RESEARCH SUMMARY

ADVANCES IN ENCEPHALITIS 2022

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Welcome to the Encephalitis Society's Research Summary 2022

Dr Ava Easton at the World Health Organization

The Research Summary-Advances in Encephalitis 2022 presents a collection of research papers published during that same year.

In 2022, a rapid spread of arboviral infections was reported with an increase in the number of encephalitis cases in existent areas (e.g., tick-borne encephalitis in Europe) and the emergence of new endemic areas (e.g., Japanese encephalitis in Australia). Future studies looking at the role of environmental changes, migration, the insufficient or inadequate vaccination programmes will not only reveal the epidemiology of these infections but also help prevent their often devastating neurological consequences. Other types of encephalitis such as those caused by amoebae, respiratory viruses or immune checkpoint inhibitors have also become more commonly identified. There is a need for clinicians to become more familiar with these developments and consider these causes in patients where the cause is proving difficult to identify. As a result, diagnosis and treatment can be improved and patient outcome will hopefully be more favourable.

Looking at the various studies published in 2022, it is important to acknowledge the discrepancy in reporting, aetiologies and management of encephalitis in different countries. This difference has potentially significant implications for the survival rates and morbidity of patients diagnosed with encephalitis. For example, whilst in New Zealand the mortality rate for encephalitis is 6.3% -12.5%, a study in Senegal reported a mortality rate of 41%.

Recently, there has been an increased number of studies looking at the outcomes of encephalitis. However, an outcome measure scale specific to encephalitis patients is still lacking. Nevertheless, it is now widely acknowledged that long-term follow-up and post-acute intensive cognitive and psychosocial intervention are crucial.

Despite the various challenges presented by the COVID-19 pandemic, the Encephalitis Society came out stronger and even more determined to increase its efforts in the fight against encephalitis. We started 2023 by focusing our attention on raising global awareness. During World Encephalitis Day (WED) Campaign, which highlighted research on mental health and encephalitis, we reached a record number of 111 million people (www.encephalitis.info/world-encephalitis-day-2023). We have continued our collaboration with global stakeholders looking at the global impact of encephalitis and this resulted in the publication of the Why Encephalitis Matters Report (https://apps.who.int/iris/handle/10665/366223) by World Health Organization on 22nd February 2023. We have also pledged to increase our spending on research to nearly 1 million pounds over the next three years (www.encephalitis.info/research-strategy).

We have launched our fifth year of research seed funding which this year is aimed at projects in Europe. The deadline is 30th September (www.encephalitis.info/seedfund). Plans for our annual conference - Encephalitis 2023 are underway. In 2022, 409 delegates from 55 countries attended in-person and/or virtually, so we urge you to book your place now (www.encephalitis.info/encephalitis-2023). The best way to keep up to date with all our news and activities and help us with our mission to save lives and build better futures is to become a member of the Encephalitis Society. Sign up for a free membership here today www.encephalitis.info/professional-membership

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 so hard to improve our understanding of this often-devastating condition.

Dr Ava Easton

Chief Executive, Encephalitis Society

Contents

Epidemiology of encephalitis

"Arthropod-borne encephalitis remains a significant global health concern and may pose a significant growing threat as the impact of climate change and human behaviour alters the transmission cycles of infectious pathogens." (Boruah and Thakur, 2022)

Tick-borne encephalitis (TBE) on the rise

In recent years, the incidence of TBE in Sweden has increased. Slunge et al. (2022) calculated the burden of disease over a 17-year period by analysing data from the Swedish National Health Data Register for TBE cases diagnosed between 1998 and 2014. Compared with a cohort of patients without TBE, patients with TBE were hospitalised for significantly more days during the first year after disease onset (11.5 vs. 1.1 days), logged more specialist outpatient visits (3.6 vs. 1.2 visits), and logged more sick leave days (66 vs. 10.7 days). The case-fatality rate for TBE was 1.1%. In another study by Varnaite et al. (2022) the standardised mortality ratio for TBE in Sweden (2004-2017) was 3.96; no cases in patients <40 years of age were fatal.

Geeraedts et al. (2022) presented a summary of epidemiology, symptoms and diagnoses of TBE in the Twente region, Netherlands between 2016-2020. All seven reported cases had confirmed diagnoses by serology. The authors concluded that the Twente region in the Netherlands may be considered a risk area for TBE, and corresponding vaccination advice could be considered for people with a risk of exposure to tick-bites.

Jenkins et al. (2022) reported that the health control measures instituted in 2020 to mitigate the COVID-19 pandemic decreased the case numbers of many infectious diseases across Europe except for the TBE. In Austria, Germany, Switzerland, Lithuania and the Czech Republic, increases of 88%, 48%, 51%, 28%, and 18%, respectively were reported. Six countries reported TBE incidences of ≥5 cases/100,000, defined as highly endemic by the World Health Organization (WHO). The authors noted that possible factors contributing to this surge may include increased participation in outdoor activities in endemic regions and increased tick counts/tick activity. However, in highly endemic regions, the WHO recommends that vaccination be offered to all age groups, including children.

Stahlman (2022) reported that the number of TBE cases per five-year period among USA military health system beneficiaries grew from one in 2012–2016 to 11 in 2017–2021. All cases reported between 2019 and 2021 occurred in Germany in the months of June and July. None of the cases had a prior history of TBE vaccination. Hills et al. (2022) reported four USA travellers to various countries in Europe and Russia who developed TBE. The researchers stress the need for clinicians to consider the diagnosis of TBE in a patient with a neurologic or febrile illness recently returned from a TBE-endemic country, particularly if a tick bite or possible tick exposure is reported.

Geeraedts F., Wertenbroek A., de Klerk J., et al. (2022) Defining a risk area for tick-borne encephalitis (TBE) in a country where TBE is emerging, the Netherlands, July 2016-October 2020. Ticks Tick Borne Dis; 13(2):101898.

Hills S.L., Broussard K.R., Broyhill J.C., et al. (2022) Tick-borne encephalitis among US travellers, 2010–20. J Travel Med; 29(2).

Jenkins V.A., Silbernagl G., Baer L.R., et al. (2022) The epidemiology of infectious diseases in Europe in 2020 versus 2017–2019 and the rise of tick-borne encephalitis (1995–2020). Ticks Tick Borne Dis; 13(5):101972.

Stahlman S. (2022) Surveillance snapshot: Tick-borne encephalitis in military health system beneficiaries, 2012–2021. MSMR; 29(5):23.

Slunge D., Boman A., Studahl M., et al. (2022) Burden of Tick-Borne Encephalitis, Sweden. Emerg Infect Dis; 28(2):314-322.

Varnaitė R., Gredmark-Russ S., Klingström J., et al. (2022) Deaths from Tick-Borne Encephalitis, Sweden. Emerg Infect Dis; 28(7): 1471–1474.

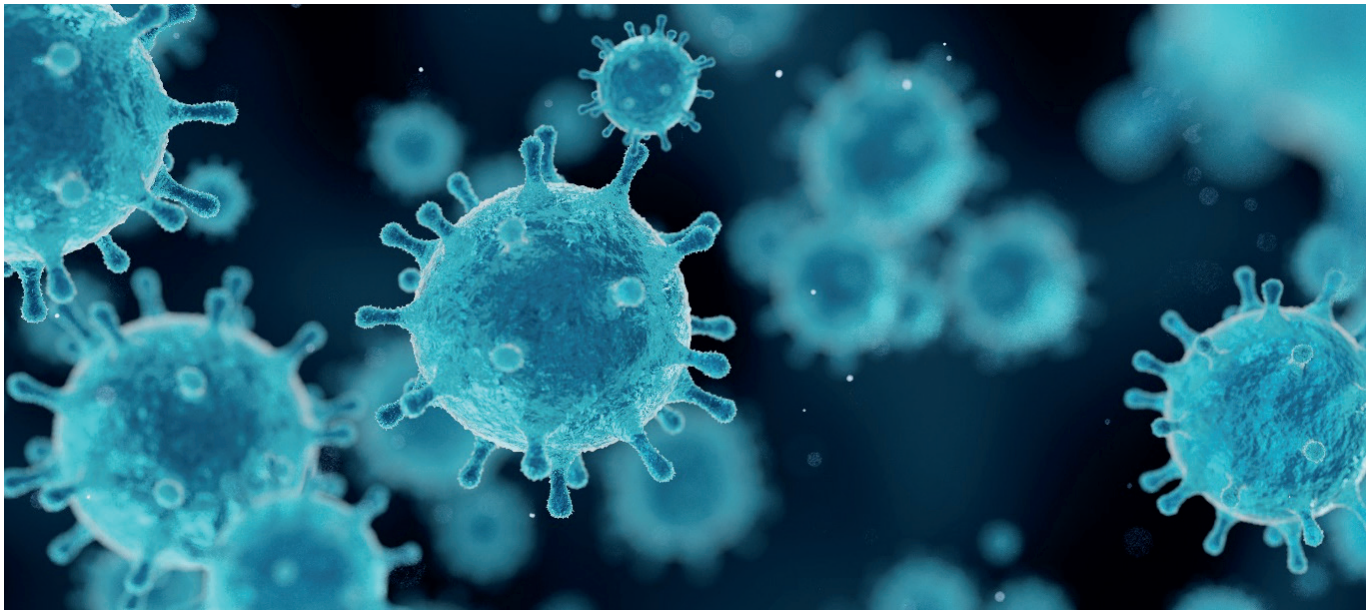
West Nile virus (WNV) circulation in Europe, Africa and North America

Riccardo et al. (2022) described the 2022 WNV transmission season in Italy, marked by early circulation and an unprecedented number of reported cases. They also compared it with the severe WNV epidemic from 2018. In 2022, there were 182 confirmed human infections with 57.7% WN neuro-invasive disease (WNND) cases of which 13 were fatal. During 2018, Italy reported 162 confirmed cases including 32.1% of WNND and 13 deaths. In Germany, Schneider et al. (2022) reported the first autochthonous WNV encephalitis in a 33-year-old kidney transplant recipient in 2019.

There is a lack of information about WNV distribution in Africa. García-Carrasco et al. (2023) established a high-resolution risk map for WNV infections that highlighted favourable areas for infections in Africa. Although WNV infections are widely spread across Africa, the risk of the disease is not homogenously distributed. Popular tourist destinations such as Morocco, Tunisia, and South Africa, are high-risk areas for WNV infection. Mencattelli et al. (2022) highlighted evidence of circulation of WNV among humans, animals and vectors in at least 28 countries; the lack of knowledge on the epidemiological situation of WNV for 19 countries; and the importance of carrying out specific serological surveys in order to avoid possible bias of WNV circulation in Africa.

In the USA, in 2020, the national incidence of neuroinvasive West Nile virus disease was 59% lower than the median annual incidence during 2010–2019. However, the neuroinvasive disease incidence for other domestic arboviral diseases (e.g., La Crosse virus, St. Louis encephalitis virus) was higher in 2020 than the median annual incidence for the preceding 10 years (Soto et al., 2022).

Riccardo F., Bella A., Barzon L., et al. (2022) Rapid increase in neuroinvasive West Nile virus infections in humans, Italy, July 2022. Euro Surveill; 27(36): 2200853.



Schneider J., Bachmann F., Choi M. et al. (2022) Autochthonous West Nile virus infection in Germany: Increasing numbers and a rare encephalitis case in a kidney transplant recipient. Transbound Emerg Dis; 69(2): 221-226.

García-Carrasco J-M., Muñoz A-R., Olivero J., et al. (2023) An African West Nile virus risk map for travellers and clinicians. Travel Medicine and Infectious Disease; 52: 102529.

Soto R.A., Hughes M.L., Stapes J.E., et al. (2022) West Nile virus and other domestic nationally notifiable arboviral diseases – United States, 2020. MMWR Morb Mortal Wkly Rep; 71: 628–632.

Mencattelli G., Dior Ndione M.H., Rosa R. et al. (2022) Epidemiology of West Nile virus in Africa: An underestimated threat. PLoS Neg Trop Dis 16(1): e0010075.

Arthropod-borne encephalitis: a review

Boruah and Thakur (2022) presented an overview of arboviral infections with the emphasis on the rapid spread of these infections in recent years which caused a wide range of clinical presentations from asymptomatic infection to fulminant neurological disease. Their review discussed the current development on the pathogenesis and virulence factors associated with neurological arboviral infections, the current clinical approaches to diagnosis, treatment and prevention of arboviral encephalitis and the re-emergence of certain arboviral infections. The main messages summarised by the authors are:

- Arthropod-borne encephalitides are a major public health threat, with significant risks associated with environmental changes and population growth.
- While a large class of pathogens transmitted by mosquitoes and ticks can cause encephalitis, significant clinic radiographic similarities exist suggesting common mechanistic pathways.
- Evidence of host and pathogen-specific factors associated with neurovirulence, with potential therapeutic targets.
- Neuroanatomical distribution of lesions across motor pathways suggests axonal transport once in the central nervous system for several arthropod-associated encephalitides.

Boruah A.P., Thakur K.T. (2022) Arthropod-borne encephalitis: an overview for the clinician and emerging considerations. Postgrad Med J 2022 Sep 19: postgradmedj-2022-142002.

Epidemiology of encephalitis in Asia

In India, Ravi et al. (2022) aimed to establish an enhanced surveillance network and use a standardised diagnostic algorithm to conduct a systematic evaluation of acute encephalitis syndrome (AES). The study included 10,107 patients with AES between 2014 and 2017. 57.8% were male and 62.7% were children ≤15 years old. Among patients who provided either serum or cerebrospinal fluid (CSF) samples, an aetiology was identified in 33.2% of 5,786 patients enrolled between 2014 and 2016 and in 34.3% of 4,321 patients enrolled in 2017. The most identified aetiologies were Japanese encephalitis virus (JEV) (1023), scrub typhus (645), and dengue virus (DENV) (161). Among participants who provided both CSF and serum specimens, an aetiology was identified in 38.3% of 3,774 patients enrolled between 2014 and 2016 and in 40.3% of 2,324 enrolled in 2017, representing a 3.1-times increase in the number of patients with acute encephalitis syndrome with an identified aetiology compared with standard care alone. The authors concluded that the implementation of a systematic diagnostic algorithm in an enhanced surveillance platform resulted in a 3.1-times increase in identification of the aetiology of AES, besides JEV alone. The authors further highlighted the importance of scrub typhus and DENV as important infectious aetiologies in India. These findings have prompted revision of the national testing guidelines for this syndrome across India.

