hospitalisation. The authors found that age, disturbance of consciousness at admission, and ≥50% slow waves on the electroencephalogram (EEG) were independent risk factors for a poor prognosis. The modified Rankin Scale (mRS) scores of 3-6 associated with poor prognosis. Wang et al. (2020) analysed the clinical manifestations of 106 patients with anti-NMDAR encephalitis in East China and the factors associated with prognosis. The binary logistic regression and receiver operating characteristic (ROC) curve analyses revealed the factors associated with poor outcomes included consciousness disturbance, number of symptoms and CSF antibody titre.

Shim et al. (2020) investigated the outcomes in 27 children with anti-NMDAR encephalitis using the mRS and Clinical Assessment Scale for Autoimmune Encephalitis (CASE) at onset and follow-up. At 12 months follow-up, 79.2% of the patients had ≤2 points on the mRS and CASE scores ranged from 0 to 5. Both mRS and CASE revealed a decreasing severity trend over 24 months. Language and memory difficulties were among the main disabilities. The study also found that younger children had a slower recovery.

Bartels et al. (2020) evaluated disease symptoms, and clinical and magnetic resonance imaging (MRI) findings and performed longitudinal volumetric MRI analyses in a European multicentre cohort of pediatric anti–N-methyl-D-aspartate receptor encephalitis (NMDARE) patients (n = 38). "Initial MRI scans showed abnormal findings in 15 of 38 (39.5%) patients, mostly white matter T2/fluid-attenuated inversion recovery hyperintensities. Volumetric MRI analyses revealed reductions of whole brain and gray matter as well as hippocampal and basal ganglia volumes in NMDARE children. Longitudinal mixed-effect models and z score transformation showed failure of age-expected brain growth in patients. Importantly, patients with abnormal MRI findings at onset were more likely to have poor outcome (Pediatric Cerebral Performance Category score > 1, incidence rate ratio = 3.50, 95% confidence interval [CI] = 1.31–9.31, p = 0.012) compared to patients with normal MRI. Ordinal logistic regression models corrected for time from onset confirmed abnormal MRI at onset (odds ratio [OR] = 9.90, 95% CI = 2.51–17.28, p = 0.009), a presentation with sensorimotor deficits (OR = 13.71, 95% CI = 2.68–24.73, p = 0.015), and a treatment delay > 4 weeks (OR = 5.15, 95% CI = 0.47–9.82, p = 0.031) as independent predictors of poor clinical outcome. Children with NMDARE exhibit significant brain volume loss and failure of age-expected brain growth. Abnormal MRI findings, a clinical presentation with sensorimotor deficits, and a treatment delay > 4 weeks are associated with worse clinical outcome. These characteristics represent promising prognostic biomarkers in paediatric NMDARE. "(Abstract from https://onlinelibrary.wiley.com/doi/10.1002/ana.25754)

Bartels, F., Krohn, S., Nikolaus M., et al. (2020) Clinical and magnetic resonance imaging outcome predictors in paediatric anti–N-Methyl-D-Aspartate Receptor Encephalitis ANN NEUROL; 88:148–159. OPEN ACCESS. https://creativecommons.org/licenses/by-nc/4.0/

Mo Y., Wang L., Zhu L., et al. (2020) Analysis of risk factors for a poor prognosis in patients with anti-N-Methyl-D-aspartate receptor encephalitis and construction of a prognostic composite score. J Clin Neurol 2020;16(3): 438-447.

Shim Y. K., Kim S.Y., Kim H., et al. (2020) Clinical outcomes of pediatric Anti-NMDA receptor encephalitis. European Journal of Paediatric Neurology; 29: 87-91.

Wang Y., Miao A., Shi Y., et al. (2020) Infuencing electroclinical features and prognostic factors in patients with anti NMDAR encephalitis: a cohort follow up study in Chinese patients.

Relapsing anti-NMDAR encephalitis

Zeng et al. (2021) aimed to analyse the clinical profile and long-term prognosis of relapsing anti-NMDAR encephalitis. Out of 82 patients with anti-NMDAR encephalitis, ten patients relapsed: three female and seven males with ages between 8-50-years-old. The relapse rate was 12.2%. Compared with onset, at relapse there were less seizures and consciousness disturbances. Other symptoms included psychiatric symptoms, cognitive impairment, speech dysfunction, movement disorders, central hypoventilation and autonomic dysfunction. At onset, all patients were cerebrospinal fluid (CSF) antibody positive and half were serum positive. At relapse, all patients were CSF positive and 67% were serum positive. The mRS score at relapse was significantly better than that at onset and patients were less likely to be admitted to the intensive care unit (ICU) at relapse. No tumours were found at initial illness or at relapse. Electroencephalography (EEG) was abnormal in all patients at both onset and relapse. Brain magnetic resonance imaging (MRI) scans showed more lesions at relapse (same or different location) than at onset.

Patients were treated with immunotherapy at both initial episode and relapse. The duration of taking anti-epileptic drugs (AEDs) was < 1 year (median 0.5 years) after first discharge, but the relapse rate of epilepsy was low. After first-onset discharge, the duration of medication intake was 3.10 ± 2.69 months; the relapse time was 18.3 ± 16.5 months. All patients relapsed after discontinuing immunotherapy. The authors concluded that stopping immunotherapy too early may lead to relapse, but long-term AED intake is unnecessary.

Zeng W., Cao L., Zheng J., Yu L. (2021) Clinical characteristics and long-term prognosis of relapsing anti-N-methyl-D-aspartate receptor encephalitis: a retrospective, multicenter, self-controlled study. Neurological Sciences;42: 199-207. OPEN ACCESS http://creativecommons.org/licenses/by/4.0/

Pregnancy outcomes in anti-NMDAR receptor encephalitis

Joubert et al. (2020) reported on the effects of anti-NMDA receptor encephalitis in pregnant patients and their babies. "We studied 11 patients; 6 developed anti-NMDAR encephalitis during pregnancy, and 5 became pregnant while recovering. There were no obstetrical complications, but 6 (55%) babies were premature. Ten newborns were healthy, and 1 (9%) developed transient respiratory distress. Nine infants had assessable follow-up (median 18 months; range, 7–96 months), and all showed normal development. We identified 21 cases in the English literature. Obstetrical complications occurred in 7 (33%) pregnancies. Two patients died of septic shock (1 baby successfully delivered), another 2 had miscarriages, and in 2, the pregnancy was terminated. Sixteen babies (76%) were delivered, 9 (56%) premature. At birth, 13/16 (81%) newborns were healthy, 2/16 (13%) had transient neurologic or respiratory symptoms, and 1 (6%) died of brain edema. Follow-up (median 12 months; range, 6–36 months) was reported for 8 children: 7 (88%) showed normal development and behavior, and 1 (13%) cortical dysplasia. Immunotherapy was used during pregnancy in 7 (64%) of our patients and 18 (86%) of the reported cases, including rituximab in 4 cases, without adverse effects. Patients who develop anti-NMDAR encephalitis during pregnancy or become pregnant during recovery often have obstetrical complications, but most of the newborns are healthy and appear to have normal development."(Abstract from https://nn.neurology.org/content/7/3/e668.long)

Joubert B., Garcıa-Serra A., Planaguma J., et al. (2020) Pregnancy outcomes in anti-NMDA receptor encephalitis. Case series. Neurol Neuroimmunol Neuroinflamm; 7: e668. OPEN ACCESS https://creativecommons.org/licenses/by-nc-nd/4.0/

Anti-NMDAR encephalitis following viral encephalitis

Dorcet et al. (2020) reported two patients (71- and 51-years-old) with anti-NMDAR encephalitis following herpes simplex encephalitis (HSE) at 12 and seven months apart, respectively. These cases were characterised by a quick onset, neuropsychiatric symptoms and poor response to first line immunotherapy, but experienced significant improvement after rituximab. Bras et al. (2020) also reported two cases of anti-NMDAR encephalitis after HSE in two female patients aged 50 years and 30 years developed after the second week and fourth week of illness with HSE, respectively. Both patients responded well to first-line immunotherapy.

Ma et al. (2020) undertook a hospital-based prospective study to determine whether Japanese encephalitis triggers anti-NMDAR immunoglobulin G (IgG) synthesis, and the incidence of JE-induced anti-NMDAR encephalitis in paediatric patients. Overall, 63 patients with JE negative for anti-NMDAR IgG in the serum and cerebrospinal fluid CSF during the acute phase were followed up. Five patients (four young children and one teenager) relapsed during the convalescence phase and manifested with choreoathetosis (young patients) and psychiatric and behavioural symptoms (teenager). CSF was positive for anti-NMDAR IgG in three patients and negative in two. The authors concluded that JE does not typically trigger anti-NMDAR IgG synthesis. The incidence of JE-induced autoimmune encephalitis in paediatric patients with JE was 7.9%, and the incidence of JE-induced anti-NMDAR encephalitis was 4.7%.

Nobrega et al. (2020) reported the occurrence of anti-NMDAR encephalitis after acute chikungunya (CHIK) infection in a five-year-old boy. The features of this occurrence included a biphasic course, positivity for both CHIK IgM and IgG and negative CHIK CSF PCR results, anti-NMDAR antibodies detected in serum and CSF, and a significant response to immunotherapy. Although a single case, the authors argued that, because of the global epidemic of CHIK infection and unknown mechanisms involving CHIK and autoimmunity, patients with acute CHIK infections and neurological manifestations should be considered for antineuronal antibody testing.