JEV continues to be the leading cause of AES in central India. Among 278 patients with AES enrolled in a study in central India by Tandale et al. (2022), infectious aetiologies were identified in 115 (41.4%) cases, including non-viral in 17 (6.1%) cases - leptospirosis (8), scrub-typhus (3) and typhoid (6); and viral in 98 (35.3%)

cases - JEV (58), herpes simplex virus (HSV) (22), DENV (15) and Chandipura virus (3).

In a multicentre, observational, prospective study of childhood encephalitis by Pommier et al. (2022), 664 children with encephalitis from four referral hospitals in Cambodia, Vietnam, Laos and Myanmar were enrolled. A confirmed or probable cause of encephalitis was identified in 425 (64%) patients: 33% JEV, 4% DENV, 4% influenza virus, 4% HSV1, 3% *Mycobacterium tuberculosis*, 3% *Streptococcus pneumoniae*, 3% enterovirus A71, 9% other pathogens, and 1% autoimmune encephalitis. Of all, 42% had conditions that could have been preventable by vaccination. At the time of discharge, 23% children had severe neurological sequelae and 13% had died. At one year follow-up of 432 children who were discharged from hospital, 5% had died, 30% had neurological sequelae, and 65% had completely recovered.

Pommier J.D., Gorman C., Crabol Y., et al. (2022) Childhood encephalitis in the Greater Mekong region (the Southeast Asia Encephalitis Project): a multicentre prospective study. Lancet Global Health; 10(7): e989-e1002.

Ravi V., Hameed S.K.S., Desai A., et al. (2022) An algorithmic approach to identifying the aetiology of acute encephalitis syndrome in India: results of a 4-year enhanced surveillance study. Lancet Glob Health; 10(5): e685-e693.

Tandale B.V., Tomar S.J., Bondre V.P., et al. (2022) Infectious causes of acute encephalitis syndrome hospitalizations in Central India, 2018–20. J Clin Virol; 153: 105194.

Childhood meningoencephalitis in the Netherlands

De Blauw et al. (2022) used data collected for the Paediatric and Adult Causes of Encephalitis and Meningitis (PACEM) study in Netherlands to investigate the incidence of childhood meningoencephalitis in children with suspected meningoencephalitis. Among 432 children included in the study, there were 66 cases of proven meningoencephalitis (15.3%), of which 61 (92.4%) were of infectious origin, and 38 cases as possible meningoencephalitis (8.8%). The majority of children (72.2%) were ≤ 1-year-old. Most causes were viral (60.7%) followed by bacterial meningoencephalitis (27.9%). In addition, 3.3% had *B. Burgdorferi*–associated meningoencephalitis identified, 7.6% had no pathogen identified and 7.6% were autoimmune encephalitis. Enteroviruses were the most frequently identified viral pathogens (67.6%). The most prevalent bacterial pathogens were *Streptococcus agalactiae* and *Neisseria meningitides* (both 23.5%). Acute disseminated encephalomyelitis was the most frequent cause of autoimmune encephalitis (40.0%). Mortality rate in patients with proven meningoencephalitis was 4.6% and in those with possible meningoencephalitis 3.1%.

De Blauw D., Bruning A.H.L., Wolthers K.C., et al. (2022) Incidence of childhood meningoencephalitis in children with a suspected meningoencephalitis in the Netherlands. Pediatr Inect Dis J; 41: 290-296.

Incidence of encephalitis in New Zealand

Liem et al. (2023) investigated the incidence of encephalitis in patients ≥15 years-old in the Auckland and Northland regions of New Zealand between 2009 and 2018. The study included 136 patients. Less than half (41.2%) had an infectious aetiology, with varicella zoster (46.4%) and herpes simplex (41.1%) being the most common causes. Less than a quarter (23.5%) had autoimmune encephalitis with LGI-1 antibody the most identified neuronal autoantibody (13.2%). No cause could be established in 35.3% of the patients. In-hospital mortality for infectious encephalitis was 12.5%, for autoimmune encephalitis 6.3%, and for encephalitis of unknown cause 10.4%. Overall, the annual incidence was 1.10 cases per 100,000 person-years. The authors concluded that compared to a previous analysis of encephalitis in adults in Auckland, the incidence of encephalitis had increased. However, the proportion of patients with an unknown cause for encephalitis had decreased.

Liem B., Anderson N.E., Wright S.L., et al. (2023) Encephalitis in adults in the Auckland and Northland regions of New Zealand, 2009 to 2018. J Clin Neruosci; 107:172-177.

Viral encephalitis in Senegal and Kenya

Kahwagi et al. (2022) aimed to characterise the main viral aetiologies of patients hospitalised for encephalitis in two hospitals in Dakar from January to December 2021. During the study period, 122 patients were enrolled. Viral aetiology was confirmed or probable in 27 patients (22.1%), with SARS-CoV-2 (n = 8), herpes simplex virus 1 (n = 7), human herpes virus 7 (n = 5), and Epstein-Barr virus (n = 4) being the most detected viruses. Age groups 40-49 was more likely to be positive for at least one virus with an odds ratio of 7.7. The mortality was high among infected patients, with 11 (41%) deaths notified during hospitalisation. The authors emphasised that these results reveal the crucial need to establish country-wide surveillance of encephalitis in Senegal to estimate the burden of this disease and implement strategies to improve care and reduce mortality.

Nyamwaya et al. (2022) conducted a clinical surveillance at the Kilifi County Hospital in Kenya over a five-year period (2014 to 2018), during which there were 18,341 admissions aged <16 years. Chikungunya virus (CHIKV) was detected in cerebrospinal fluid samples from 367 (9.2%) of 3,980 hospitalised children. The authors estimated an incidence of 77 CHIKV-associated neurological disease cases/100,000 person-years for children aged <5 years, which is higher than the incidence for bacterial meningitis (7 per 100,000 person-years) and cerebral malaria (20 per 100,000 person-years) during the same period.

Nyamwaya D.K., Otiende M., Mwango L., et al. (2022) Incidence of chikungunya virus infections among Kenyan children with neurological disease, 2014– 2018: A cohort study. PLoS Med 19(5).

Kahwagi J., Seye A. O., Mbodji A.B., et al. (2022) Surveillance of viral encephalitis in the context of COVID-19: A one-year observational study among hospitalized patients in Dakar, Senegal. Viruses; 14(5):871.

Epidemiology of autoimmune encephalitis

Zuliani et al. (2022) reviewed a 13-year-long biobank-data collection and provided the incidence of neuronal surface antibody (NSAb)-associated autoimmune encephalitis (NSAE) in two Italian provinces (Treviso and Trento) over a five-year period (July 2013-June 2018). NSAbs were diagnosed in 75 (6.4%)/1179 tested patients. The most common NSAbs were anti-LGI1 (n=30), followed by NMDAR (n=24). In the two provinces, 11 cases of NSAE were diagnosed making an estimated incidence of 1.54 per 1,000,000 population (LGI1-encephalitis 0.84). The authors concluded that LGI1-E is the most frequent NSAE among adults.

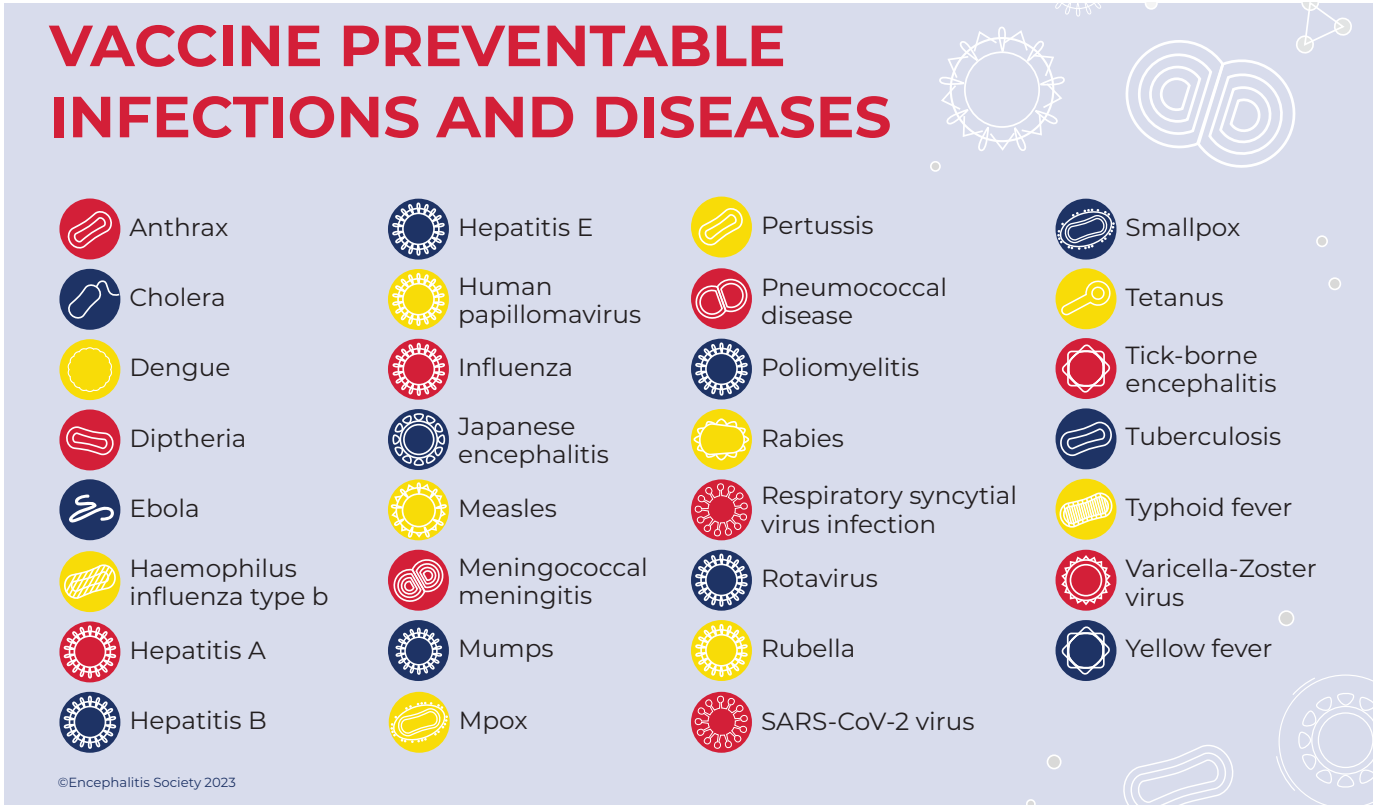
Kunchok et al. (2022) determined the frequency of detection and the age and sex associations of autoimmune/paraneoplastic encephalitis antibody biomarkers (AE-Abs) in 42,032 patients tested in the Mayo Clinic Neuroimmunology Laboratory. Adult serum analysis (22,472 patients; 56% female) revealed that 814 (3.6%) were positive: NMDA-R-IgG (24.6%), GAD65-IgG (21.5%), LGI1-IgG (20.5%), others (33.4%). Of children (5649; 50% female), 251 (4.4%) were positive: NMDA-R-IgG (53.1%), MOG-IgG1 (32%), GAD65-IgG (7.1%), others (7.8%). Adult CSF analysis (18,745 patients; 54% female) revealed that 796 (4.2%) were positive: NMDA-R-IgG (39.7%), GAD65-IgG (28.5%), LGI1-IgG (11.4%), others (32.9%). Of children (5136; 50% female), 282 (5.5%) were positive: NMDA-R-IgG (88.1%), GAD65-IgG (8.7%), others (3.2%). Age younger than 20 years was associated with NMDA-R-IgG and MOG-IgG1. Age older than 65 years was associated with $GABA_B$-R-IgG, LGI1-IgG, CASPR2-IgG and ANNA1-IgG. Women accounted for 60% of NMDA-R-IgG (CSF) and 78% of GAD65-IgG (CSF and serum) cohorts. Men accounted for 62% of the LGI1-IgG cohort. Age and sex interacted for NMDA-R-IgG, particularly in female patients younger than 20 years. The authors concluded that the most frequent AE-Abs detected were NMDA-R-IgG, GAD65-IgG, LGI1-IgG, and MOG-IgG1. Age and sex associations may suggest aging influences neurologic autoimmunity.

Uy et al. (2021) reported autoantibody testing, using antigen-specific live cell-based assays, in a series of 134 patients (cerebrospinal fluid and sera) and 55 blood donor controls (sera) undergoing lumbar puncture for suspected meningoencephalitis admitted in Vientiane, Laos. Eight of 134 (6%) patients showed detectable serum neuronal autoantibodies, against the N-methyl-D- aspartate and gamma-aminobutyric acid A receptors (NMDAR and $GABA_A$R), and contactin-associated protein-like 2 (CASPR2). Three of eight patients had accompanying autoantibodies in cerebrospinal fluid (two with NMDAR and one with $GABA_A$R antibodies) and, in two of these, the clinical syndromes were typical of autoimmune encephalitis. Three of the other five patients had proven central nervous system infections, highlighting a complex overlap between diverse infectious and autoimmune causes of encephalitis. No patients in this cohort were treated with immunotherapy, and the outcomes were poor, with improvement observed in a single patient. The authors concluded that in Laos, autoimmune encephalitis is underdiagnosed and has a poor prognosis. Empiric immunotherapy should be considered after treatable infectious aetiologies are considered unlikely. Awareness and diagnostic testing resources for autoimmune encephalitis should be enhanced in South-East Asia.

Kunchok A., McKeon A., Zekeridou A., et al. (2022) Autoimmune/Paraneoplastic Encephalitis Antibody Biomarkers: Frequency, Age, and Sex Associations. Mayo Clin Proc; 97(3):547-559.

Zuliani L., Marangoni S., De Gaspari P., et al. (2022) Epidemiology of neuronal surface antibody-mediated autoimmune encephalitis and antibody-based diagnostics. J Neuroimmunol; 357:577598.

Uy C.E., Mayxay M., Harrison R., et al. (2022). Detection and significance of neuronal autoantibodies in patients with meningoencephalitis in Vientiane, Lao PDR. Trans R Soc Trop Med Hyg; 116(10):959-965.



Pathogenesis of encephalitis

"Our multimodal evaluations provide convergent anatomical and functional evidence of NMDAR-autoantibody production from active germinal centres within both intratumoral tertiary lymphoid structures and traditional secondary lymphoid organs, the cervical lymph nodes." (Al-Diwani et al., 2022)

Anti-NMDAR encephalitis

Andrzejak et al. (2022) employed a patient-derived monoclonal antibody targeting the NR1 subunit of NMDAR and tested its effects in vitro. They reported that this hNR1 antibody drives cortical networks to a hyperexcitable state and disrupts mechanisms stabilising network activity such as Npas4 signalling. Network hyperactivity is in part a result of a reduced synaptic output of inhibitory neurons, as indicated by a decreased inhibitory drive and levels of presynaptic inhibitory proteins, specifically in inhibitory-to-excitatory neuron synapses. Importantly, on a single-cell level hNR1 antibody selectively impairs NMDAR-mediated currents and synaptic transmission of cortical inhibitory neurons, yet has no effect on excitatory neurons, which contrasts with its effects on hippocampal neurons. Together, these findings provide a novel, cortex-specific mechanism of antibody-induced neuronal hyperexcitability, highlighting regional specificity underlying the pathology of autoimmune encephalitis.

Al-Diwani et al. (2022) characterised and identified human germinal centres actively participating in NMDAR-specific autoimmunisation. From serum, both NR1-IgA and NR1-IgM were detected more frequently in NMDAR-antibody encephalitis patients versus controls. Within patients, ovarian teratoma status was associated with a higher frequency of NR1-IgA positivity in serum and cerebrospinal fluid (CSF), particularly early in disease and before ovarian teratoma resection. Furthermore, ovarian teratomas showed structural and functional evidence of NR1-specific germinal centres. On exploring classical secondary lymphoid organs, B cells cultured from cervical lymph nodes of patients with NMDAR-antibody encephalitis produced NR1-IgG in 3/7 cultures, from patients with the highest serum NR1-IgG levels. By contrast, NR1-IgG secretion was observed neither from cervical lymph nodes in disease controls nor in patients with adequately resected ovarian teratomas. The authors argued that the multimodal evaluations provide convergent anatomical and functional evidence of NMDAR-autoantibody production from active germinal centres within both intra tumoral tertiary lymphoid structures and traditional secondary lymphoid organs, the cervical lymph nodes. Furthermore, they developed a cervical lymph node sampling protocol that can be used to directly explore immune activity in health and disease at this emerging neuroimmune interface.

Al-Diwani A., Theorell J., Damato V., et al. (2022) Cervical lymph nodes and ovarian teratomas as germinal centres in NMDA receptor-antibody encephalitis. Brain;145(8):2742-2754.

Andrzejak E., Rabinovitch E., Kreye J., et al. (2022) Patient-derived anti-NMDAR antibody disinhibits cortical neuronal networks through dysfunction of inhibitory neuron output. J Neurosci; 42(15): 3253-3270.

Anti-LGI1 encephalitis

Peris Sempere et al. (2022) studied human leukocyte antigen (HLA) allele associations in anti-leucine–rich glioma inactivated 1 (LGI1) encephalitis. DRB1*07:01 and DQA1*02:01, two alleles in strong linkage disequilibrium, were associated with the disease across ethnicity independent of variation at DRB3 and DQB1, two flanking HLA loci. DRB1*07:01 homozygosity was associated with a doubling of risk, suggesting causality. DRB1*07:01 negative subjects were younger and more frequently female. Three patients with malignant thymomas did not carry DRB1*07:01, whereas patients with other tumours had high DRB1*07:01 frequency, suggesting that the presence of tumours other than thymomas may be coincidental and not causal. In both DRB1*07:01 heterozygous individuals and DRB1*07:01 negative subjects, DRB1*04:02 was associated with anti-LGI1 encephalitis, indicating an independent effect of this allele. DRB1*04:02 was also independently associated with younger age at onset. Major histocompatibility complex peptide-binding predictions using LGI1-derived peptides revealed divergent binding propensities for DRB1*04:02 and DRB1*07:01 alleles, suggesting independent pathogenic mechanisms. The authors conclude by emphasizing the secondary effect of DRB1*04:02 with lower age at onset and that this study provides evidence for secondary effects within HLA locus that correlate with clinical phenotypes in anti-LGI1 encephalitis.

*Peris Sempere V., Muñiz-Castrillo S., Ambati A., et al. (2022) Human leukocyte antigen association study reveals DRB1*04:02 effects additional to DRB1*07:01 in anti-LGI1 encephalitis. Neurol Neuroimmunol Neuroinflamm; 9(2): e1140.*

Tick-borne encephalitis (TBE)

Chmielewska et al. (2022) investigated the role of IFITM1, IFITM2, and IFITM3 in the inhibition of TBEV infection and in protection against virus-induced cell death. The authors demonstrated that the most significant role is that of IFITM3, including the dissection of its functional motifs by mutagenesis. They also showed the important role of IFITM proteins in the inhibition of TBEV infection and virus-mediated cell death. Their findings suggest that TBEV cell-to-cell spread may be less prone to both interferon- and IFITM-mediated suppression, potentially facilitating escape from IFITM-mediated immunity.

Chmielewska A.M., Gómez-Herranz M., Gach P., et al. (2022) The Role of IFITM proteins in tick-borne encephalitis virus infection. J Virol; 96(1).

Infectious encephalitis

"In scrub typhus endemic areas clinicians should have a low threshold for empirical antibiotic therapy in patients presenting with acute encephalitis syndrome, whilst undertaking investigations for alternative aetiologies." (Alam et al., 2022)

Herpes simplex virus (HSV): morbidity, mortality and acyclovir dosage

Berkhout et al. (2022) provided a comprehensive review of HSV central nervous system (CNS) infection in children in Australia. The study included 43 children diagnosed over a 13-year period, 17 neonates and 26 non-neonates. Most children (76.7%) were in the first 12 months of age. The annual incidence for HSV CNS infection in Queensland children aged ≤16 years was 0.3/100000 with neonates at highest risk (incidence 2.5/100000 live births). HSV1 was the predominant serotype in both neonates and non-neonates. Mortality rate was high (16.3%) of which 29.4% were neonates. Twenty-five (58.1%) of patients reported morbidity at discharge and 20/27 (74.1%) reported long-term neurological morbidity at follow-up. Interestingly, seven children (two neonates and four non-neonates) with long-term neurological sequelae had no neurological morbidity identified at discharge. The authors concluded that significant long-term neurological sequelae were seen in children with HSV CNS infection. Careful neurodevelopmental follow-up of all children is recommended.

Mulatero et al. (2022) conducted a retrospective monocentric study to determine the precise and most effective modalities of the treatment for HSE. The study included 76 patients ≥16 years old. The mean time from admission to treatment was 2.4 ± 6.0 days. Treatment with acyclovir prescribed was consistent with recommendations (10–15 mg/kg/8 h) for 14–21 days, but with differences between patients: < 10 mg/kg/8 h for 8 patients (11%), 10 mg/kg/8 h for 35 patients (46%), 10–15 mg/kg/8 h for nine patients (12%), and 15 mg/kg/8 h for 22 patients (29%). The authors also noted a difference between the theoretical dosage (prescribed by the doctor) and the actual dosage administered (dose administered according to the patient's infusion sheet) because of the development of acute renal failure.

Mortality rate was 12%, half of the patients (49%) had complete recovery and 39% reported sequelae. Two patients relapsed. Poor outcome was associated with persistent confusion, aphasia, or impaired consciousness at day five; superinfection; status epilepticus and admission-magnetic resonance imaging delay. The authors concluded by suggesting that acyclovir management in HSE can be modified for low-weight patients (< 79 kg) with a minimum dosage of 2550 mg/day (850 mg/8 h), when possible.

McKenna et al. (2022) reported three children with granulomatous herpetic encephalitis developed between one to 10 years after the initial presentation with acute herpes simplex encephalitis (HSE). The dominant neuroimaging phenotype in these cases was that of confluent gyriform cortical enhancement with predominantly solid foci of enhancement in the subjacent white matter +/− deep gray nuclei. No specific lobar predilection was apparent. All cases were accompanied by extensive vasogenic oedema within the involved brain and varying degrees of mass effect. In all three patients, cerebrospinal fluid was negative for HSV DNA. In two patients, granulomas were demonstrated at biopsy. The authors suggest that in a child presenting with encephalitis months to years after HSE the diagnosis of postherpetic granulomatous encephalitis should be considered, concluding that HSE can be a long-lasting central nervous system disorder. The authors hypothesised that dysregulation of the inflammasome response may have a role in the prolonged neuroinflammation seen following some cases of herpes simplex encephalitis.

Berkhout A., Kapoor V., Heney C., et al. (2022) Epidemiology and long-term neurological sequelae of childhood herpes simplex CNS infection. J Peadiatr Child Health; 58(8): 1372-1378.

Mulatero M., Boucekine M., Felician O., et al. (2022) Herpetic encephalitis: which treatment for which body weight? Journal of Neurology; 269: 3625–3635.

McKenna B., Malone C., Merwe A., et al. (2022) Granulomatous herpetic encephalitis a possible role for inflammasomes. Journal of Child Neurology; 37(5); 359-365.

Neurological manifestations of scrub typhus infection

Alam et al. (2022) conducted a systematic review and meta-analysis to report the clinical features and case fatality ratio (CFR) in patients with central nervous system (CNS) scrub typhus infection. Nineteen studies with 1,221 (656 adults and 565 paediatric) patients were included. The most common clinical features in CNS scrub typhus were those consistent with non-specific acute encephalitis syndromes (AES), such as fever (100.0%), altered sensorium (67.4%), headache (65.0%) and neck stiffness (56.6%). Classical features of scrub typhus were infrequently identified; an eschar was found in only 20.8% and lymphadenopathy in 24.1%. The pooled CFR (95% CI) was 3.6%. Paediatric cohorts had a CFR of 6.1% whilst adult cohorts reported 2.6%. The authors suggest that clinicians should have a high index of suspicion for scrub typhus in patients presenting with AES in endemic regions and consider starting empiric treatment whilst awaiting results of investigations, even in the absence of classical signs such as an eschar or lymphadenopathy.

Alam A.M., Gillespie C.S., Goodall J., et al. (2022) Neurological manifestations of scrub typhus infection: A systematic review and meta-analysis of clinical features and case fatality. PLoS Negl Trop Dis; 16(11).

The initial and second phases of tick-borne encephalitis (TBE)

Bogoviča et al. (2022) evaluated laboratory and immune findings in the initial and second (meningoencephalitic) phases of TBE in 88 well-defined adult patients. The laboratory findings in both phases of TBE revealed that laboratory abnormalities, consisting of low leukocyte and platelet counts and increased liver enzymes levels, were predominately associated with the initial phase of TBE and resolved thereafter. Assessment of 29 immune mediators in serum during the initial phase, in serum and cerebrospinal fluid (CSF) during the second phase of TBE revealed highly distinct clustering patterns among these three groups. In the initial phase of TBE, the primary finding in serum was a rather heterogeneous immune response involving innate (CXCL11), B cell (CXCL13, BAFF), and T cell mediators (IL-27 and IL-4). During the second phase of TBE, growth factors associated with angiogenesis (GRO-α and VEGF-A) were the predominant characteristic in serum, whereas innate and Th1 mediators were the defining feature of immune responses in CSF. These findings imply that distinct immune processes play a role in the pathophysiology of different phases of TBE and in different compartments.

Bogoviča P., Kastrinb A., Lotrič-Furlana S., et al. (2022) Comparison of laboratory and immune characteristics of the initial and second phase of tick-borne encephalitis. Emerging Microbes & Infections; 11.

Encephalitis caused by pseudorabies virus (PRV)

Hou et al. (2023) reported a case of viral encephalitis caused by PRV in China and summarised 12 cases already reported in the literature. Their patient had been left with psychiatric disorders, intermittent blurred vision, and an impaired cognitive function. All the reported patients had a history of direct or indirect contact with living pigs and more than a half had significant hand trauma before the onset of the clinical symptoms, which suggested that they may have contracted the virus through mucosal or blood contact with infected pigs or contaminated objects. Prodromal symptoms included fever and headache. All patients manifested severe central nervous system involvement with rapid progression and developed severe clinical signs within two weeks after the onset. The magnetic resonance imaging showed involvement in the limbic system, frontal and temporal lobes, basal ganglia, and thalamus in 11 patients. All patients were diagnosed using next-generation sequencing (NGS). Treatment included antiviral therapy, immunotherapy, and symptomatic supportive treatment. The authors concluded that patients with recent exposure to pigs should be screened for PRV encephalitis with a brain MRI and CSF NGS as early diagnosis and treatment are crucial.

Hou Y., Wang Y.M., Zhang Y., et al. (2023) Human encephalitis caused by pseudorabies virus in China: A case report and systematic review. Vector-borne and zoonotic diseases; 22(7).

Parechovirus encephalitis (PE)

Tierradentro-García et al. (2023) presented three patients with PE (two newborn and one adolescent, with comorbidities) focusing on the magnetic resonance imaging (MRI) brain patterns. In neonates, neuroimaging findings included restricted diffusion of the subcortical and periventricular white matter with frontoparietal predominance, in association with corpus callosum signal abnormality and bilateral swollen thalami. In teenager, it also presented with an additional pattern of white matter signal abnormality in the corona radiata in continuity with the corticospinal tracts. The differences noted in the imaging patterns between the newborns and the adolescent in the involvement of white matter may relate to the degree of myelination at the time of infection. The authors concluded that PE has typical features on brain MRI, so PE should be considered in the differential diagnosis when the MRI demonstrates white matter injury especially in those with comorbidities or an immunosuppressive status.