Bras A., Andre´ A., Sa L., et al. (2020) Anti-NMDAR encephalitis following Herpes Simplex Virus Encephalitis: 2 cases From Portugal. The Neurohospitalist; 10(2): 133-138.

Dorcet G, Benaiteau M, Bost C, et al. (2020) Two cases of late-onset anti-NMDAR auto-immune encephalitis after Herpes Simplex Virus 1 Encephalitis. Front. Neurol ; 11:38.

Ma J., Han W., Jiang L. (2020) Japanese encephalitis-induced anti-N-methyl-D-aspartate receptor encephalitis: A hospital-based prospective study. Brain & Development; 42: 179–184.

Nóbrega P.R., Morais N.M.d.M., Braga-Neto P., et al. (2020) NMDAR encephalitis associated with acute Chikungunya virus infection: A New Trigger? Front. Pediatr. 8:176.

Case reports

Tappata et al. (2020) reported a female patient with anti-NMDAR encephalitis that was retrospectively diagnosed after 15 years from disease onset with a long-term persistence of NMDAR antibodies and a probable MS diagnosis.

Nishimura et al. (2020) reported a 10-month-old boy with IRAK4 deficiency presenting with anti-NMDAR encephalitis and human herpes virus 6 (HHV6) reactivation. The study established a NF-κB reporter assay system that enabled precise evaluation of IRAK4 mutations and confirmed that two novel mutations in IRAK4 identified in the patient are deleterious.

Liu et al. (2020) reported a case of optic neuritis associated with anti NMDAR antibody in a seven-year-old patient in the remission phase of anti-NMDAR encephalitis.

Liu X, Giri M, Ling W, Li T. (2020) Optic neuritis associated with anti-NMDA receptor antibody in the remission phase of anti-NMDA receptor encephalitis. Neurol India. 68:474-7.

Tappatà M., Riguzzi R., Volpi L., et al. (2020) Long-term persistence of NMDAR antibodies after encephalitis with de novo occurrence of demyelinating disorder. Neurological Sciences.

Nishimura S., Kobayashi Y., Ohnishi H., et al. (2020) RAK4 Deficiency presenting with Anti-NMDAR encephalitis and HHV6 reactivation. Journal of Clinical Immunology.

Anti-LGI1 antibody and anti-Caspr2 antibody encephalitis

"Laboratories should stop testing for VGKC antibodies and, instead, test only for LGI1 and CASPR2 antibodies."

(Michael et al., 2020)

Testing for autoantibodies to the VGKC-complex

Michael et al. (2020) discussed the diagnostic tests for anti-LGI1 and anti-CASPR2 antibodies. "Autoantibodies to LGI1 and CASPR2 are associated with clinically distinctive syndromes that are highly immunotherapy responsive, such as limbic encephalitis, faciobrachial dystonic seizures, Morvan's syndrome and neuromyotonia. These autoantibodies target surface-exposed domains of LGI1 or CASPR2 and appear to be directly pathogenic. In contrast, voltage-gated potassium channel (VGKC) antibodies that lack LGI1 or CASPR2 reactivities ('doublenegative') are common in healthy controls and have no consistent associations with distinct syndromes. These antibodies target intracellular epitopes and lack pathogenic potential. Moreover, the clinically important LGI1 and CASPR2 antibodies comprise only ~15% of VGKC-positive results, meaning that most VGKC-antibody positive results mislead rather than help. Further, initial VGKC testing misses some cases that have LGI1 and CASPR2 antibodies. These collective observations confirm that laboratories should stop testing for VGKC antibodies and instead, test only for LGI1 and CASPR2 antibodies. This change in practice will lead to significant patient benefit." (Abstract from https://pn.bmj.com/content/20/5/377.long)

Michael S., Waters P., Irani S.R. (2020) Stop testing for autoantibodies to the VGKC-complex: only request LGI1 and CASPR2. Pract Neurol; 20:377–384.OPEN ACCESS https://creativecommons.org/licenses/by/4.0

Motor manifestations and the role of imaging in diagnosing anti-LGI1 encephalitis

Liu et al. (1) (2020) investigated the motor manifestations of 16 patients with anti-LGI1 encephalitis by analysing the video-electroencephalogram (VEEG) recordings. The authors identified 14 types of seizures recorded in nine patients: typical ictal electroencephalogram (EEG) evolution (n = 8), EEG electro decremental events (EDE) at onset but without further evolution (n = 3), and three could be only judged by analysing semiology. Faciobrachial dystonic seizures (FBDS) were registered in six patients, and these were followed by epileptic seizures. Other motor manifestations included simple hyperkinetic movements, such as jerk-like or twisting movements in half of the patients and manipulating movements or mimics of daily activities during sleep in six patients. The authors argued that anti-LGI1 encephalitis is characterised by high frequency of motor manifestations (with epileptic or nonepileptic origins, which points to an underlying mechanism that involves cortical-subcortical network disruption.

Liu et al. (2) (2020) performed a cohort study to investigate the clinical metabolic characteristics and diagnostic value based on 18F-FDG-PET in 34 patients with LGI1 AE: 18 patients (53%) in the acute phase and 16 patients (47%) in the chronic phase. The authors argued that 18F-FDG-PET imaging was more sensitive than MRI in the diagnosis of LGI1 AE. Isolated basal ganglia (BG) hypermetabolism was more frequently observed in subjects with FBDS, suggesting the potential involvement of the BG.

Liu X. (1), Han Y. , Yang L., et al. (2020) The exploration of the spectrum of motor manifestations of anti-LGI1 encephalitis beyond FBDS. Seizure: European Journal of Epilepsy; 76: 22–27.

Liu X.(2), Shan W, Zhao X, et al. (2020) The clinical value of 18F-FDG-PET in autoimmune encephalitis associated with LGI1 Antibody. Front. Neurol. 11:418. doi: 10.3389/fneur.2020.00418. OPEN ACCESS https://creativecommons.org/licenses/by/4.0

Case reports

Gillespie et al. (2020) presented the first reported case of familial VGKC autoimmune encephalitis in two brothers (seven-year-old and eight-year-old) at two years apart, which manifested with different symptoms within various timelines and different responses to treatment. Genetic testing and their specific HLA subtypes were not performed at the time. The authors argued for a likely genetic component to their illness; nevertheless, environmental factors also playing a role.

Ji et al. (2020) reported a rare case of LGI1-LE with overlapping symptoms and simultaneous positive NMDAR antibodies in serum and cerebrospinal fluid.

Endres et al. (2020) reported a patient of 50 years old who experienced neurocognitive deficits and predominant delusions for over one and a half years before his diagnosis of probable chronified anti-LGI1 encephalitis. The authors argued that this case proves that spotting the red flags of anti-LGI1 encephalitis (epileptic seizures, hyponatremia, atypical age of psychosis onset) is essential for starting early treatment and subsequent good outcomes, and even may avoid the development of dementia in some cases.

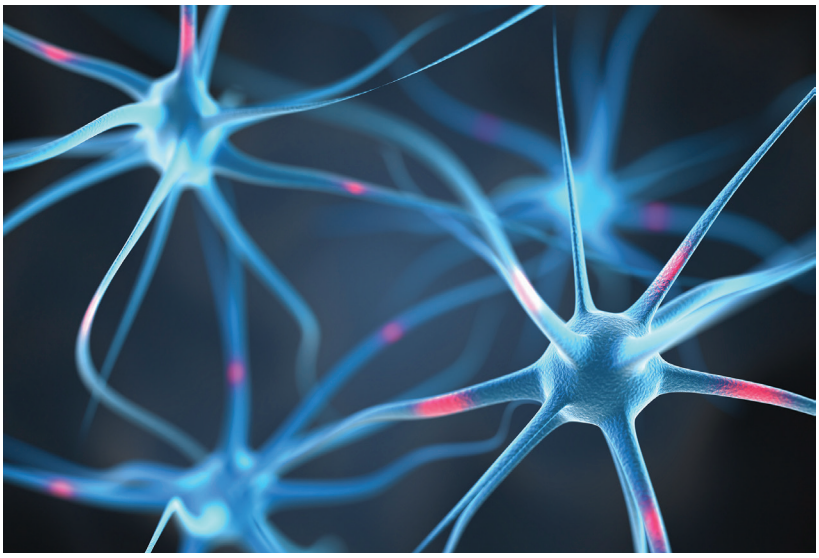
Endres D., Prüss H., Dressing A., et al. (2020) Psychiatric manifestation of anti-LGI1 encephalitis. Brain Sci ; 10 : 375.

Gillespie L.E., Dave A., Goldstein A. (2020) A tale of two brothers: familial voltage-gated potassium channel autoimmune encephalitis. Cureus ; 12(6): e8723.

Ji T., Huang Z., Lian Y. et al. (2020) A rare case of anti-LGI1 limbic encephalitis with concomitant positive NMDAR antibodies. BMC Neurology; 20:336.