Tierradentro-García L.O., Zandifar A., Kim J.D.U., et al. (2022) Neuroimaging findings in parechovirus encephalitis: A case series of pediatric patients. Pediatric Neurology; 130: 41e45.

Nipah virus

Alam (2022) presented an overview of Nipah virus infection, highlighting that raising awareness of the epidemiology, clinical presentation and risk factors of contracting Nipah virus is vital to recognise and manage potential outbreaks of this disease. The key points of his review are:

- Nipah virus is a zoonotic disease which can cause severe and fatal encephalitis.
- It is endemic to Southeast Asia and the Western Pacific, with outbreaks occurring in Malaysia, Singapore, Philippines, India and Bangladesh.
- It can present non-specifically, but neurological symptoms are often common; uniquely it can cause a late-onset and relapsing encephalitis.
- Risk factors for transmission include contact with its reservoir host of fruit bats, contact with known intermediate hosts such as pigs or contact with known Nipah virus patients.
- No licenced medications or vaccines are currently available, with prevention and education being key to controlling outbreaks of this pathogen with pandemic potential.

Alam A.M. (2022) Nipah virus, an emerging zoonotic disease-causing fatal encephalitis. Clinical Medicine; 22 (4): 348–52.

Lyme neuroborreliosis (LNB) with encephalitis

Knudtzen et al. (2022) described LNB encephalitis via a literature review and a Scandinavian (Denmark, Sweden and Norway) retrospective cohort study. The literature review included 45 patients from 18 countries spanning 35 years. The cohort study (1990-2019) included 35 patients (median age 67 years). Symptoms included confusion, personality changes, aphasia, ataxia, seizures, unconsciousness. In the cohort study, the encephalitis prevalence was 3.3% among 1019 screened patients with LNB. Electroencephalography and neuroimaging showed findings suggestive of encephalitis in 93.8% and 20.6%, respectively. Median delay from symptom onset to hospital was 14 days, with further seven days delay until targeted therapy. At follow-up (median 298

days post-treatment), 65.6% had residual symptoms. None had died. Among patients from the literature research, at a median follow-up of 12 months, 32 had fully or partially recovered, two had died. The authors concluded that encephalitis is an uncommon, but likely overlooked manifestation of LNB. As the high frequency of residual symptoms may be related to prolonged treatment delay, prompt LNB testing of patients with encephalitis in *Borrelia burgdorferi*-endemic areas should be considered.

Knudtzen F.C., Eikeland R., Bremell D., et al. (2022) Lyme neuroborreliosis with encephalitis; a systematic literature review and a Scandinavian cohort study Clin Microbiol Infect; 28: 649

Infectious encephalitis. Case reports

Cole et al. (2022) reported a case of a previously healthy woman with monkeypox with encephalitis complicated by transverse myelitis who made an almost complete recovery after treatment with tecovirimat, cidofovir, steroids and plasma exchange.

Rao et al. (2022) reported a case of herpes simplex encephalitis (HSE) in a four-year old patient receiving dupilumab for atopic dermatitis.

Nakamura et al. (2022) reported a cat scratch disease-associated encephalitis which resulted in severe neurological sequelae and post-encephalitic parkinsonism.

Grammatikos et al. (2022) reported a case of chronic enteroviral meningoencephalitis (EME) in a 27-years-old patient with Good's syndrome treated successfully with pocapavir.

Zhanga et al. (2022) reported a critical case of acute encephalitis caused by the H5N6 virus in a six-year-old girl. An epidemiological investigation confirmed that wild waterfowls were the direct source of infection in this case.

Zhao et al. (2022) reported two elderly men with Epstein–Barr virus (EBV) encephalitis which manifested excessive daytime sleepiness as a clinical manifestation.

Regnault et al. (2022) reported a 59-year-old patient without specific past medical history with an epidemiological context that did not suggest rabies but died from encephalitis caused by the European bat lyssavirus type 1 (EBLV-1). People exposed to bats should be strongly advised to be vaccinated with rabies vaccines, which are effective against EBLV-1.

de Oliveira et al. (2023) presented a case of meningoencephalitis due to *Penicillium chrysogenum*, in an immunocompetent patient.

Frank et al. (2022) reported three patients with BoDV-1 encephalitis outside of Bavaria, in the north and east of Germany highlighting the need for BoDV-1 testing in acute encephalitis cases with residence or rural exposure history in known Borna disease-endemic areas.

Martinez-Poles et al. (2022) reported the clinical and radiological characteristics, treatment, and prognosis of an immunocompromised patient with meningoencephalitis due to *Mycobacterium lentiflavum*.

Mylonaki et al. (2022) reported a family outbreak of tick-borne encephalitis (TBE) resulting from alimentary transmission of TBE RNA found in frozen goat's milk.

Cole J., Choudry S., Kular S., et al. (2022) Monkeypox encephalitis with transverse myelitis in a female patient. Lancet Infect Dis; 23: e115–20.

de Oliveira R.V.M., Corrêa-Moreira D., Mendes T.V., (2023) First report of fungal meningoencephalitis by Penicillium chrysogenum in Brazil International Journal of Infectious Diseases 126: 94–97.

Frank C., Wickel J., Brämer D., et al. (2022) Human Borna disease virus 1 (BoDV-1) encephalitis cases in the north and east of Germany, Emerging Microbes & Infections; 11(1): 6-13.

Grammatikos A., Bright P., Pearson J., et al. (2022) Chronic enteroviral meningoencephalitis in a patient with Good's Syndrome treated with Pocapavir. Journal of Clinical Immunology; 42: 1611–1613.

Martinez-Poles J., Saldaña-Díaz AI., Esteban J., et al. (2022) Meningoencephalitis due to Mycobacterium lentiflavum in an immunocompromised patient: Case report. Eur J Neurol; 30: 1152-1154.

Mylonaki E., Seiberl M., Jones N., et al. (2022) Tick-borne encephalitis virus RNA found in frozen goat's milk in a family outbreak. Int. J. Mol. Sci; 23: 11632.

Nakamura M., Ura S., Yabe I. et al. (2022) Cat scratch disease-associated encephalitis followed by Parkinsonism. Intern Med 61: 3115-3120.

Rao M., Grove D., Haggstrom A. (2022) A rare presentation of herpes simplex virus encephalitis occurring in a pediatric patient on dupilumab for atopic dermatitis. Pediatr Dermatol; 39: 288–290.

Regnault B., Evrard B., Plu I. et al. (2022) First case of lethal encephalitis in Western Europe due to European Bat Lyssavirus Type 1. Clinical Infectious Diseases;74(3): 461–6.

Zhanga L., Kaituo Liub, Qin Su., et al. (2022) Clinical features of the first critical case of acute encephalitis caused by the avian influenza A (H5N6) virus. Emerging Microbes & Infections; 11.

Zhao H., Zhang X., Yang H., Gu J. (2022) Epstein–Barr virus encephalitis with excessive daytime sleepiness as the main manifestation: Two case reports. Medicine; 101:34.

Japanese encephalitis (JE)

The data from this study showed significant burden of JE in the form of disability: 63.08% of children developed neurological sequelae at different levels of severity, and 15.4% of children died after hospital discharge at home." (Srivastava et al., 2022)

Japanese encephalitis virus (JEV) in Australia

Howard-Jones et al. (2022) presented a cross-sectional analysis of JEV diagnoses in New South Wales (NSW), Australia. The detection of a new and unexpected JEV outbreak in March 2022 in Australia, where JEV is not endemic, demanded the rapid development of a robust diagnostic framework to facilitate the testing of suspected patients across the state of NSW. Over the first three months of the outbreak (4 March - 31 May 2022), 1,061 prospective samples were received from 878 NSW residents for JEV testing. 12 confirmed cases of Japanese encephalitis (JE) were identified, including 10 cases diagnosed by serology alone, one case by metagenomic next-generation sequencing and real-time polymerase chain reaction (RT-PCR) of brain tissue and serology, and one case by RT-PCR of cerebrospinal fluid, providing an incidence of JE over this period of 0.15/100,000 persons in NSW. As encephalitis manifests in <1% of cases of JEV infection, the population-wide prevalence of JEV infection is likely to be substantially higher.

Howard-Jones, A.R., Pham, D., Jeoffreys, N. et al. (2022) Emerging Genotype IV Japanese encephalitis virus outbreak in New South Wales, Australia. Viruses; 14: 185.

JE mortality and morbidity

Cheng et al. (2022) made updated estimates of the JE high case fatality ratio (CFR) and the proportion of JE survivors with long-term neurological sequelae by performing a systematic review and developing statistical and machine learning models. They estimated JE CFR decreased over time, with estimates of 26% in 1961–1979, 20% in 1980–1999, 14% in 2000–2018 and 14% in 2019–2030. Countries without JE vaccination, younger JE patients, higher population growth rate, and lower rural population percentage were associated with higher JE CFR. They estimated that 36% of patients with JE recovered fully at hospital discharge. One year after hospital discharge, 46% JE survivors were estimated to live normally but 49% of patients with JE still had neurological sequelae. The authors argued that these findings will be important in evaluating and updating current JE disease burden among all endemic areas.

Srivastava et al. (2022) determined the JE-associated long-term functional and neurological outcomes, the extent of reduced social participation and predictors of poor outcomes among paediatric JE survivors. In this study, 74.6% of children developed neurological sequelae at different levels of severity. Age-expected social participation was compromised in 90 out of 118 children. In multivariate logistic regression analysis, a combination of parameters, JE unvaccinated status, low Glasgow Coma Score (GCS) at admission (≤8), malnutrition and requirement of endotracheal intubation statistically significantly predicted the poor outcome with 77.8% sensitivity and 94.6% specificity. The authors conclude that this study estimated the burden of JE-presenting post-discharge deaths (15.4%) and disability (63.08%).

Cheng Y., Tran Minh N., Tran Minh Q., et al. (2022) Estimates of Japanese encephalitis mortality and morbidity: A systematic review and modeling analysis. PLoS Negl Trop Dis; 16(5).

Srivastava N., Deval H., Mittal M., et al. (2022) Extent of disability among paediatric Japanese encephalitis survivors and predictors of poor outcome: a retrospective cohort study in North India. BMJ Open ;12: e060795

JE and Dengue (DENV) neurological infection

Pichl et al. (2022) performed a systematic review of brain imaging findings in JE and DENV to identify characteristic lesions. The findings included: thalamic lesions were the most reported magnetic resonance imaging finding in both diseases but appeared to occur more often in JE (74% in 23 studies) than DENV (29.4% in 58 studies). In cases diagnosed with antigen or nucleic acid tests, thalamic lesions were reported frequently in both JE (76.5% in 17 studies) and DENV (65.2% in 23 studies). These results suggest that thalamic lesions frequently occur in both JE and DENV. No radiological findings were found to be pathognomonic of either disease. The authors concluded that, although brain imaging may support a diagnosis, laboratory confirmation with highly specific tests remains crucial.

Pichl T., Wedderburn C.J., Hoskote C., et al. (2022) A systematic review of brain imaging findings in neurological infection with Japanese encephalitis virus compared with Dengue virus. International Journal of Infectious Diseases 119: 102–110.

Dystonia in patients with JE

Aryal et al. (2022) summarised the clinical features and management of dystonia among patients with JE following a comprehensive literature search. The study identified 19 studies with a total of 1547 patients, the diagnosis of which was confirmed by IgM detection in serum and/or cerebrospinal fluid in most of the patients (88.62%). Dystonia was reported in 234 (15.13%) patients and several types of focal dystonia being present in 131 (55.98%) either alone or in combination. Neuroimaging showed predominant involvement of thalami, basal ganglia, and brainstem. Oral medications including anticholinergics, GABA agonists, and benzodiazepines followed by botulinum toxin were the most common treatment modalities. The study's conclusion was that dystonia can be a disabling consequence of JE, and various available medical therapies can significantly improve the quality of life.

Aryal, R., Shrestha, S., Homagain, S., et al. (2022). Clinical spectrum and management of dystonia in patients with Japanese encephalitis: A systematic review. Brain and Behavior; 12: e2496.

Anti-NMDAR encephalitis

"The similarity between the post-acute stage of anti-NMDAR encephalitis and the psychiatric–cognitive alterations of individuals with schizophrenia spectrum disorders needs to be considered in the differential diagnosis of patients with psychiatric disorders." (Guasp et al., 2022)

Anti-NMDAR encephalitis and schizophrenia spectrum/mental disorders

Guasp et al. (2022) reported clinical features of post-acute anti-NMDAR encephalitis and compared it with schizophrenia spectrum disorders. Their study included 82 participants (aged 12–60 years): 28 with anti-NMDAR encephalitis, 27 with schizophrenia spectrum disorders and 27 healthy participants. At four months follow-up, many acute stage symptoms in participants with anti-NMDAR encephalitis had resolved. However, 89% participants showed deficits in at least one cognitive domain. Overall, 68% of cognitive domain variables were impaired. By the third follow-up (12 months), only 36% of the variables were altered. Features that predicted cognitive domain outcomes were decreased consciousness and no improvement within the first four weeks of treatment (both in the acute illness) and a visuospatial task (serial biases) at four months. In participants with schizophrenia spectrum disorders, 50% of 22 variables were impaired at four months and unchanged at 12 months.

All patients presented similar psychiatric features, but only in those with anti-NMDAR encephalitis, symptoms have improved (mostly between four and six months). Four of the patients with anti-NMDAR encephalitis would have met the criteria for schizophrenia spectrum disorder if the antibody positive would not have pointed towards anti-NMDAR encephalitis.

The authors concluded that the clinical features of the post-acute stage of anti-NMDAR encephalitis are substantially different than those from the acute stage. They are long-lasting and include cognitive–psychiatric alterations that closely resemble those of individuals with stable symptoms of schizophrenia spectrum disorders. The first six months post-acute require intensive cognitive and psychosocial intervention to maximise recovery.