Sleep disorders in autoimmune encephalitis

"Sleep disorders are frequent, often severe, and usually persist beyond the acute disease stage, interfering with patients' recovery and quality of life."
(Muñoz-Lopetegi et al., 2020)



Muñoz-Lopetegi et al. (2020) conducted a review of sleep disorders in autoimmune encephalitis (AE), including insomnia, parasomnia, hypersomnia and sleep-disordered breathing. In patients with AE, these disorders have specific features. For example, AE-related insomnia is usually acute, characterised by reduced or absent sleep for days or weeks, and is usually associated with hallucinations or abnormal behaviours. Parasomnias and movement disorders during sleep can be classified into four groups: irregular body or limb jerks, or periodic limb movements awake or during sleep; quasi-purposeful, non-violent movements, with the eyes closed, seeming to manipulate imaginary objects and imitating daytime activities; jerky movements of dream enactment, with vocalisations; confusional arousals, in which patients suddenly wake up from sleep, open the eyes, look around disoriented, sit up, or talk. The authors argued that these sleep disorders have specific characteristics depending on the type of AE; anti-NMDAR encephalitis and anti-IgLON5 having the most prominent sleep disorders. In anti-NMDAR encephalitis, the sleep disorder symptoms vary according to the stage of the illness: insomnia at the disease onset, sleep time and sleep need reduced at the peak of the disease and ending with hypersomnia in the recovery stage.

The authors also discuss a clinical and neurophysiological approach to the management of these sleep disorders. They argue that the best way to assess the sleep disorders is using a combined clinical and video polysomnography (V-PSG) evaluation. There are various symptoms that suggest sleep disorders; however, the other neurological and psychiatric symptoms characteristic to each type of AE can overshadow them. Two main features distinguish the sleep disorders in AE: a defined onset (e.g., a particular day or week), and the presence of more than one disorder in the same patient. Clinical assessment should include information gathered from both patient and partner/caregiver and comparison with premorbid sleep pattern. Regarding treatment, the authors remarked that this is symptomatic although there are no specific drugs for AE-sleep related symptoms and medications used in conventional sleep disorders might be less effective. In addition, the drugs used to treat AE might also alter sleep. Due to the severity of these disorders and the impact they have on the patient recovery and quality of life, the authors concluded by emphasising the need for comprehensive, systematic multicentre studies to characterise sleep disorders and their mechanisms.

Ariño et al. (2020) conducted a prospective observational single-centre study that included 18 patients with anti-NMDAR encephalitis and 21 controls aiming to describe sleep disorders in anti-NMDAR encephalitis. Comprehensive clinical, V-PSG sleep assessment and neuropsychological evaluations were conducted. Most patients were female (89%), and the median age was 26 years. Six patients reported pre-morbid sleep problems: sleepwalking and/or sleep talking, chronic sleep onset and sleep fragmentation insomnia and active sleep-talking. During the acute stage, sleep problems were reported in all patients: 16 patients had insomnia (13 before hospital admission), seven had nightmares and two had hypersomnia. After the acute stage, 14 patients reported hypersomnia. After a median of 183 days following the disease onset, eight patients still had hypersomnia and one had insomnia. Compared with controls, patients had more daytime sleepiness and more frequent, multiple, and longer confusional arousals in non-rapid eye movement (NREM) sleep on V-PSG. Patients also had a higher body mass index (median 23.5 vs 20.5) and higher scores in all psychiatric scales (HAM-D, YMRS, PANSS) compared with controls. In the patient group, 13 patients had impairment in one or more cognitive domains (memory, attention, or executive function), 12 had psychological, social or occupational disability (GAF scale), and six had depression or mania. At the last follow-up, behavioural changes associated with sleep disorders included hyperphagia (n=14) and hypersexuality (n=6). The authors concluded that sleep disorders are frequent in anti-NMDAR encephalitis, and they should be better appreciated as a diagnostic clue initially and followed up, due to the big impact they have during recovery. These sleep disorders have different patterns according to the stage of the illness: mostly insomnia during the initial stage and hypersomnia in the recovery stage. They are correlated with behavioural and cognitive changes after anti-NMDARE and can occur with confusional arousals during NREM sleep.

Ariño H., Muñoz-Lopetegi A., Martinez-Hernandez E., et al. (2020) Sleep disorders in anti-NMDAR encephalitis. Neurology; 95(6): e671-e684.

Muñoz-Lopetegi A., Graus F., Dalmau J., Santamaria J. (2020) Sleep disorders in autoimmune encephalitis. Lancet Neurol; 19: 1010–22.

Autoimmune encephalitis in children

Presentation and management

Cellucci et al. (2020) developed provisional paediatric autoimmune encephalitis (AE) classification criteria and an algorithm to facilitate early diagnosis. These proposed guidelines were developed based on the existing consensus criteria for AE in adults. The authors acknowledged that diagnosis of paediatric AE is challenging because of a wide range of differential diagnosis, complex normal behavioural changes, and communication difficulties in young age children. Most children with AE are healthy and develop neuropsychiatric symptoms rapidly (acute and sub-acute). Symptoms suggestive of AE may include cognitive changes (e.g., developmental regression, language loss or speech impairments), seizures, movement abnormalities, behavioural changes (e.g., repetitive or stereotypical behaviours, irritability, hyperactivity, hypersexuality, insomnia, anger outbursts) and psychiatric symptoms (e.g., mood swings, personality changes, psychosis). Children with AE are more likely to present with multifocal neuropsychiatric symptoms, rather than isolated clinical syndromes. In the presence of clinical presentation consistent with paediatric AE, the next step is to conduct investigations (e.g., blood, cerebrospinal fluid-CSF, magnetic resonance imaging-MRI, urine).

Antibody testing should be performed in both CSF and serum to avoid false-negative and false-positive results. Children who have positive LE associated-antibody testing meet the criteria for definite antibody-positive paediatric AE, whilst children who have negative antibody testing, meet the criteria for probable antibody-negative paediatric AE. Additional evidence is required when antibodies are present only in serum. The most common antibodies present in children are NMDAR, MOG, GAD65, and GABAAR. The authors also highlighted the overlap of various antibody-associated types and suggested testing a panel of neural autoantibodies for any child with suspected AE. The response to treatment was not included in the diagnosis algorithm as children, compared with adults, vary in their treatment response time from immediate response to a longer response (months). Differential diagnosis needs to distinguish AE from various other conditions, such as other brain inflammatory diseases (CNS vasculitis), infection-associated encephalopathy disorders, pediatric acute-onset neuropsychiatric syndrome (PANS) and paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), monogenic autoinflammatory syndromes and primary psychiatric disorders.

The authors argued that AE in children differs from that in adults with regards to presentation, diagnosis, treatment responses and long-term outcomes. They concluded that diagnosis of paediatric AE needs to consider both the presentation consistent with AE and diagnostic tests results.

Rutatangwa et al. (2020) reported on a retrospective case series of paediatric patients who were evaluated for AE at the University of California: five patients met a definite diagnosis of autoimmune encephalitis (four with anti-NMDAR) encephalitis and one with GFAP-associated encephalitis) and six had probable AE (four antibody-negative AE and two steroid-responsive encephalopathy associated with thyroiditis-SREAT). The median age at presentation was six years, and 81% of patients were female. Three patients had a preceding infection prior to onset. The time from onset of the symptoms to hospital admission was a median of seven days. The most common symptoms were seizures and behaviour changes in half of the children (54%). Other symptoms included altered mental status, autonomic dysfunction, speech difficulties, movement disorder, and cognitive changes. Cerebrospinal fluid (CSF) showed inflammation in six children and the magnetic resonance imaging (MRI) was abnormal in three patients. No tumours were identified. Electroencephalography (EEG) was abnormal in eight patients. Two patients improved spontaneously without treatment. For the others, treatment included first-line immunotherapy followed by second-line treatment with rituximab, cyclophosphamide and mycophenolate mofetil in 64% of patients. One patient with anti-NMDAR encephalitis died. The other patients had a good response to treatment, although none of the patients showed complete recovery at nine months follow-up. The authors concluded that, although anti-NMDAR encephalitis is the most common type of AE in children, children may lack an identifiable antibody.

Shekunov et al. (2020) presented four children with complicated psychiatric symptomatology and isolated neurologic signs and symptoms who were evaluated at a large tertiary medical centre for suspected AE, to demonstrate the complexity of diagnosis and treatment. All patients manifested neurological and psychiatric symptoms, but had negative autoantibody panels, normal or inconclusive MRI results and non-specific CSF changes. All patients were treated with immunosuppressive/immunomodulatory treatments, but the outcomes were poor. The authors emphasised that paediatric AE could have a heterogeneous presentation. Those seronegative patients can be misdiagnosed, and/or may not respond adequately to treatment. Those patients need careful examination, and their management requires strict application of consensus guidelines.