Guasp (2) et al. (2022) investigated the use of serum neurofilament light chain (NfL) in differentiating NMDAR encephalitis from first-episode psychosis caused by a psychiatric disease (pFEP). Their observational single-centre study included 118 patients with anti-NMDAR encephalitis of which 33 had isolated psychosis at presentation, 45 patients with pFEP, 36 patients with herpes simplex encephalitis and 36 healthy controls. They found that young patients with first-episode psychosis and elevated serum NfL (≥15pg/mL) had a higher likelihood (120 times) of being subsequently diagnosed with NMDARe compared with pFEP. Testing serum NfL at disease onset had a sensitivity of 85% and a specificity of 96% for distinguishing NMDARe from pFEP.

Yasuda et al. (2022) described a patient diagnosed with anti-NMDAR encephalitis who developed two psychotic episodes two and four years after the initial illness. Anti-NMDAR antibodies were not detected during these two episodes, (both episodes three months post-partum) so the diagnosis made was schizophrenia. The authors suggested that schizophrenia developed due to stressors such as postpartum changes in hormonal balance and psycho-environmental changes, which lowered the threshold of psychosis after anti-NMDAR encephalitis.

Wang et al. (2022) reviewed a series of anti-NMDA receptor encephalitis patients with a long-term medical history of psychiatric disorders through a review of literature and described a patient with anti-NMDA receptor encephalitis with a long-term history of major depressive disorder. A total of 14 patients with anti-NMDA receptor encephalitis and a long-term history of mental disorders were included in the study. Most patients were adult (92.9%), female (78.6%) and first visited a psychiatric department (71.43%). The mean disease course of psychiatric disorders was more than nine years. Speech impairment (71.4%), abnormal behaviours (64.3%), and catatonia (64.3%) were the most common clinical symptoms. Most patients (85.7%) had a satisfactory prognosis after immunotherapy. The authors concluded that mental and behavioural impairments are more frequently observed in newly diagnosed anti-NMDA receptor encephalitis patients with a long-term history of mental disorders than those without mental illness. A diagnosis of anti-NMDA receptor encephalitis should be considered when patients with mental illness show sudden fluctuations in psychiatric symptoms.

Guasp M., Rosa-Justicia M., Muñoz-Lopetegi A. et al. (2022) Clinical characterisation of patients in the post-acute stage of anti-NMDA receptor encephalitis: a prospective cohort study and comparison with patients with schizophrenia spectrum disorders Lancet Neurol; 21: 899–910.

Guasp M. (2), Martin-Aguilar L., Sabater L., et al. (2022) Neurofilament light chain levels in anti-NMDAR encephalitis and primary psychiatric psychosis. Neurology; 98(14).

Yasuda K., Uenishi U., Sakamoto H., et al. (2022) Schizophrenia after remission of anti-NMDA receptor encephalitis. Asian Journal of Psychiatry; 70: 103027.

Wang H-Y., Yang X-Y., Han J. et al. (2022) Clinical characteristics of anti-N-methyl-d-aspartate receptor encephalitis in patients with a long-term history of mental disorders. European Journal of Medical Research; 27:38.

Disease progression and brain atrophy in anti-NMDAR encephalitis

Lee et al. (2022) investigated the longitudinal pattern, determining factors, and clinical implications of brain volume changes in NMDAR encephalitis. Thirty-six patients were followed-up for 28.5 months. The volume ratio at last magnetic resonance imaging (MRI) to baseline was the lowest in the cerebellum (94.4 5.7%, $p < 0.001$). Once developed, cerebellar volume reduction followed a progressive course until two years from disease onset. The degree of cerebellar volume reduction was positively correlated with mRS and total CASE scores, and CASE scores in the domains of memory, language, and psychiatric problems, gait instability/ataxia, and weakness. In linear mixed model analyses, the degree of cerebellar volume reduction was associated with cumulative disease burden up to two years and duration of status epilepticus, and delayed removal of teratoma for ≥one month. The authors concluded that cerebellar volume reduction was progressive once developed. Cerebellar volume reduction might reflect disease burden and extent of progression and be associated with poor outcomes in multiple functional domains.

Lee W-J., Lee S-T., Kim D-Y., et al. (2022) Disease progression and brain atrophy in NMDAR encephalitis: Associated factor & clinical implication. Annals of Clinical and Translational Neurology; 9(7): 912–924.

Triggers for anti-NMDAR encephalitis (NMDARE)

Nikolaus et al. (2022) reported atypical NMDAR expression in glioneuronal brain tumours, in which dysmorphic neurons might induce antibody formation leading to autoimmune encephalitis. Their patient (21-month-old) developed an atypical anti-NMDAR encephalitis which improved with immunotherapy. Subsequently, the child suffered a refractory relapse with a presumed suspected cerebellar tumour. A biopsy detected a diffuse astrocytoma, MYB or MYBL1-altered with MYBL1:MMP16-fusion. A third relapse and followed by a subtotal tumour resection resulted in a sharp decrease in anti-NR1 titre and significant sustained clinical improvement. A further analysis of the tumour sample revealed atypical NMDAR expression on the patient's dysmorphic neurons and suggested that autoantibodies binding the tumour were also responsible for NMDARE. Based on their findings of this study the authors propose an etiologic concept in which, in addition to herpes simplex encephalitis, the immunogenic properties of dysmorphic neurons, whether outside or inside the brain, serve as triggers for NMDARE.

Luo et al. (2022) reported clinical features of anti-NMDAR encephalitis following Japanese encephalitis (JE). Their study included 20 children with ages between 3-11 years. The median time from JE to developing anti-NMDAR was 29 days. Compared with 142 children with classical anti-NMDAR, the children with anti-NMDAR post JE had substantial more decreased level of consciousness, more autonomic dysfunction, fewer psychiatric or behavioural symptoms, fewer seizures, lesser improvement four weeks after immunotherapy, and worse outcomes at 12 months. The prognosis of those children also depended on the level on disability after JE.

Nikolaus M., Koch A., Stenzel W., et al. (2022) Atypical NMDA receptor expression in a diffuse astrocytoma, MYBor MYBL1-altered as a trigger for autoimmune encephalitis. Acta Neuropathologica; 144: 385–389.

Luo H., Ding X., Li Y., et al. (2022) Clinical characteristics of children with anti-N-Methyl-D-Aspartate receptor encephalitis after Japanese encephalitis. Pediatric Neurology; 130: 46e52

Prognostic markers for anti-NMDAR encephalitis

Ma et al. (2022) investigated if neurofilament light chains (NfL) could be a prognostic marker for anti-NMDAR encephalitis by measuring NfL of 64 patients with anti-NMDARE and compare it with 84 healthy controls. Serum NfL levels were significantly elevated in patients with anti-NMDAR encephalitis compared to healthy controls especially in patients with severe impairments or with limited response to treatment. Serum NFL was positively associated with the initial admission mRS and 1-year mRS.

Kashyap et al. (2022) conducted a retrospective chart review of 36 paediatric patients with anti-NMDAR to investigate if the neutrophil-to-lymphocyte ratio (NLR) may predict poor outcomes. They found that high NLR was associated with intubation and rehabilitation LOS, but did not correlate with one-year outcomes, inpatient length of stay (LOS), or with tumour.

Tang et al. (2022) investigated if neutrophil percentage-to-albumin ratio (NPAR) is associated with the severity at admission and discharge (short-term prognosis) in a retrospective study of 181 patients with anti-NMDAR encephalitis. Their results showed that NPAR had good sensitivity and specificity in assessing disease severity at admission and predicting short-term prognosis.

Kashyap N., Morris M., Loerinc L.B., et al. (2022) The neutrophil-to-lymphocyte ratio is associated with intubation in paediatric anti-NMDA receptor encephalitis: A retrospective study. Journal of Neuroimmunology; 370: 577931.

Tang Y., Hou H., Li L., et al. (2022) Neutrophil percentage-to-albumin ratio: a good parameter for the evaluation of the severity of anti- NMDAR encephalitis at admission and prediction of short-term prognosis. Front. Immunol; 13:847200.

Ma X., Lu Y., Peng F., et al. (2022) Serum NfL associated with anti-NMDA receptor encephalitis. Neurological Sciences; 43:3893–3899.

Case reports

Fredrich et al. (2022) reported a refractory anti-NMDAR encephalitis in early pregnancy, treated successfully in second trimester of pregnancy with cyclophosphamide.

Bai et al. (2022) reported a patient with anti-NMDAR encephalitis with overlapping symptoms of GFAP antibody positivity.

Berek et al. (2022) reported a patient with anti-NMDAR who developed a relapse at 44 months with anti-MOG and anti-Caspr2 antibodies. Treatment with plasmapheresis, steroids and rituximab led to improvement although anti-Caspr2 antibodies persisted, whilst anti-NMDAR decreased and anti-MOG were negative.

Leonard et al. (2022) reported a paediatric patient (18-year-old girl) with anti-NMDAR encephalitis not treated for 14 years which progressed to an advanced stage within a few weeks of onset with no return to the normal function, highlighting the importance of timely diagnosis and early initiation of immunotherapy.

Palleiko et al. (2022) reported a 25-year-old woman who was diagnosed with anti-NMDAR encephalitis and subsequently was found to have thymic hyperplasia for which she underwent thymectomy.

Akanuma et al. (2022) reported a patient with paraneoplastic encephalitis associated with small cell lung cancer (SCLC) and NMDAR antibodies with a cytotoxic T-cell immune response and atypically rapid clinical course.

Iorio et al. (2022) reported a patient with anti-NMDAR encephalitis presented with isolated memory dysfunction as an initial symptom highlighting the unusual monosymptomatic presentation of anti-NMDAR encephalitis.

Akanuma H., Iizuka T., Abe D., et al. (2022) Paraneoplastic anti-N-methyl-D aspartate receptor encephalitis associated with small cell lung cancer and cytotoxic T-cell-mediated pathology: Case report. Front. Immunol. 13:952868.

Bai P., Liu B., Li M. et al. (2022) Anti-NMDAR encephalitis with GFAPα IgG: a case report. BMC Neurol; 22: 424.

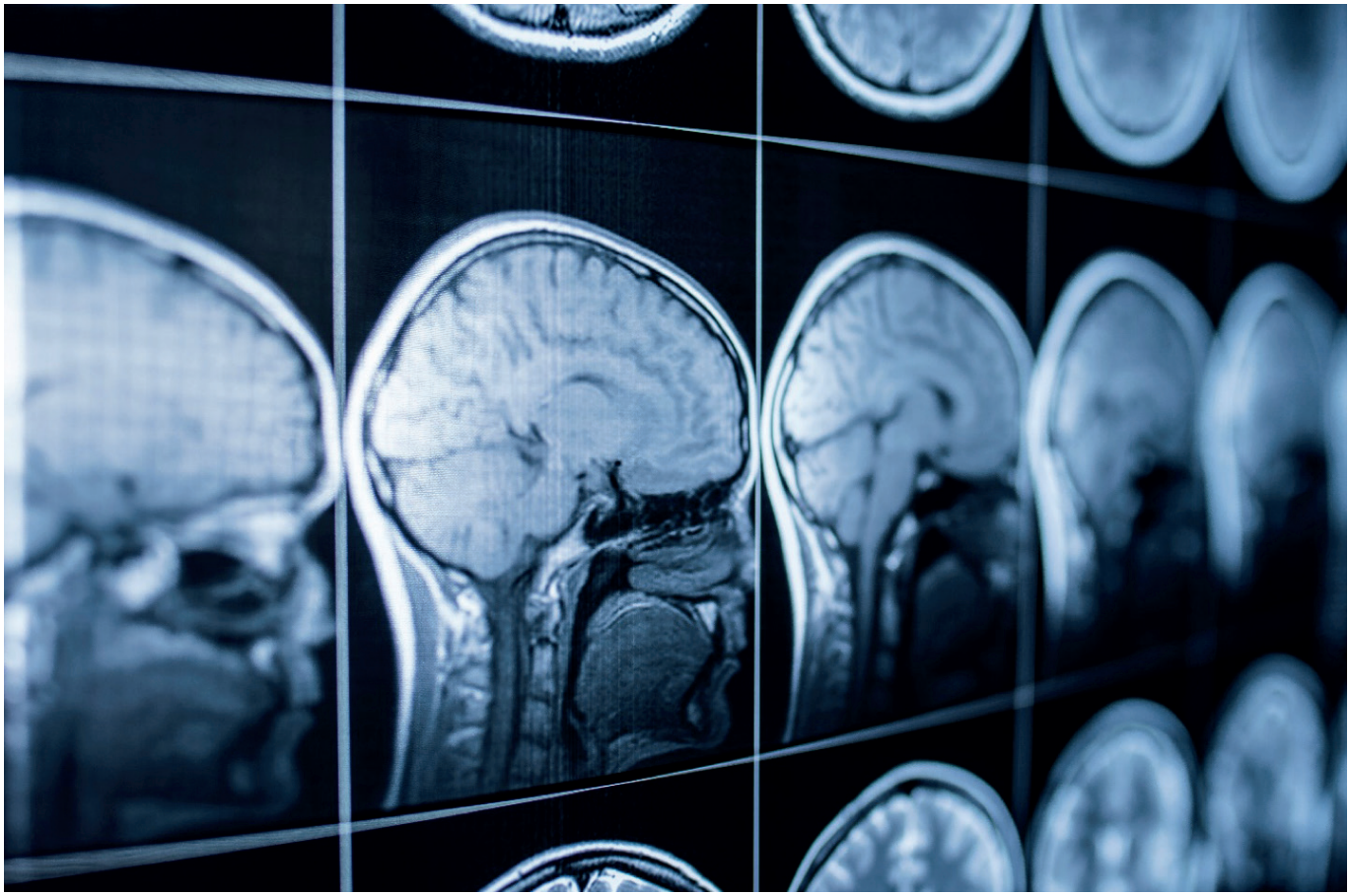
Berek K., Grams A., Uprimny C. et al. (2022) Anti-NMDA receptor encephalitis and MOG-associated demyelination – a case report with long-term follow-up and a systematic review. BMC Neurol; 22: 434.

Fredrich S., Wang C., Narayan R., et al. (2022) Refractory anti-NMDA receptor encephalitis in early pregnancy: a case report of treatment course and pregnancy outcomes. Neurol Neuroimmunol Neuroinflamm; 9(5).

Iorio R., Sabatelli E., Campetella L., Papi C. (2021) Isolated memory loss in anti-NMDAR encephalitis. Neurol Neuroimmunol Neuroinflamm; 9(2): e1128.

Leonard S., Budhram A., Shevell M. (2022) A story that begins too soon: a girl with untreated Anti-N-Methyl-D-Aspartate receptor encephalitis for 14 Years. The Canadian Journal of Neurological Sciences; 49(6).

Palleiko B.A., Salamatbad G., Bludevich B.M., Maxfield M.W. (2022) Thymectomy for treatment of anti-NMDA receptor encephalitis. Eur J Cardiothorac Surg; 62(4).



Anti-LGI1 encephalitis

"Acute treatment with corticosteroids may be more effective than IVIg in improving acute outcomes in patients with LGI1 antibody encephalitis." (Rodriguez et al., 2022)

Treatment, cardiac arrythmia and cerebrospinal fluid (CSF) biomarkers

Rodriguez et al. (2022) investigated acute treatment responses and long-term outcome in anti-LGI1 antibody encephalitis. Compared with 21 patients treated with intravenous immunoglobulin (IVIg), 49 patients treated with single-agent acute corticosteroids (intravenous, oral or both) were more likely to experience resolution of faciobrachial dystonic seizures and improvements in mRS score and median Kokmen STMS scores. At follow-up (≥2 years), 54 patients had the median mRS score 1 (range 0–6) and the median Kokmen STMS score 36 (range 24–38) after all combinations of immunotherapy. Short-term memory impairments were reported in 32% of the patients followed-up. The authors concluded that corticosteroids appeared more effective acutely than IVIg in improving LGI1 antibody encephalitis; while improvement with immunotherapy is typical and long-term outcome is favourable, short-term memory deficits are noted in approximately a third of the patients.

Zhao-Fleming et al. (2022) evaluated cardiac arrythmias associated with anti-LGI1 encephalitis in a retrospective descriptive study of 137 patients. They found that only 8% of patients had bradyarrhythmia during the initial presentation, mostly asymptomatic. One patient had a severe episode requiring a pacemaker, the others had favourable outcomes having full resolution without further cardiac intervention.

Lardeux et al. (2022) compared CSF biomarkers' levels in 24 patients with anti-LGI1 encephalitis with patients with neurodegenerative conditions [39 Alzheimer's disease (AD), 20 Creutzfeldt–Jakob's disease (CJD)] and primary 20 psychiatric (PSY) disorders. The authors noted that there was no significant difference in T-tau, P-tau, and Aβ1-42 levels between LGI1 encephalitis and PSY patients. T-Tau and P-Tau levels were significantly lower in LGI1 encephalitis than in AD and CJD patients. Neurofilaments light chains (Nf L) concentrations of LGI1 encephalitis were like AD and significantly higher compared to PSY, but significantly lower than those of CJD. Higher levels of Nf L were observed in LGI1 encephalitis presenting with epilepsy compared to LGI1 without epilepsy. The authors concluded that these findings suggest axonal or synaptic damage linked to epileptic seizures.

Lardeux P., Fourier A., Peter E., et al. (2022) Core cerebrospinal fluid biomarker profile in anti-LGI1 encephalitis. J Neurol; 269(1): 377-388.

Rodriguez A., Klein C.J., Sechi E., et al. (2022) LGI1 antibody encephalitis: acute treatment comparisons and outcome. J Neurol Neurosurg Psychiatry; 93: 309–315.

Zhao-Fleming H.H., Zahid A., Lu T., et al. (2022) Characterization of cardiac bradyarrhythmia associated with LGI1-IgG autoimmune encephalitis. Front. Immunol; 13:948479.

Prognostic markers and outcomes

Liu et al. (2022) investigate prognostic significance and brain metabolic mechanism of hyponatremia in anti-LGI1 encephalitis. The study found that patients with moderate and severe hyponatremia had significantly increased risk of poor functional outcome and sequelae of seizures. In addition, serum sodium was negatively correlated with normalised ratio of the standardised uptake value of medial temporal lobe (MTL), basal ganglia (BG), and hypothalamus on positron emission tomography (PET).

Rissanen et al. (2022) investigated if cortical and subcortical dysmetabolism are dynamic markers of clinical disability and course in anti-LGI1 encephalitis by analysing FDG-PET scans from 49 age-matched and sex-matched subjects (anti-LGI1, AE, Alzheimer disease and healthy controls) and follow-up scans from eight patients with LGI1 AE on a median six months after immunotherapy. The authors found that semiquantitative measurement of putamen hypermetabolism with FDG-PET may be used to distinguish LGI1-AE from other pathologies. Metabolic abnormalities in LGI1-AE extend beyond putamen and MTL into other subcortical and cortical regions. FDG-PET may be used in evaluating disease evolution in LGI1-AE.

In a study by Li et al. (2023), Chitinase 3-like 1 (CHI3L1) levels in cerebrospinal fluid (CSF) and serum were highly elevated in 35 patients with anti-LGI1 encephalitis at admission compared with 22 controls. Additionally, patients presenting with cognitive impairment had significantly higher CSF CHI3L1 levels and mRS scores than those without cognitive impairment symptoms. Patients presenting with only faciobrachial dystonic seizures at admission had lower CSF CHI3L1 levels than those with other symptoms. Finally, CSF CHI3L1 levels were positively correlated with CSF lactate levels. The authors concluded that CHI3L1 level in CSF is correlated with the severity and prognosis of anti-LGI1 encephalitis.

Liu X., Li G., Yu T., et al. (2022) Prognostic significance and extra-hypothalamus dysfunction of hyponatremia in anti-leucine-rich glioma-inactivated protein 1 encephalitis. J Neuroimmunol; 373:578000.

Rissanen E., Carter K., Cicero S., et al. (2022) Cortical and subcortical dysmetabolism are dynamic markers of clinical disability and course in anti-LGI1 encephalitis. Neurol Neuroimmunol Neuroinflamm; 9(2): e1136.

Li J., Li H., Wang Y., et al. (2023) CHI3L1 in the CSF is a potential biomarker for anti-leucine rich glioma inactivated 1 encephalitis. Front. Immunol; 13: 1071219.

Other autoimmune encephalitis

"Understanding that sleep/wake disorders can be the first symptom of autoimmune encephalitis (AIE) is often prominent throughout the course of the disease, sometimes phenotypic of particular AIE, and should prompt screening for AIE." (Ralls et al., 2022)

Paediatric autoimmune encephalitis

Sabanathan et al. (2022) described the clinical presentation, investigations, management, and disease course in 25 children (<18 years old) with paediatric autoimmune limbic encephalitis (LE). The children were identified from six tertiary centres between 2008 and 2021 and were followed up for a median of 24 months. All children presented with seizures, and more than a half (60%) were admitted to intensive care. Eight children presented with asymmetric mesial temporal changes and nine with extra-limbic changes with claustrum involvement on neuroimaging. Two children were positive for serum anti-NMDAR Abs, two for anti-Hu Abs and two children had serum and CSF anti- GAD antibodies. Initial immune therapy included steroids in 92%, intravenous immunoglobulin (IVIg) in 56%, and plasma exchange in 28%. Second-line treatment included rituximab in 15 children. Median duration of hospital admission was 21 days. One child died from relapsing neuroblastoma. At last follow-up, 52% had refractory seizures and 64% had memory impairment. There was no significant difference in mRS, or long-term cognitive and epilepsy outcomes in those who received rituximab versus those who did not. The authors concluded that paediatric autoimmune LE was associated with significant morbidity.

Rosello et al. (2022) characterised the features and course of psychiatric symptoms in children and adolescents with autoimmune encephalitis. Their retrospective study included 16 patients: 13 females and three males with ages between four and 15. Two patients had pre-existent neurodevelopmental disorder and one patient had herpes simplex encephalitis four months before. Only three patients had a neurological presentation at onset. The initial psychiatric presentation of the other 13 patients was characterised by predominantly agitation (87%), anger outbursts/aggressiveness (68%), sleep disturbances (75%), hallucinations (75%), and emotional lability (75%). Over the course of the illness, all patients had two or more psychiatric symptoms. Comparing the patients with anti-NMDAR with those without, sleep disturbances were present in all with anti-NMDAR compare with only 5/9 without anti-NMDAR. Antipsychotic treatment worsened symptoms in four cases. Benzodiazepines were commonly used. The authors conclude that this psychiatric phenotype associated with a poor cognitive function, and poor reaction to anti-psychotics should make clinicians suspect the diagnosis of AE.

Harmon et al. (2022) reported ten children with ages <18 years with GAD encephalitis. Median time from symptom to diagnosis was 20 months. Four children had premorbid psychiatric diagnoses, including depression, anxiety, attention-deficit/hyperactivity disorder and oppositional defiant disorder. On initial presentation, all children manifested with cognitive difficulties, seven had language difficulties and six children had seizures (complex partial). Nine children reported psychiatric symptoms, three of them presenting with psychosis. Other symptoms included fatigue, sleep disruption, and movement disorders in nearly half of the children. All children received steroids, immunoglobulin and rituximab and five children also received mycophenolate mofetil. Eight children were still on immunotherapy at their most recent appointments (up to 6.5 years). This study utilised a symptom scale developed by the Duke ABD clinic, to assess the current state and changes over time in the domains impacted by the illness. From all the symptoms only cognition and fatigue improved significantly over time. Seizures, psychiatric symptoms and sleep difficulties persisted. The authors concluded that this study demonstrated the variability of symptom profiles of paediatric GAD encephalitis. Symptom profiles and progression vary in this population.

Sabanathan S., Abdel-Mannan O., Mankad K., et al. (2022) Clinical features, investigations, and outcomes of pediatric limbic encephalitis: A multicenter study. Ann Clin Transl Neurol; 9(1):67-78.

Rosello R, Girela-Serrano B, Gómez S, et al. (2022) Characterizing the features and course of psychiatric symptoms in children and adolescents with autoimmune encephalitis. Eur Arch Psychiatry Clin Neurosci; 272(3):477-482.

Harmon A., Stingl C., Rikhi A., et al. (2022) Paediatric GAD-65 autoimmune encephalitis: assessing clinical characteristics and response to therapy with a novel assessment scale. Pediatr Neurol; 128: 25-32.

Early-stage CASPR2 limbic encephalitis

Benoit et al. (2022) aimed to describe the onset and progression of CASPR2-encephalitis and to assess long-term outcomes. Forty-eight patients were included (98% males; median age 64 years). At onset, 81% had at least one neurologic symptom among the following: limbic (54%), peripheral nerve hyperexcitability (PNH; 21%), and/or cerebellar symptoms (17%). Limbic symptoms at onset included mostly seizures (33%), while memory disturbances were less frequent (10%). PNH signs were mostly neuropathic pain (9/10 patients). Other symptoms seen at onset included asthenia (33%), mood disorders (25%), and insomnia (21%); 19% of patients did not show any limbic, peripheral, or cerebellar symptom at onset but only asthenia (15%), mood disorders (6%), weight loss (8%), dysautonomia (4%), and/or insomnia (2%). The peak of the disease was attained in median 16.7 months after onset. Over the study period (median follow-up, 58.8 months, range 10.6–189.1), 77% of patients developed ≥3 core CASPR2 symptoms and 42% fulfilled the diagnostic criteria for autoimmune limbic encephalitis, although all patients ultimately developed limbic symptoms. At the last visit (five years after onset), most interviewed patients (28/35 patients) had recovered functional independence (FAQ <9) while only the vitality sub score of the SF36 was lower than normative data (mean 49.9 vs 58.0, p = 0.0369).

Garrido Sanabria et al. (2022) reported the clinical presentations and outcomes of CASPR2-IgG-associated seizures in 20 patients (all male, median age 68 years) CASPR2-IgG+. Eighteen patients had seizures at initial presentation. Two patients had coexisting LGI1-IgG and one patient had a tumour. Fifteen patients met criteria for autoimmune encephalitis and five patients presented with isolated seizures. Most patients (n=14) presented with focal onset, nonmotor seizures with impaired awareness, whilst 11 patients also had focal motor and/or sensory seizures. The majority of patients (n=11) developed generalised tonic–clonic seizures during their disease course. Seizure clusters occurred in 12 patients. Other manifestations included cognitive disturbance (n = 16), episodic emotional lability (n = 13), paroxysmal dizziness (n = 9), episodic ataxia (n = 6), and chronic ataxia (n = 9). Frontotemporal or temporal ictal and/or interictal electroencephalographic abnormalities were present among nine patients, and three had multifocal epileptiform abnormalities. Thirteen patients reached seizure freedom following initiation of only antiseizure medication (n = 4) or a combination of immunotherapy and anti-seizure drugs (n = 9). The authors concluded by suggesting that CASPR2-IgG evaluation should be considered among older male patients with new onset focal seizures and impaired awareness often occurring in clusters with/without features of encephalitis.

Benoit J., Muñiz-Castrillo S., Vogrig A., et al. (2023) Early-stage Contactin-Associated Protein-like-2 limbic encephalitis clues for diagnosis. Neurol Neuroimmunol Neuroinflamm; 10 (1).

Garrido Sanabria E.R., Zahid A., Britton J., et al. (2022) CASPR2-IgG-associated autoimmune seizures. Epilepsia; 63(3): 709-722.

Sleep in autoimmune encephalitis (AE)

Ralls et al. (2022) provided a review of sleep disorders in AE focusing on recognising their new onset to facilitate a prompt early diagnosis. Sleep disorders are quite common and distinct in some types of AE. In anti-NMDAR encephalitis, patients can present with insomnia, then hypersomnia and sleep-related central hypoventilation. Fragmented sleep and hypersomnia are seen in paraneoplastic syndromes associated with anti-MA protein encephalitis. Patient with anti-LGI1 or CASPR-2 antibody encephalitis can present with rapid eye movement sleep behaviour disorder. Anti-IGLON5 disease presents with unique complex sleep disturbances: obstructive sleep apnoea, inspiratory stridor, disorganised nonrapid eye movement sleep and excessive movements and parasomnias fragmenting nonrapid and rapid eye movement sleep. The authors concluded that sleep/wake disorders are frequent in AE and sometimes are the earliest symptom. It is important to recognise them to enable early treatment initiation to reduce morbidity.