De Bruijn et al. (2020) undertook a study to ascertain the incidence of AE and acute disseminated encephalomyelitis (ADEM) in children and to validate the currently used clinical criteria to diagnose AE. The study included three groups of patients: 21 children with antibody-mediated AE, 32 children with ADEM and 60 children with suspicion of an autoimmune aetiology. Of all, 103 children fulfilled the criteria of possible AE. Twenty-one children had antibody-mediated AE with a mean incidence rate of 1.54 children/million: 19 had anti-NMDAR, one had anti-AMPAR, and one had anti-LGI1 encephalitis. Thirty-four children had ADEM with a mean incidence rate of 2.49 children/million. Two children had Hashimoto's encephalopathy. The authors concluded that, in children, the most common AE types are anti-NMDAR encephalitis and ADEM. The current guidelines for managing AE in adults are also appropriate for children. However, in children with nonspecific symptoms, it is important to carefully assess all clinical data and to consult specialised neuroinflammatory centres.

Cellucci T., Van Mater H., Graus F., et al. (2020) Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. Neurol Neuroimmunol Neuroinflamm; 7: e663.

De Bruijn M.A.A.M, Bruijstens, A.L., Bastiaansen, A.E.M., et al. (2020) Pediatric autoimmune encephalitis. Recognition and diagnosis. Neurol Neuroimmunol Neuroinflamm;7: e682.

Rutatangwa, A., Mittal N., Francisco C., et al. (2020) Autoimmune encephalitis in children: A case series at a tertiary care center. Journal of Child Neurology; 35(9): 591-599.

Shekunov J., Blacker C.J., Vande Voort J.L., et al. (2020) Immune mediated pediatric encephalitis – need for comprehensive evaluation and consensus guidelines. MC Neurology; 20:44.

Myelin oligodendrocyte glycoprotein (MOG) antibodies

Armangue et al. (2020) undertook a prospective observational study to investigate the spectrum of myelin oligodendrocyte glycoprotein (MOG) antibodies-associated syndromes in children. The study included 239 children with demyelinating syndromes (cohort A) and 296 with encephalitis other than acute disseminated encephalomyelitis (ADEM) (cohort B). Of all, 39% from cohort A and 7% from cohort B had MOG antibodies. Among children with autoimmune encephalitis in cohort B, MOG antibodies were more frequent than all the other neuronal antibodies taken together. The clinical syndromes of patients with MOG antibodies included ADEM (68%), encephalitis other than ADEM (19%), optic neuritis (17%), myelitis (11%), neuromyelitis optica spectrum disorders (5%) and other disorders (8%). Relapses occurred in 28% of all patients with MOG antibodies after a median follow-up of 42 months. Treatment included immunotherapies in 86% of patients at diagnosis and 97% of patients who relapsed. Rituximab was also used in 33% of patients who relapsed. Substantial recovery was reported in 85% of all patients with MOG antibodies and moderate to severe deficits in 15% of patients. The authors concluded that the spectrum of paediatric MOG antibody-associated syndromes is wider than previously reported and includes demyelinating syndromes and encephalitis.

Wegener-Panzer et al. (2020) described the presentations, radiologic features, and outcomes of ten children with AE associated with MOG antibodies. The patients include four girls and six boys with a median age at onset of 8 years. The initial presentation included a combination of encephalopathy (n = 10), headache (n = 7), focal neurologic signs (n = 7) or seizures (n = 6). One child had NMDAR antibodies at initial presentation. Nine children presented pleocytosis. Imaging showed cortical and deep gray matter involvement in all in addition to juxtacortical signal alterations in six children. The outcome was good in nine children (modified Rankin scale of <2). Five children had up to three additional demyelinating relapses associated with persisting MOG antobodies. A second child had a third demyelinating episode with MOG antibodies with overlapping NMDAR encephalitis. The authors argued that AE associated with serum MOG abs represents a distinct form of autoantibody-mediated encephalitis in children.

Armangue T., Olivé-Cirera G., Martínez-Hernandez E., et al. (2020) Associations of paediatric demyelinating and encephalitic syndromes with myelin oligodendrocyte glycoprotein antibodies: a multicentre observational study. Lancet Neurol; 19: 234–46.

Wegener-Panzer A., Cleaveland R., Wendel E-M., et al. (2020) Clinical and imaging features of children with autoimmune encephalitis and MOG antibodies. Neurol Neuroimmunol Neuroinflam;7.

Other autoimmune encephalitis

Anti-GAD65 antibody encephalitis

Zhang et al. (2020) and Zhu et al. (2020) investigated the clinical characteristics of anti-GAD65 antibody encephalitis. Both studies found that this type of encephalitis is more common in young and middle-aged women and manifests with more seizures and cognitive decline and less psychiatric symptoms than other types of autoimmune encephalitis. Abnormal imaging of temporal lobe and hippocampus were common in both studies and no tumour was found in any of the patients. Whilst in the first study of three patients (Zhang et al. 2020) the course of the illness was acute and subacute and none of the patients had other autoimmune antibodies present, the second study (Zhu et al., 2020) included six patients (6/7) with a subacute and chronic presentation who had abnormal thyroid function or positive thyroid antibodies.

Vrillon et al. (2020) undertook a systematic review of literature to describe psychiatric symptoms associated with anti-GAD associated encephalitis. Overall, 21 patients with anti-GAD associated encephalitis were included in this study. There were 81% female with a median age at onset of 27 years. Psychiatric symptoms were present in more than 60% of patients and included anxiety, depressive symptoms, apathy and behavioural changes. In some patients, these appeared months before the development of seizures and cognitive symptoms. The authors argued that identifying these symptoms as an early suspicion of the autoimmune condition can help a prompt recognition and an effective treatment.

Vrillon A., Carle G., Berzero G., et al. (2020) Psychiatric symptoms in anti glutamic acid decarboxylase associated limbic encephalitis in adults: a systematic review. Neuroscience and Biobehavioral Reviews; 119: 128–137.

Zhang Y-f., Yu. N., Lin X-j., et al. Clinical characteristics and outcomes of autoimmune encephalitis patients associated with anti-glutamate decarboxylase antibody 65. Clinical Neurology and Neurosurgery. 196:106082

Zhu F., Shan W., Lv R., et al. (2020) Clinical characteristics of GAD 65-associated autoimmune encephalitis. Acta Neurol Scand;142: 281-293.

Anti-GABA$_B$R encephalitis in China

Zhu et al. (2020) analysed clinical characteristics of 14 patients with anti-GABABR encephalitis. The illness was more common in middle-aged and elderly men and had a sudden onset. Prodromal, a few patients (three) experienced fever and non-specific respiratory symptoms. Clinical manifestations included epileptic seizures, cognitive dysfunction and abnormal behaviour. Magnetic resonance imaging (MRI) and positron emission tomography revealed abnormal signals and local metabolism in the temporal lobe. Three patients were discovered to have lung cancer.

Lin et al. (2020) investigated the long-term cognitive and neuropsychiatric outcomes of 31 patients with anti-GABABR encephalitis. At 24 months' follow-up, 80% of patients presented with cognitive impairments including memory, executive functions and nonverbal reasoning, and 50% of patients had neuropsychiatric impairments that included depressive symptoms and irritation.

Zhang et al. (2020) conducted a retrospective study of 19 patients with anti-GABAB receptor encephalitis and compared clinical characteristics of patients with favourable prognosis (mRS ≤ 2) (11 patients) with those with poor prognosis (mRS > 2) (eight patients). Clinical symptoms for all patients included memory deterioration, epileptic seizures, psychiatric disorders, and conscious disturbance. In the favourable-prognosis group, the MRI indicated an involvement of the limbic system in three patients. Lung cancer was detected in one patient. After an average follow-up period of 11.7 months, four patients recovered substantially, and seven patients showed significant improvements. In the poor-prognosis group, other manifestations included convulsive status epilepticus (five) and respiratory failure (five); MRI indicated an involvement of the limbic system in seven patients. Tumours were detected in five patients. After an average follow-up of 14.8 months, seven patients died, and one patient had significant difficulties. The authors concluded that patients with status epilepticus, respiratory failure and involvement of the limbic system have a poor outcome. Early diagnosis and appropriate treatment are essential.

Lin J., Li C., Li A., et al. (2020) Long-term cognitive and neuropsychiatric outcomes of anti-GABABR encephalitis patients: A prospective study. Journal of Neuroimmunology; 351: 577471.

Zhu F., Shan W., Lv R., et al. (2020) Clinical characteristics of anti-GABA-B receptor encephalitis. Front. Neurol. 11:403. doi: 10.3389/fneur.2020.00403. OPEN ACCESS. https://creativecommons.org/licenses/by/4.0/

Zhang X., Lang Y., Sun L., et al. (2020) Clinical characteristics and prognostic analysis of anti-gamma-aminobutyric acid-B (GABA-B) receptor encephalitis in Northeast China. BMC Neurology 20:1. OPEN ACCESS https://creativecommons.org/licenses/by/4.0/

Limbic encephalitis associated with AMPA receptor and CRMP5 antibodies

Jia et al. (2020) presented a case study and conducted a literature review looking at the association of AMPAR and CRMP5 antibodies. To date, five encephalitis patients, including the authors' patient, have been found to be positive for AMPAR and CRMP5 antibodies. There were four females and one male with ages between 26 and 62 years old. In all patients, clinical manifestations included various neuropsychiatric symptoms, such as insomnia and abnormal behaviour; seizures; extrapyramidal symptoms and autonomic dysfunction. Four patients had tumours (three invasive thymomas and one suspected lymphoma), and three of them died within a short period of time. Although one patient had no tumour, the outcome was poor– the patient developing cachexia. One patient had a good response to treatment and a substantial recovery. The authors concluded that the prognosis of encephalitis associated with both, AMPAR and CRMP5 antibodies is worse than that of the encephalitis associated with AMPAR antibodies alone.