Wiao et al. (2022) reported three patients with anti-DPPX encephalitis who had sleep disorders with rapid eye movement sleep behaviour disorder adding the sleep behaviour to the initial prodromal clinical manifestations of anti-DPPX encephalitis alongside the gastrointestinal symptoms.

Mutti et al. (2022) performed a polysomnographic analysis in a 32-years-old patient with antibody-negative AE, performing cyclic alternating pattern (CAP) scoring during the subacute phase of the disease and at follow-up. The initial polysomnography showed deviations both at macro and microstructure levels, with a marked reduction of CAP rate compared to healthy sleepers (20.8% vs 33%). At six months follow-up, the sleep macrostructure improved, whilst CAP parameters remained abnormal compared with health sleepers (21.2%). The authors concluded their report with a hypothesis: neuroinflammation-related phenomena in AE could severely affect sleep regulatory mechanisms, targeting especially CAP circuits as occurs in neurodegenerative disorders.

Ralls F., Cutchen L., Grigg-Damberger M.M. et al. (2022) Recognizing new-onset sleep disorders in autoimmune encephalitis often prompt earlier diagnosis. J Clin Neurophysiol;3 9(5): 363-371.

Xiao J., Fu P.C., Li Z.J., et al. (2022) Clinical and imaging analysis to evaluate the response of patients with anti-DPPX encephalitis to immunotherapy. BMC Neurol; 22(1).

Mutti C., Angeli M.C., Rausa F., (2022) Sleep macro- and micro-structure in autoimmune encephalitis: single case report from the subacute phase of the disease to the follow-up, Neurocase; 28(2):235-238.

Olfactory impairment in autoimmune encephalitis (AE)

Morano et al. (2022) investigated olfaction in patients with AE. Their study included 19 patients (median age 64 years) of which 14 were diagnosed with definite AE and five with possible AE. Nine patients had a specific antibody: one anti-NMDAR, four anti-LGI1, three anti-CASPR2 and one anti-SOX1. The Brief Smell Identification Test (B-SIT), a 12-item, forced-choice, scratch-and-sniff measure, was used to assess the patients' olfactory function. Fifteen patients and five health controls were classified as olfactory impaired. Nine patients were qualified as hyposmic and six patients as anosmic. The B-SIT score was not influenced by age, gender or smoking habits. Olfactory dysfunction was influenced by the type of AE (definite or possible, but not type of antibody), higher modified Rankin Scale (mRS) scores at AE onset and bilateral ictal/interictal EEG abnormalities. The authors concluded that smell deficits may represent an additional feature of immune-mediated encephalitis.

Morano A., Cerulli Irelli E., Fanella M. et al. Olfactory impairment in autoimmune encephalitis: another piece of the puzzle. J Neurol; 269:2762–2768.

$GABA_AR/GABA_BR$ antibody encephalitis

Chen et al. (2022) investigated factors influencing the outcomes in 22 patients (average age of 55 years) with anti-$GABA_BR$ encephalitis looking at their clinical manifestations, laboratory and imaging features, tumour comorbidities and responses to treatment. Seven patients (all with lung cancer) died. Most of the surviving patients (92.9%) became functionally independent, however all of them presented sequelae: seizures (14.3%), neuropsychiatric (21.4%), cognitive impairment (21.4%). The authors found that elderly patients with anti-$GABA_BR$ antibodies, especially those with severe symptoms, serum tumour markers and additional onconeural antibodies have lung cancer; patients with tumours have a poor prognosis; most patients without tumours achieve self-care, but some still experience remaining neurological deficits.

Ronchi and Silva (2022) compared the two clinical syndromes, anti-$GABA_A$ and anti-$GABA_B$ associated encephalitis by doing a systematic literature review. Although both syndromes were characterised by prominent seizures, their presentations varied. Anti-$GABA_A$R patients were younger and showed multifocal encephalitis, whilst anti-$GABA_B$R patients were older and presented temporal limbic encephalitis. Tumour was more common in anti-$GABA_B$R encephalitis, mainly lung cancer. In anti-$GABA_A$R, only 20% of patients presented with tumour, mainly thymoma.

Deng at al. (2022) characterised the neuroimaging profile of ten patients with anti-$GABA_A$R encephalitis: eight male and two female with ages between 17-73 years. All patients had prominent seizures. They found that anti-$GABA_A$R encephalitis has distinctive neuroimaging phenotype with cingulate gyri. The authors argues that the topology of lesions might be associated with the distribution of β3 subunit–containing $GABA_A$R reflecting patients' disease severity and outcomes.

Hoshina et al. (2022) reported three patients with anti-$GABA_A$R encephalitis following a diagnosis of autologous hematopoietic stem cell transplant (aHSCT) for multiple myeloma (MM). All patients presented with seizures and altered cognitive function in addition to headache and visual disturbances (two patients) and intractable vertigo and mania (one patient). The authors highlighted the importance of considering anti-$GABA_A$R encephalitis in patients with seizures, multifocal non enhancing brain lesions, and a history of aHSCT for MM as prompt recognition of the condition can avoid brain biopsy and delays in initiation of immunotherapy.

Chen W., Wang Y., Guo X., et al. (2022) A prognostic analysis of the outcomes in patients with anti-g-aminobutyric acid B receptor encephalitis. Front. Immunol. 13: 847494.

Deng B., Cai M., Qiu Y., et al. (2022) MRI characteristics of autoimmune encephalitis with autoantibodies to $GABA_A$ Receptor: A case series. Neurol Neuroimmunol Neuroinflamm; 25: 9(3).

Hoshina Y., Galli J., Wong K.H., et al. (2022) GABA-A receptor encephalitis after autologous hematopoietic stem cell transplant for multiple myeloma: three cases and literature review. Neurol Neuroimmunol Neuroinflamm; 26: 9(6).

Ronchi N.R., Silva G.D. (2022) Comparison of the clinical syndromes of anti-GABAa versus anti-GABAb associated autoimmune encephalitis: A systematic review. Journal of Neuroimmunology; 363: 577804

Neuropsychological performance in autoimmune limbic encephalitis

In a 2022 study conducted in Germany by Mueller et al. (2022), the researchers provide a comprehensive analysis of the neuropsychological performance of autoimmune limbic encephalitis (ALE) in patients who have not received immune therapy. The study aimed to better define the neuropsychological profile of ALE and explore potential patterns associated with different autoantibodies. The findings of the study confirm that memory impairment and symptoms of depression are common features of ALE. However, the study also revealed additional insights:

1. Memory impairment primarily affects the consolidation of new information, resulting in deficits in long-term memory and recognition.
2. Short-term and working memory can be impaired, but typically at a subclinical level.
3. Recall of retrograde autobiographical episodes can be affected in ALE patients.
4. Deficits in emotion recognition, particularly related to fear, are observed in ALE patients.
5. ALE patients may also experience apraxia in pantomimes and imitation of gestures, a novel finding in this population.
6. Other potential deficits include impaired visuo-construction, processing speed, and flexibility. However, the performance in these areas can vary significantly among patients.

Overall, the study suggests that neuropsychological impairments in ALE may extend beyond the limbic system, indicating possible involvement of other brain networks. The authors recommend that a comprehensive neuropsychological assessment for diagnosing ALE should include evaluation of long-term memory, memory recognition, autobiographical-episodic memory, emotion recognition, and a detailed investigation of symptoms of depression.

Mueller C., Langenbruch L., Rau J.M.H., et al. (2022) Neuropsychological performance in autoimmune limbic encephalitis: Evidence from an immunotherapy-naïve cohort. Arch Clin Neuropsychol; 37(4): 738-752.

Anti-AK5 antibody autoimmune encephalitis

McKeon-Makki et al. (2022) reported three patients (all female) seen at Mayo Clinic with a rapidly progressive memory decline. The neuropsyhcometric testing showed inefficient learning and decreased visual naming and semantic fluency. All patients developed psychiatric manifestations: anxiety or depression early in the course of the diseases without any history of psychiatric illness. None of the patients had or developed seizures or cancer. One patient had recurrent burning smell sensation six months prior to the illness. All patients had bilateral mesio-temporal lobe T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities with gadolinium enhancement in the initial brain MRIs that evolved to atrophy in subsequent MRIs. Cerebrospinal fluid (CSF) analysis revealed inflammatory CSF and was positive for AK5. All patients received immunotherapy (steroids and IVIg) and, for one patient, long-term mycophenolate mofetil. At the last follow-up (median 20 months) all patients required help with daily living.

The authors concluded that AK5-IgG-associated neurological autoimmunity presents as severe limbic encephalitis with a predominant amnestic syndrome, associated depression, and anxiety, that is poorly responsive to immunotherapy. Better treatments are needed for this condition.

Guillaume et al. (2023) reported a chronic and insidious presentation of anti-AK5 encephalitis in a male patient (54-years old) with a history of psychiatric symptoms: depression, delusion and pseudologia fantastica. Symptoms such as pathological

lying, false memories and temporo-spatial disorientations were neglected due to previous psychiatric diagnosis. The authors emphasised that the clinical presentation of anti-AK5 may be wider than thought and it is important to reconsider psychiatric diagnosis when atypical symptoms appear.

Guillaume C., Saguin E., Peroux E., et al. (2023) Anti-AK5 encephalitis: subacute anterograde amnesia is not the only clinical presentation. Acta Neurol Belg; 123(1): 299-301.

McKeon-Makki I., McKeon A., Yang B., et al. (2022) Adenylate kinase 5 (AK5) autoimmune encephalitis: Clinical presentations and outcomes in three new patients. J Neuroimmunol; 367:577861.

Mortality and relapses in anti-NMDAR, anti-LGI1 and anti-GABABR encephalitis

Zhong et al. (2022) aimed to investigate the mortality rate and identify the predictors of death in patients with anti-NMDAR, anti-LGI1, and anti-$GABA_BR$ encephalitis. Of 100 hospitalised patients, 15 (15%) died during a median follow-up period of 18 months. The mortality rates were 10% for anti-NMDAR encephalitis, 2.8% for anti-LGI1 encephalitis and 41.7%for anti-$GABA_BR$ encephalitis. The multivariable analysis results showed that older age at onset was independently associated with an increased risk of death. Zhong et al. (2) (2022) also investigated relapse rate and the factors that may predict relapse in these types of autoimmune encephalitis. The authors found that the general relapse rate of anti-NMDAR, anti-$GABA_BR$ and anti-LGI1 encephalitis was 26%. The risk of subsequent relapse was elevated in those with delayed immunotherapy in the first episode. In subgroup of anti-LGI1 encephalitis, higher antibody titter was the risk factors of relapse.

Zhong R., Chen Q., Zhang X., et al. (2022) Risk factors for mortality in Anti-NMDAR, Anti-LGI1, and Anti-$GABA_BR$ encephalitis. Front. Immunol. 13: 845365.

Zhong R, Chen Q, Zhang X, et al. (2022) Relapses of Anti-NMDAR, Anti-GABABR and Anti-LGI1 encephalitis: a retrospective cohort study. Front. Immunol; 13: 918396.

Case reports

Cucuzza et al. (2022) reported a 10-year-old child with autoimmune encephalitis (AE) with a high level of mGluR3 in cerebrospinal fluid (CSF) and serum, suggesting a possible pathogenetic role.

Gong et al. (2022) reported a patient presenting with seizures and memory impairment diagnosed with both anti-SOX1 and anti-$GABA_BR$ paraneoplastic limbic encephalitis with small cell lung cancer.

Tappata et al. (2022) reported a patient with both anti-$GABA_AR$ and anti-titin antibodies AE presenting with thymoma.

Jia et al. (2022) reported a patient with anti-mGluR5 which presented with isolated focal motor seizures.

Vinke et al. (2022) reported a patient with mGluR1 antibodies with mainly limbic and without cerebellar symptoms (focal seizures, cognitive disturbances and auditory hallucinations).

Sobstyl et al. (2022) reported an extremely rare case of ADEM in a heroin-addicted patient with a very difficult diagnostic course in which the diagnosis was confirmed via neuropathology after a bilateral stereotaxic aspiration as a lifesaving procedure for the treatment of intracranial pressure.

Qi and Maheshwari (2023) reported a four-year old girl with ANNA-1- associated paraneoplastic limbic encephalitis who was found to have temporal lobe signal abnormality several months before seizure presentation and tumour diagnosis; hence her diagnosis was delayed by six months.

Muccioli et al. (2022) reported a 43-year-old man who was initially diagnosed as transient global amnesia. However, an in-depth neurological assessment diagnosed transient epileptic amnesia as well as anti-Ma2-associated limbic encephalitis.

Xu et al. (2022) reported the identification of a novel antibody against collapsing response mediator protein 2 (CRMP2) associated with suspected AE.

Cucuzza M.E., Pavone P., D'Ambra A., et al. (2022) Autoimmune encephalitis and CSF anti-AMPA GluR3 antibodies in childhood: a case report and literature review. Neurol Sci; 43(9): 5237-5241.

Gong S., Han Y., He E., et al. (2022) Coexistence of anti-SOX1 and anti-GABAB receptor antibodies with paraneoplastic limbic encephalitis presenting with seizures and memory impairment in small cell lung cancer: A case report. Front Immunol; 13: 955170.

Jia Y., Guo B., Li J., et al. (2022) Focal motor seizure as a presenting symptom in anti-mGluR5 encephalitis: A case report. Seizure; 103: 82-85.

Muccioli L., Romoli M., Giannini G., et al. (2022) Anti-Ma2-associated limbic encephalitis presenting with transient epileptic amnesia. Epileptic Disord; 24(4): 723-725.

Qi J., Maheshwari M. (2023) ANNA-1-associated paraneoplastic limbic encephalitis in a patient with pelvic ganglioneuroblastoma. Semin Roentgenol; 58(1): 3-5.