Jia Y., Wang J., Xue L., Hou Y. Limbic encephalitis associated with AMPA receptor and CRMP5 antibodies: A case report and literature review. OPEN ACCESS https://creativecommons.org/licenses/by/4.0/

Neuro-ophthalmic and cardiovascular autonomic dysfunction features of autoimmune encephalitis (AE)

Bohm et al. (2020) presented an overview of the neuro-ophthalmic features of several AE types, aiming to raise awareness among neuro-opthalmologists. Different types of AE manifest with specific neuro-ophthalmic features. Patients with anti-NMDAR encephalitis can report optic neuritis, higher cortical visual deficits, oculogyric crisis, inverse ocular bobbing, increased blink rate, complete bilateral ptosis or opsoclonusmyoclonus. DPPX antibody encephalitis may include simultagnosia, apraxia of eyelid opening, nystagmus, skew deviation, saccadic pursuit, impaired vestibulo-ocular reflex suppression, dysmetric saccades and opsoclonus. Autoimmune-related retinopathy and optic neuropathy, nystagmus (most commonly downbeat), skew deviation, opsoclonusmyoclonus and supranuclear vertical gaze palsy with syndrome mimicking progressive supranuclear palsy can manifest in patients with anti-GAD65 antibody encephalitis. The authors also reviewed the general principles for diagnosis and management, highlighting the importance of avoiding delays in immunotherapy.

Yamakawa et al. (2020) investigated the autonomic symptoms in 19 patients with AE. These manifestations included orthostatic hypotension, orthostatic intolerance, and arrhythmia in 16 participants; pupillary abnormalities in four; hypersalivation in four (all with anti-NMDAR); anhidrosis or hyperhidrosis in ten; gastrointestinal tract dysfunction in seven; and urinary retention in seven. The study showed that cardiovascular symptoms were very common in patients with AE. The luciferase immunoprecipitation system (LIPS) assay detected anti-gAChRα3 antibodies in the sera of five patients with AE; the authors argued that this may be a new feature of AE pathogenesis.

Bohm P.E., Chen, J.J., Bhatti T.M., Eggenberger E.R. (2020) Neuro-Ophthalmic features of autoimmune encephalitides. J Neuro-Ophthalmol 2020; 40: 385-397.

Yamakawa M., Mukaino A., Kimura A., et al. (2020) Antibodies to the α3 subunit of the ganglionic-type nicotinic acetylcholine receptors in patients with autoimmune encephalitis. Journal of Neuroimmunology 349: 577399.

Brainstem encephalitis (BE)

"In many cases, the spatial distribution of lesions and other associated radiological lesions can provide the radiologists and clinicians the clues to an accurate diagnosis."
(Sotoudeh et al., 2020)

Brainstem encephalitis (BE) affects the rhombencephalon (pons, cerebellum, medulla oblongata). The most common symptoms are ataxia, ocular dysfunction, bulbar dysfunction and limb weakness. It is important to diagnose it quickly as it can be fatal. Wei et al. (2020) provided an overview of listeria BE. Listeria BE affects mainly healthy people. It has a prodromal phase with non-specific symptoms, such as malaise, fever, headache, vomiting and sweating. After this stage (4-15 days), patients develop progressive brainstem deficits, including cranial nerve palsy and cerebellar dysfunction/ataxia, motor and/or sensory deficits of extremities, respiratory distress, consciousness impairment, seizure, fever and meningitis. MRI can reveal abnormalities in the medulla oblongata, cerebellum, pons, midbrain and supratentorial regions. CSF findings include pleocytosis, polymorphonuclear leucocytes and increased protein concentration. Empirical treatment with antimicrobial therapy should be started as soon as possible. The most effective treatment proved to be intravenous ampicillin (combined with one of the aminoglycosides) or penicillin; in case of allergy to any of these, vancomycin, meropenem or linezolid can be used. Mortality is high and survivors can be left with neurological sequelae. In addition to the trigeminal nerve as a way of invading the brainstem, the authors also propose the vagus nerve as a pathway through which L. monocytogenes reaches the brainstem after it infects enteric neurons in the walls of the gastrointestinal tract.

Pfefferkorn et al. (2020) conducted a retrospective observational study to ascertain clinical and imaging features of BE in neuroborreliosis. The study included five patients. Clinical manifestation featured non-specific symptoms over a prolonged time up to six months, such as wasting, fatigue and headache. All examined patients had markedly elevated values of CXCL13. MRI showed symmetrical brainstem changes in all patients. When present, brain stem signs included dysarthria, dysmetria, hoarseness, gait disturbances and double vision. Treatments consisted of antibiotics (ceftriaxone 2 g daily for 2-3 weeks) in all patients. Three patients fully recovered, and two patients were left with fatigue. The authors concluded that some patients with neuroborreliosis may develop BE with a typical clinical course and distinct MRI findings.

Pfefferkorn T., Röther J., Eckert B., Janssen H. (2020) Brainstem encephalitis in neuroborreliosis: typical clinical course and distinct MRI findings. Journal of Neurology 2. https://doi.org/10.1007/s00415-020-10188-9

Sotoudeh, H., Razaei, A., Saadatpour Z., et al. (2020) Brainstem encephalitis. The role of imaging in diagnosis current problems. Diagnostic Radiology 00: 1-15.

Wei P., Bao R. and Fan Y. (2020) Brainstem encephalitis caused by Listeria monocytogenes. Pathogens; 9: 715.

Immune checkpoint inhibitor therapy-associated encephalitis

"Immune checkpoint inhibitors (ICIs) can cause a wide spectrum of immune-related adverse events, including encephalitis. To date, no prospective randomised controlled trials examining the patient characteristics, treatment and outcomes of ICI-associated encephalitis have been published. Therefore, Johann et al. (2020) aimed to review case reports and to provide recommendations for the management of ICI-associated encephalitis. Five different ICIs caused encephalitis in the 47 patients included in this case series. Nivolumab was the most frequently involved drug (27/47, 57%). The median time between treatment and onset of symptoms was 65 (4–630) days. Patients presented with rapidly evolving confusion, reduced level of consciousness, headache, seizures and focal neurological deficits. A total of 19 out of the 44 (43%) magnetic resonance imaging (MRI) scans performed revealed findings suggestive of encephalitis. No specific electroencephalogram (EEG) pattern consistent with encephalitis was found, but epileptiform discharges were detected in 7/20 (35%) of all tested patients. Typical findings of cerebrospinal fluid (CSF) analysis were pleocytosis, elevated protein levels and normal glucose concentrations. Forty-four out of 47 (94%) patients received corticosteroids. Intravenous immunoglobulins (IVIG), rituximab and plasma exchange therapy were less frequently prescribed. Nine out of 47 (19%) patients died during the index hospitalisation. Encephalitis should be suspected in patients treated with ICIs who present with rapidly evolving confusion. Blood tests, CSF analysis, cerebral MRI and an EEG should be performed. Therapy with intravenous corticosteroids is recommended. Steroid unresponsiveness is rare and should lead to a review of the diagnosis. Alternative treatment options are IVIG, plasma exchange therapy and rituximab." (Abstract from https://smw.ch/article/doi/smw.2020.20377)

Johann S., Thomas H., Guido C.N., et al. (2020) Immune checkpoint inhibitor therapy-associated encephalitis: a case series and review of the literature. OPEN ACCESS https://emh.ch/en/emh/rights-and-licences

Seizures and encephalitis

Autoimmune-associated epilepsy or acute symptomatic seizures in patients with neural antibodies

Rada et al. (2020) investigated seizure outcome in 39 patients with neural antibodies who were followed up for at least three years. Twenty-five patients had surface antibodies (anti-NMDAR, anti-LGI1 and anti-CASPR2) and 14 patients had antibodies against intracellular antigens (GAD65 and Ma2). The first group achieved first seizure-freedom and terminal seizure-freedom in 88% and 80% of cases, respectively. In the second group, only one patient achieved seizure freedom. The time to discontinuation of anti-epileptic drugs was shorter for the first group and their seizure-free status did not depend on these drugs. In addition, the surface neural antibodies group experienced a decrease in the antibody titres during the follow-up. The authors argued that, in most patients with surface antibodies, seizures are acute symptomatic and transient and do not require long-term immunological or anti-epileptic drugs or social restrictions.

Shen et al. (2020) investigated the risk of epilepsy in 119 patients with anti-NMDAR, anti-LGI1, and anti-GABABR encephalitis. Patients were followed up for a median of 30.5 months. Overall, 83 patients developed new-onset seizures at acute stage and 17 patients were considered to develop epilepsy (they had seizure relapses after intermittent seizure remission or exhibited uncontrolled seizure episodes). The study found that predictors of epilepsy included delay in immunotherapy and interictal epileptic discharges (IEDs). The authors emphasised the importance of early diagnosis and treatment. Special consideration should be given to patients with the above risk factors.

Rada A., Birnbacher R., Gobbi C., et al. (2021) Seizures associated with antibodies against cell surface antigens are acute symptomatic and not indicative of epilepsy: insights from long term data. Journal of Neurology; 268: 1059–1069.

Shen C-H., Fang G-L., Yang F., et al. (2020) Seizures and risk of epilepsy in anti-NMDAR, anti-LGI1, and anti-GABABR encephalitis. Annals of Clinical and Translational Neurology; 7(8): 1392–1399.

Anti-epileptic drugs (AEDs) in encephalitis

Chavez-Castillo et al. (2020) undertook a single-centre retrospective review case series of 31 paediatric patients with a confirmed diagnosis of anti-NMDAR encephalitis and epileptic seizures admitted to the National Institute of Pediatrics in Mexico City from January 2012 to July 2019. Most of the patients (85%) presented epileptic seizures during the illness, predominantly focal onset seizures. In the acute stage, patients were administered two

AEDs on average to control their seizures. In patients with human herpesvirus detected in cerebrospinal fluid (CSF) (19%), their seizures were more resistant to pharmacological treatment during the acute phase, requiring a higher number of AED (median 2.5). Only one patient continued to have epileptic seizures at 24 months after the acute stage. The authors concluded that the development of epilepsy after acute encephalitis was uncommon, thus sustained use of AEDs after the acute phase of anti-NMDAR encephalitis is controversial. However, the continuation of AEDs after the acute phase could be considered in the following scenarios: status epilepticus, inadequate response to immunotherapy at four weeks, and a high mRS score at discharge and during follow-up.

Peng et al. (2020) investigated the role of AEDs in acute encephalitis. Their study included 327 patients with acute encephalitis who presented with seizure/s. The patients were followed for five years after the acute phase. Seizure types included focal (40.9%), general (54.7%), combined (4.4%) and status epilepticus (23.5%). Overall, more than 40% of patients had seizure relapse after the acute phase and most relapses happened in the first three months after discharge. The relapses were associated with status epilepticus, more than one seizure, CSF protein level, abnormal magneto resonance imaging findings, temporal lobe involvement, and epileptiform discharge on univariate analysis. On multivariate regression analysis, more than one seizure and temporal lobe involvement predicted seizures. Patients with only one seizure and no temporal lobe involvement had low risk of relapses, irrespective of taking or not taking AEDs. The most common AEDs used were sodium valproate and levetiracetam; both had similar effects. The authors concluded that for patients with one seizure and no temporal lobe involvement, AEDs may not be necessary.

Chavez-Castillo M, Ruiz-Garcia M, Herrera-Mora P (May 20, 2020) Characterization and outcomes of epileptic seizures in Mexican pediatric patients with anti-N-Methyl-D-Aspartate receptor encephalitis. Cureus; 12(5): e8211. DOI 10.7759/cureus.8211 OPEN ACCESS https://creativecommons.org/licenses/by/4.0/

Peng A., Lai W., Li W., et al. (2020) Antiepileptic drugs for acute encephalitic patients presented with seizure. Epilepsy Research 164: 106347.

Surgery for intractable epilepsy following viral encephalitis

Epilepsy surgery may be offered to drug-resistant patients after herpes simplex encephalitis (HSE) but carries a high risk of HSE relapse. Fohlen et al. (2020) reported the outcomes of surgery in four children with drug-resistant epilepsy post-HSE. Three children underwent a tailored focal resection following invasive recordings and one child a complete callosotomy with the systematic administration of acyclovir. None of the patients had a relapse. Two children experienced seizure-freedom. The authors concluded that epilepsy surgery in this specific aetiology should be considered more often.

Liu et al. (2020) reported on surgical outcome in children with intractable epilepsy after viral encephalitis. Twenty-three children who underwent surgery were included in the study. Thirteen children had status epilepticus. The mean age at surgery was 6.1 years and the mean patient follow-up was 37.2 months. One child died three months after the surgery due to viral reactivation, 13 children had a good outcome, and nine children had a poor outcome. The seizure outcome was associated with the latency from infection to the first unprovoked seizure, unilateral abnormalities on magneto resonance imaging (MRI), concordance of positron emission tomography and MRI abnormalities and acute postoperative seizures. The authors noted that the study was mainly about functional outcomes after surgery (68% of children walked independently and 64% had no further progress in hemiparesis); however, 59% of children had language difficulties and significant behavioural problems. The authors concluded that surgery may be successful in stopping or reducing seizures and protecting motor function; however, a comprehensive pre-operative assessment is needed.

Fohlen M., Taussig D., Ferrand-Sorbets S., et al. (2020) Management and results of epilepsy surgery associated with acyclovir prophylaxis in four pediatric patients with drug-resistant epilepsy due to herpetic encephalitis and review of the literature. European Journal of Paediatric Neurology; 29: 128-136.

Liu C., Liu Q., Yu H., et al. (2020) Surgical treatment in children with intractable epilepsy after viral encephalitis. Epilepsy Research; 166: 106426.

Diagnosis, management and outcomes

"Encephalitis management and compliance with the guidelines were suboptimal accounting for the underutilization of currently available diagnostic tests and empirical therapy in a significant proportion of patients." (Samannodi et al., 2020)

Compliance to diagnosis and management guidelines in adults

Samannodi et al. (2020) performed a retrospective multicentre study at 17 hospitals in the Greater Houston area from 2008 to 2017 to evaluate the appropriate management and compliance to the current guidelines in adults with encephalitis. The study included 241 adults, aged >17 years diagnosed with encephalitis. All cases met the definition for possible or probable encephalitis as per the international encephalitis consortium guidelines. Nearly half of the cases (41.9 %) had an unknown cause, whilst 27.8 % had a viral and 21.2 % an autoimmune cause. A high compliance with guidelines (>90 %) was only seen in performing tests such as a brain computerised tomography (CT) scan, blood cultures and cerebrospinal fluid CSF gram stain and culture. A CSF herpes virus simplex (HSV) polymerase chain reaction (PCR) took place in 84% of patients; however, a repeat CSF-PCR was performed in only 14.2% of patients with an initial negative result. Regarding other possible causes, investigations were carried out as following: 57.3% arboviral serologies, 35.7% CSF anti-NMDAR antibody, and 32% CSF varicella zoster virus VZV PCR. Only two-thirds of patients were started empirically on intravenous acyclovir and antibiotics. The authors concluded that the management of encephalitis as per current guidelines is suboptimal.

Samannodi M., Hansen M., Allana A., et al. (2020) Compliance with international guidelines in adults with encephalitis. Journal of Clinical Virology; 127: 104369

Treatment in autoimmune encephalitis (AE)

Scheibe et al. (2020) described a 60-year-old patient with therapy-refractory anti-CASPR2 who received daratumumab, however subsequently died of Gram-negative septicemia. The authors drew attention to the fact that, although improving neurological sequalae, daratumumab has severe side effects.

Turnbull et al. (2020) reported an 18-year-old patient with progressive and medically refractory anti-NMDA receptor encephalitis. Despite having administered high-dose intravenous steroids, plasma exchange, immunoglobulin and rituximab, the patient failed to respond and bortezomib was commenced. Fifteen days after the bortezomib administration, the patient started to improve significantly. At one month follow-up, the patient showed a dramatic improvement in cognitive skills.

Nepal et al. (2020) conducted a meta-analysis to investigate the effectiveness and safety of rituximab as a second-line therapy for the treatment for AE. The study found that 72.2% of patients reported a good functional outcome at follow-up following rituximab therapy. Only 14.2% of patients reported relapses. Adverse effects included infusion related reactions in 15.7%, pneumonia in 6%, and severe sepsis in 1.1%. Loehrer et al. (2020) reported a patient with clinical remission of neurexin-3a-associated autoimmune encephalitis after immunosuppressive treatment and rituximab therapy. Dou et al. (2020) reported the use of rituximab in eight children with refractory anti-NMDAR encephalitis. Five patients had a good outcome, four of them with complete recovery. However, two patients had severe infectious adverse effects at 36 and 104 days after initiation of treatment and died. One patient had no response to rituximab. The authors argued that rituximab can be efficient in children with anti-NMDAR encephalitis; however, it should be restricted to being used in patients with high risk of disability and mortality.

Hao et al. (2020) explored the effectiveness of mycophenolate mofetil (MMF) in treating six children with anti-NMDAR encephalitis: three patients had one relapse and three patients had two relapses. The mean duration of MMF initiation was 19.2 months after disease onset at a mean dose of 25.6 mg/kg for 14 months. Two patients discontinued the treatment: one after a relapse and one after 26 months of asymptomatic application. The other four cases had no relapses and were still on MMF at the date of the study. Only two patients were reported having side effects (mild diarrhoea). The authors concluded that MMF may be effective and safe in paediatric anti-NMDAR encephalitis.

Dou X, Li D, Wu Y, Wang Z, Yang L, Ma N, Wang D and Li X (2020) Efficacy and Safety of Rituximab in Chinese Children With Refractory Anti-NMDAR Encephalitis. Front. Neurol. 11:606923. doi: 10.3389/fneur.2020.606923

Hao X-s, Wang J-t, Chen C., et al. (2020) Effectiveness of mycophenolate mofetil in the treatment of pediatric anti-NMDAR rncephalitis: a retrospective analysis of 6 Cases. Front. Neurol. 11:584446. doi: 10.3389/fneur.2020.584446.

Loehrer P.A., Bien C.I., Dusoic A-E., et al. (2020) Neurexin-3a-associated autoimmune encephalitis: a case report of full recovery after rituximab therapy. European Journal of Neurology ; 7(12):e91-e93.

Nepal G., Shing Y.K., Yadav J.K., et al. (2020) Efficacy and safety of rituximab in autoimmune encephalitis: A meta-analysis. Acta Neurol Scand. 2020; 142:449–459.

Scheibe F., Ostendorf L., Reincke M., et al. (2020) Daratumumab treatment for therapy refractory anti CASPR2 encephalitis. Journal of Neurology. 267:317–323.

Turnbull M.T., Siegel J.L., Becker T.L., et al. (2020) Early Bortezomib therapy for refractory anti-NMDA receptor encephalitis. Front. Neurol. 11:188.

Next-generation sequencing (NGS)

"The long and expanding list of viral pathogens associated with causing encephalitis confounds current diagnostic procedures, and in up to 50% of cases, the etiology remains undetermined. Sequence-agnostic metagenomic next-generation sequencing (mNGS) obviates the need to specify targets in advance and thus has great potential in encephalitis diagnostics. However, the low relative abundance of viral nucleic acids in clinical specimens poses a significant challenge. Manso et al. (2020)'s protocol employs two novel techniques to selectively remove human material at two stages, significantly increasing the representation of viral material. The author's bioinformatic workflow using open-source protein- and nucleotide sequence-matching software balances sensitivity and specificity in diagnosing and characterizing any DNA viruses present. A panel of 12 cerebrospinal fluid (CSFs) from encephalitis cases was retrospectively interrogated by mNGS, with concordant results in seven of nine samples with a definitive DNA virus diagnosis, and a different herpesvirus was identified in the other two. In two samples with an inconclusive diagnosis, DNA viruses were detected and in a virus-negative sample, no viruses were detected. The authors concluded that this assay has the potential to detect DNA virus infections in cases of encephalitis of unknown etiology and to improve the current screening tests by identifying new and emerging agents." (Abstract from www.frontiersin.org/articles/10.3389/fmicb.2020.01879/full)

"Xing et al. (2020) assessed the performance of metagenomic next-generation sequencing (mNGS) in the diagnosis of infectious encephalitis and meningitis. This was a prospective multicenter study. Cerebrospinal fluid samples from patients with viral encephalitis and/or meningitis, tuberculous meningitis, bacterial meningitis, fungal meningitis, and non-central nervous system (CNS) infections were subjected to mNGS. In total, 213 patients with infectious and non-infectious CNS diseases were enrolled from November 2016 to May 2019; the mNGS-positive detection rate of definite CNS infections was 57.0%. At a species-specific read number (SSRN) ≥2, mNGS performance in the diagnosis of definite viral encephalitis and/or meningitis was optimal (area under the curve [AUC] = 0.659, 95% confidence interval [CI] = 0.566-0.751); the positivity rate was 42.6%. The authors concluded that mNGS of cerebrospinal fluid effectively identifies pathogens causing infectious CNS diseases, and that mNGS should be used in conjunction with conventional microbiological testing." (Abstract from www.frontiersin.org/articles/10.3389/fcimb.2020.00088/full)

Manso, C.F., Biddy, D.F., Mohamed, H. et al. (2020) Enhanced detection of DNA viruses in the cerebrospinal fluid of encephalitis patients using metagenomic next-generation sequencing. Frontiers in Microbiology. Aug 2020. 12:11:1879. DOI: 10.3389/fmicb.2020.01879. OPEN ACCESS https://creativecommons.org/licenses/by/4.0/.

Xing, X.-W., Zhang, J.-T., Ma, Y.-B., et al. (2020) Metagenomic Next-Generation Sequencing for Diagnosis of Infectious Encephalitis and Meningitis: A Large, Prospective Case Series of 213 Patients. Frontiers in Cellular and Infection Microbiology. Mar 2020. 5:10:88. DOI: 10.3389/fcimb.2020.00088. OPEN ACCESS https://creativecommons.org/licenses/by/4.0/.

Outcomes of Japanese encephalitis (JE)

Mayxay et al. (2020) prospectively followed up 123 JEV-infected patients (70 children ≤ 15 years and 53 adults ≥ 15 years) admitted at Mahosot Hospital, Vientiane, from 2003 to 2013. "Neurological sequelae were assessed using the Liverpool Outcome Score (LOS), total (maximum score = 75), and final (maximum score = 5). The median (interquartile range [IQR]) age of the patients was 12.0 (7.5-18.8) years, and 57% were male. The median (IQR) duration of patients' follow-up was 4.5 (3.2-7.3) years. Of all patients, 8.1% died during hospitalization, and 10.6% died at home after discharge, giving a mortality of 18.7% (26.8% patients were lost to follow-up). The frequency of neurological sequelae at the last follow-up was 61.2% (48.4% in adults and 69.4% in children, P = 0.135). The proportion of patients with severe and moderate functional impairment at the last follow-up was significantly higher in children (25%) than adults (6.5%), P = 0.042. Half of the patients who were still alive at the last follow-up (67) and for whom LOS data were available (22) had improvements in their total and final LOS between discharge and the last follow-up. The total and final LOS at discharge were not significantly different between children and adults, but total LOS at the last follow-up was significantly higher in adults than children (median [IQR]: 74.5 [73-75] versus 73.0 [73-75], P = 0.019). The authors concluded that at least 1/5 of Lao inpatients with JEV dies, and nearly 2/3 of the survivors had neurological sequelae (half of them minor sequelae) after a median duration of follow-up of 4.6 years. The authors called for a longer follow up of survivors, assessments of economic impact, and trials of rehabilitation interventions." (Abstract from www.ajtmh.org/view/journals/tpmd/104/2/article-p567.xml)

Mayxay, M., Douangdala P., Vilayhong C., et al. (2020) Outcome of Japanese Encephalitis Virus (JEV) infection in peadatric and adult patients at Mahosot Hospital, Vietnae, Lao, PDR. American Journal of Tropical Medicine and Hygiene 104:2. OPEN ACCESS https://creativecommons.org/licenses/by/4.0/.

Outcomes among patients with herpes simplex encephalitis (HSE), other cause encephalitis and unknown cause encephalitis

Harris et al. (2020) compared neuropsychological and psychiatric outcomes across three encephalitis aetiological groups: herpes simplex virus (HSV), other infections or autoimmune causes (Other), and encephalitis of unknown cause (Unknown). "Patients recruited from NHS hospitals in the UK underwent neuropsychological and psychiatric assessment in the short-term (4 months post-discharge), medium-term (9-12 months after the first assessment), and long-term (>1-year). Healthy control subjects were recruited from the general population and completed the same assessments. Patients with HSV were most severely impaired on anterograde and retrograde memory tasks. In the short-term, they also showed executive, IQ, and naming deficits, which resolved in the long-term. Patients with Other or Unknown causes of encephalitis showed moderate memory impairments, but no significant impairment on executive tests. Memory impairment was associated with hippocampal/

medial temporal damage on magnetic resonance imaging (MRI), and naming impairment with left temporal and left frontal abnormalities. Patients reported more subjective cognitive complaints than healthy controls, with tiredness a significant problem, and there were high rates of depression and anxiety in the HSV and the Other encephalitis groups. These subjective, self-reported complaints, depression, and anxiety persisted even after objectively measured neuropsychological performance had improved. The authors concluded that neuropsychological and psychiatric outcomes after encephalitis vary according to aetiology. Memory and naming are severely affected in HSV, and less so in other forms. Neuropsychological functioning improves over time, particularly in those with more severe short-term impairments, but subjective cognitive complaints, depression, and anxiety persist, and should be addressed in rehabilitation programmes."(Abstract from https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0230436)

Harris, L. Griem, J., Gummery, A. et al. (2020) Neuropsychological and psychiatric outcomes in encephalitis: A multi-centre case-control study. PLoS One;. 25:15:3. OPEN ACCESS https://creativecommons.org/licenses/by/4.0/

Pathologic tearfulness in patients with autoimmune limbic encephalitis (LE)

Argyropoulos et al. (2020) investigated the mechanisms that lead to pathologic tearfulness in patients after autoimmune LE. The study included 26 men and 12 women post-acute autoimmune LE and 67 age- and sex-matched healthy controls. Half of the patients reported pathologic tearfulness (moved to tears by minor stimuli which would not have happened premorbid), but none of the patients reported pathological laughing. The most common triggers for crying reported by patients and families were sad stories on media and witnessing other people crying. There was no association between pathological tearfulness and cognitive and emotional difficulties post-acute LE or amygdalar abnormalities in the acute stage. However, tearfulness was associated with changes in specific emotional brain networks: volume reduction in the right anterior hippocampus, left fusiform gyrus, and cerebellum, abnormal hippocampal resting-state functional connectivity with the posteromedial cortex and right middle frontal gyrus, and abnormal hemodynamic activity in the left fusiform gyrus, right inferior parietal lobule, and ventral pons. The authors concluded that pathologic tearfulness after autoimmune LE is common. It is not a manifestation of post-acute depression or part of the dysexecutive syndrome. Instead, it is linked to abnormalities in the networks of emotion regulation beyond the acute hippocampal focus.

Argyropoulos G.P.D., Moore L., Loane C., et al. (2020) Pathologic tearfulness after limbic encephalitis. A novel disorder and its neural basis. Neurology; 00:1-16.

Recovery and rehabilitation after encephalitis

"Educational interventions at point of discharge could improve care transitions, potentially improving both caregiver burden and patient outcome."
(Tomlinson et al., 2020)

Patients and carers burden in encephalitis

Blum et al. (2020) investigated long-term psychosocial outcomes of patients with anti-NMDAR encephalitis. Their study included 61 patients (adolescents and adults) with a mean age of 33.7 years. Most of the participants were females. The study took place at a mean duration of 4.4 years since symptom onset. More than a half of participants (n = 36) were initially misdiagnosed, and 30 patients received at least one psychiatric diagnosis.

Post-acutely, 56 participants reported persistent symptoms such as fatigue, memory problems, attention and concentration issues, sleep problems, headache and seizures. Ongoing neuropsychiatric issues occurred in 45 participants. Nearly one-third of patients (31.1%) did not resume their prior work or schooling after illness. Six participants did not return to driving after the illness. After discharge, 95.1% of participants saw a neurologist and 37.7% of participants a psychiatrist. At least one form of rehabilitation (occupational therapy, physical therapy, speech therapy and cognitive-behavioural therapy) was received by 47 participants.

Factors associated independently with poor psychosocial outcome included psychiatric comorbidities, the use of psychotropic medication, younger age, and persistent symptoms such as emotional or impulse control issues, attention or concentration problems, sleep difficulties and seizures. Returning to work/school was positively associated with having a follow-up with a psychiatrist. The authors also found that all patients as a group reported worse psychosocial function than a comparison sample enriched for chronic illness.

The authors concluded that anti-NMDAR encephalitis can result in poor psychosocial outcomes. This finding combined with the lack of current standards for long-term assessment or management of such symptoms in this population suggests a great need for long-term rehabilitation programmes aimed at these patients.

Tomlinson et al. (2020) provided an overview of perceptions and experiences of caregivers of patients with anti-NMDAR encephalitis regarding care transitions from inpatient to outpatient and long-term caregiver burden. Care transition was evaluated using the Care Transition Measure 15, which is a 15-item questionnaire. To assess caregiver burden, the authors used the Zarit Burden Interview, which is a 22-item questionnaire. The study included 76 caregivers recruited via patient organisation websites. Overall, caregivers reported high levels of dissatisfaction regarding care transitions due to the lack of knowledge about what will happen with the patient care after discharge and what they were required to do in their caregiver role. Notably, 73% of caregivers disagreed or strongly disagreed with the statement: "when the patient left the hospital, I had a readable and easily understood written plan that described how all of their healthcare needs were going to be met". In addition, 62% of respondents disagreed with "when the patient left the hospital, I was confident that I know how to manage their health."

Caregivers expressed moderate to severe levels of caregiver burden, mostly about the impact on their personal lives. Poor care transitions impacted on the caregiver burden with the worst care transitions significantly associated with higher caregiver burden scores. High caregiver burden was also reported when patients did not return to driving after their illness. The authors suggested that adequate discharge planning and education regarding the illness, consequences and future care are essential to improve the overall outcomes. The needs of these patients and the care burden may change over time, so this also should be considered. Existing successful caregiver interventions for other conditions (e.g., depression, stroke) could be used as a model.

Tomlinson, A.R., Blum, R.A., Jetté, N., et al. (2020) Assessment of care transitions and caregiver burden in anti-NMDA receptor encephalitis. Epilepsy & Behavior. Mar 2020. 108: 107066.

Blum, R.A., Tomlinson, A.R., Jetté, N., et al. (2020) Assessment of long-term psychosocial outcomes in anti-NMDA receptor encephalitis. Epilepsy & Behavior.May 2020. 108: 107088.

About the Encephalitis Society

How we help

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

- Supporting adults, children, families and carers of those affected by encephalitis.
  Support Line: +44(0)1653 699599
  support@encephalitis.info
- Producing high quality, evidence-based and peer-reviewed information about encephalitis.
  www.encephalitis.info
- Raising awareness about encephalitis, its consequences and the need for improved services.
  World Encephalitis Day 22nd February
  www.worldencephalitisday.org
- Conducting and funding research and working in partnership with other researchers. www.encephalitis.info/grants

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.

Support life-changing encephalitis research

Gifts in Wills are one major way of ensuring that we can continue to fund ground-breaking research into encephalitis in the future and to make sure those affected will continue to receive the best treatment possible.

If you are thinking about making or changing your Will, please consider leaving your very own Encephalegacy. An Encephalegacy is a life-changing gift in your Will which will help build a better world for the 500,000 people affected by encephalitis each year. We fully recognise that your family and friends come first. If the time is right to ever leave a gift in your Will to a charity, please consider supporting the Encephalitis Society.

How to leave a Gift in Will

Did you know that writing your Will can take less than 30 minutes and can be done for free and from the comfort of your own home using our dedicated online Will writing service?

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We can also accept legacy donations from our friends in the USA through our dedicated fund. More details are available on our website at www.encephalitis.info/leave-legacy

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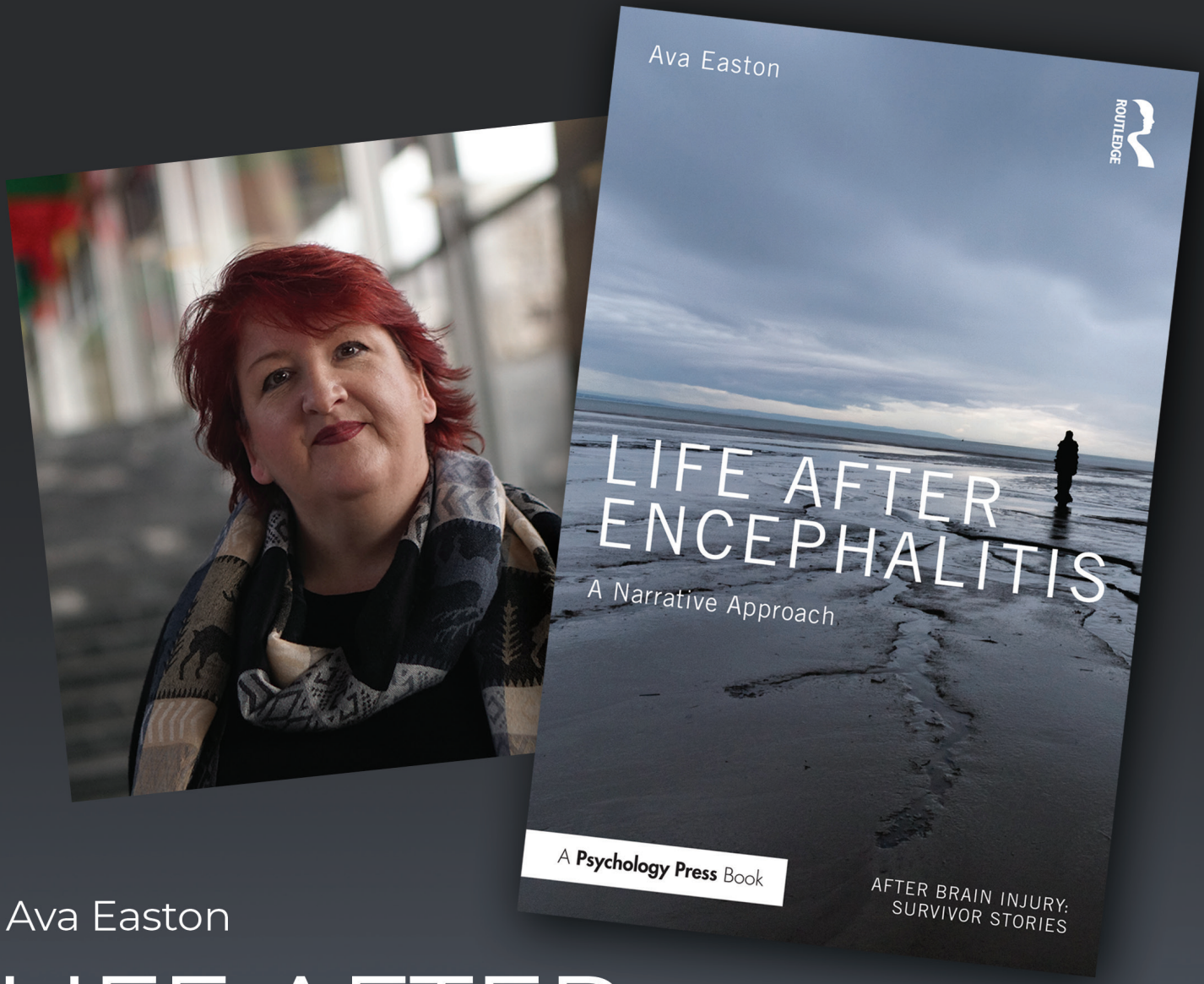

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