Sobstyl M., Rzehak A., Szczechowski D., et al. (2022) Acute disseminated encephalitis in an adult patient addicted to heroin. Neuropathological, neuroradiological and clinical features. Folia Neuropathol; 60(4):449-456.

Tappatà M., Giannoccaro M.P., Romoli M., et al. (2022) GABAA receptor and anti-titin antibody encephalitis in a patient with thymoma. Neurol Sci; 43(9): 5633-5636.

Vinke A.M., Zong S., Janssen J.H., et al. (2022) Autoimmune encephalitis with mGluR1 antibodies presenting with epilepsy, but without cerebellar signs: A case report. Neurol Neuroimmunol Neuroinflamm; 9(4).

Xu K., Wang D., He Y., et al. (2022) Identification of anti-collapsin response mediator protein 2 antibodies in patients with encephalitis or encephalomyelitis. Front. Immunol. 13: 854445.

Other types of encephalitis

"As these infections are under-reported, it is imperative to estimate the current burden of amoebic encephalitis and to know whether the infections are indeed increasing or just better registered." (Sarink et al., 2022)

Amoeba - the deadly brain infection

Sarink et al. (2022) provided an overview of the current understanding of the brain infections by free-living amoebae. *Naegleria fowleri* causes primary amoebic meningoencephalitis (PAM), a rapid and acute infection characterised by necrotic and haemorrhagic patches in the brain. *Balamuthia mandrillaris*, and *Acanthamoeba* spp cause chronic but fatal granulomatous amoebic encephalitis (GAE), which has a slower onset and disease progression.

Amoebae can cause devastating brain infections in humans which almost always result in death. The authors looked at the symptoms of these infections, biology, epidemiology, pathogenesis and the course of the disease. Although the symptoms of these deadly infectious overlap, the mechanisms by which they produce the illness differ. *N. fowleri*, which can infect immunocompetent hosts, circumvents the immune system by travelling via the olfactory nerve to the central nervous system (CNS), resulting in an impaired adaptive immune response involving neutrophils, and causing a very rapid disease course. *Acanthamoeba spp.* and *B. mandrillaris*, which mainly affect immunocompromised hosts via lung and skin, first must deal with the immune system in the blood and initiate an immune response with limited inflammation which involves granuloma formation.

The authors concluded that an understanding of how these amoebae operate is the basis of the development of strategies to prevent and treat these infections. It is also essential to understand if the infections are indeed increasing or just better registered and what roles are played by the genetics of the hosts or of the amoebae in the pathogenesis of this condition.

Tootla et al. (2022) reported the first case of *B. mandrillaris* granulomatous amoebic encephalitis acquired in Africa in a three-year-old, previously healthy child with no comorbidities, from a rural part of South Africa and with no history of travel outside the country. Ai et al. (2022) and Peng et al. (2022) reported two cases of *B.mandrillaris* amoebic encephalitis in mainland China diagnosed by metagenomics next-generation sequencing, with different outcomes: one fatal and one survival.

Ai J., Zhang H., Yu S., et al. (2022) A case of fatal amoebic encephalitis caused by Balamuthia mandrillaris, China. Infect Genet Evol; 97.

Peng L., Zhou Q., Wu Y., et al. (2022) A patient with granulomatous amoebic encephalitis caused by Balamuthia mandrillaris survived with two excisions and medication BMC Infectious Diseases; 22:54.

Sarink M.J., van der Meijs N.L., Denzer K., et al. (2022) Three encephalitis-causing amoebae and their distinct interactions with the host. Trends Parasitol; 38(3): 230-245.

Tootla H.D., Eley B.S., Enslin J.M.N. et al. (2022) Balamuthia mandrillaris granulomatous amoebic encephalitis: the first African experience. Journal of the Pediatric Infectious Diseases Society; 11(12): 578–81.

Rasmussen's encephalitis (RE): hemispherectomy and predisposition factors

Sundar et al. (2022) investigated long-term seizure and functional outcomes in patients with RE who underwent hemispherectomy. Their study included 30 patients with RE who underwent 35 hemispherectomies (five reoperations). The authors reported seizure-freedom rate of 81.5%, 63.6%, and 55.6% at one, five and 10 years after surgery, respectively. Patients with shorter duration of hemiparesis preoperatively was associated with lower likelihood of seizure-freedom at follow-up and increased likelihood reoperation. Furthermore, an increased risk of reoperation was noted in patients with shorter duration of epilepsy and preoperative bilateral MRI abnormalities. Complete disconnection of diseased hemisphere on postoperative MRI after the first operation improved seizure-freedom and resulted in fewer reoperations. Reoperation was associated with seizure freedom in every case. The authors conclude that hemispherectomy is a curative surgery for most patients with RE, with excellent long-term seizure outcome.

Fauser et al. (2022) investigated comorbidity and laterality factors that might predispose to RE. In this study, the median/mean age at symptom onset in RE was 7/10 years (range = 1–53 years), and 58.1% of the patients were female. The left hemisphere was affected in 65.6%. Perinatal complications (preterm birth, twin pregnancies, early acquired brain lesions) were more frequent in RE than in control patients. Ipsilateral facial autoimmune conditions (scleroderma en coup de sabre, uveitis, or chorioretinitis) were only observed in RE patients (6.9%). Onset of RE was more frequently associated with fever. In 33.1% of RE patients, ≥1 potential risk factor was found. Moreover, 11.9% of patients had one-sided early brain lesions or facial autoimmune lesions ipsilateral to subsequent RE; none had such a lesion contralaterally. The authors concluded that perinatal complications and facial autoimmune conditions may act as predisposing factors for RE. Fever might trigger RE manifestation. Further genetic or infectious contributors may be identified in the future. Ipsilateral early comorbid lesions or facial autoimmune processes might in part explain the enigmatic unilaterality of RE.

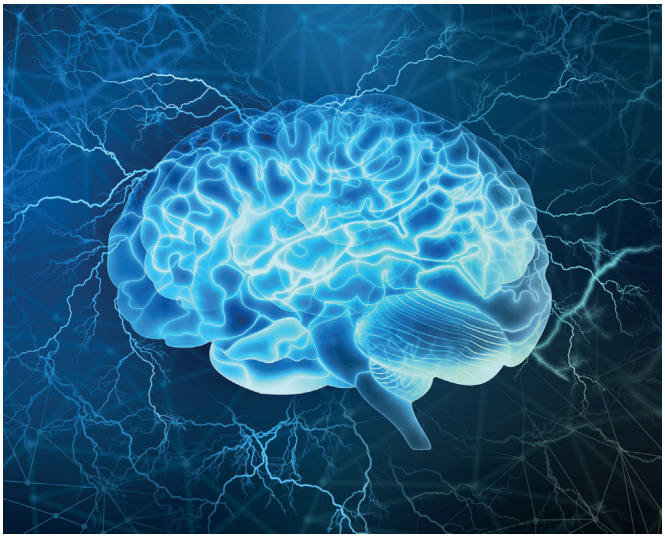
Fauser S., Elger C.E., Woermann F., Bien C.G. (2022) Rasmussen encephalitis: Predisposing factors and their potential role in unilaterality. Epilepsia; 63: 108–119.

Sundar S.J., Lu E., Schmidt E.S., et al. (2022) Seizure outcomes and reoperation in surgical Rasmussen encephalitis patients. Neurosurgery;91(1): 93-102.

Immune checkpoint inhibitor-induced encephalitis (ICI-iE)

Müller-Jensen et al. (2022) aimed to identify the characteristics of ICI-iE and compare it with herpes simplex virus (HSV)-1 encephalitis and anti-LGI1 encephalitis. The study included 30 patients with ICI-iE, 25 with HSV-1 encephalitis and 21 with anti-LGI1 encephalitis. Clinical presentation of ICI-iE was highly variable (impairment of consciousness, disorientation, aphasia) which mimics that of HSV-1 encephalitis, but not of anti-LGI1 encephalitis. Patients with ICI-iE had no antineuronal antibodies (except one) and only 60% of them had changes on magnetic resonance imaging (MRI). Cerebrospinal fluid (CSF) showed pleocytosis and/or elevated protein levels in almost all patients (97%). Three patients died (six with HSV1 and none with anti-LGI1). Full recovery was reported in 13 patients (only five in HSV1 and five in anti-LGI1) and it was associated with early immunosuppressive treatment.

Chisaki et al. (2022) compared the frequency of encephalitis due to ICIs with encephalitis due to other drugs by using the Japanese Adverse Drug Event Report (JADER) database and Bayesian confidence propagation neural networks for signal detection. Their study revealed that encephalitis occurs more frequently for atezolizumab, pembrolizumab, nivolumab, and ipilimumab compared with the frequency for other drugs. As the time of onset varied widely the authors suggest that patients should be monitored for more than one year after the last administration of ICIs.



Chisaki Y., Hata H., Matsumura C., Yano Y. (2022) The occurrence of encephalitis due to Immune Checkpoint Inhibitors: A pharmacovigilance study. Ther Innov Regul Sci; 56(2):323-332.

Müller-Jensen L., Zierold S., Versluis J.M., et al. (2022). Characteristics of immune checkpoint inhibitor-induced encephalitis and comparison with HSV-1 and anti-LGI1 encephalitis: A retrospective multicentre cohort study. Eur J Cancer; 175:224-235.

COVID-19 and encephalitis

"Although it is clear that empirical immunotherapy is beneficial in some patients, a better understanding of the pathophysiology to determine the subset of cases that is more likely to benefit, if immunotherapy can prevent neuropsychiatric post-acute COVID-19 sequelae and which is the best therapeutic approach required." (Ariño et al., 2022)

Neuroimmune disorders in COVID-19

Ariño et al. (2022) systematically described data from 133 reported series on the Neurology and Neuropsychiatry of COVID-19 blog (https:// blogs. bmj. com/ jnnp/ 2020/ 05/ 01/ the- neuro logy-and- neuropsychiatry- ofcovid- 19/), providing a comprehensive overview concerning the diagnosis, and treatment of patients with neurological immune-mediated complications of SARS-CoV-2. In most cases the latency to neurological disorder was highly variable and the immunological or other mechanisms involved were unclear. Despite specific neuronal or ganglioside antibodies only being identified in 10, many had apparent responses to immunotherapies. Although the proportion of patients experiencing immune-mediated neurological disorders is small, the total number is likely to be underestimated. Potential issues regarding the use of immunotherapies in patients with pre-existent neuro-immunological disorders are also discussed.

Hilado et al. (2022) reported three paediatric patients with serum SARS-CoV-2 antibodies who presented with neurological findings suggestive of postinfectious autoimmune-mediated encephalitis. Cerebrospinal fluid showed lymphocytic pleocytosis. High-dose intravenous corticosteroids resulted in substantial improvement in neurological symptoms. The authors concluded that although this association does not imply a causal link, the lack of other explanations and the excellent response to treatment may suggest autoimmune-mediated encephalitis is yet another SARS-CoV-2-related complication.

Ariño H., Heartshorne R., Michael B.D., et al. (2022) Neuroimmune disorders in COVID-19. J Neurol; 269(6): 2827-2839.

Hilado M., Banh M., Homans J., Partikian A. (2022) Pediatric autoimmune encephalitis following COVID-19 infection. J Child Neurol; 37(4): 268-272.

Brainstem encephalitis after COVID-19

Shamier et al. (2022) reported a clinically distinctive phenotype of brainstem and cerebellar symptoms in six out of the eight patients suspected to have central nervous system symptoms directly related to COVID-19 among thousands of hospitalised COVID-19 patients. This phenotype included myoclonia, ataxia, dysarthria, and eye movement disorders, with only minor cognitive disorders. SARS-CoV-2 polymerase chain reaction (PCR) in cerebrospinal fluid (CSF) was negative in all tested patients, and CSF pleocytosis was absent in all but one case. Intrathecal antibody synthesis specific to SARS-CoV2 could be confirmed in 3/5 patients classified as probable. This finding, in association with clinical findings and no other alternative explanation, led the authors to consider SARS-CoV-2-related aetiology in these three patients. Although proving causality between CNS symptoms and SARS-CoV-2 is challenging, the authors concluded that in a small subset of patients with SARS-CoV-2, a clinically distinctive phenotype of brainstem encephalitis with cerebellar involvement is found. In select cases, the SARS-CoV-2 antibody index can be a useful diagnostic tool to differentiate between aetiologies.

Shamier M.C., Crijnen Y.S., Bogers S., et al. (2022) Brain stem encephalitis is a rare complication of COVID-19. J Neuroimmunol; 374:578007.

CSF biomarkers in COVID-19-associated encephalopathy and encephalitis

Guasp et al. (2022) aimed to evaluate the diagnostic and prognostic role of CSF in patients with acute COVID-19 and associated neurologic manifestations (neuro-COVID). They prospectively included 60 hospitalised patients with neuro-COVID, 25 of them with encephalopathy and 14 with encephalitis, and followed them for 18 months. They found that, compared to healthy controls (HC), patients with neuro-COVID presented elevated levels of IL-18, IL-6, and IL-8 in both serum and CSF. MCP1 was elevated only in CSF, while IL-10, IL-1RA, IP-10, MIG and NfL were increased only in serum. Patients with COVID-associated encephalitis or encephalopathy had distinct serum and CSF cytokine profiles compared with HC, but no differences were found when both clinical groups were compared to each other. None of the patients had any antibodies against neural antigens. While the levels of neuroaxonal damage markers, 14-3-3 and NfL, and the proinflammatory cytokines IL-18, IL-1RA and IL-8 significantly associated with acute COVID-19 severity, only the levels of 14-3-3 and NfL in CSF significantly correlated with the degree of neurologic disability in the daily activities at 18 months follow-up. These findings point to a blood-brain barrier disruption in patients with neurological involvement. The authors conclude that the fact that levels of pro-inflammatory cytokines do not predict long-term functional outcome suggests that prognosis is more related to neuronal damage than to the acute neuroinflammatory process.

Guasp M., Muñoz-Sanchez G., Martinez-Hernandez E, et al. (2022) CSF biomarkers in COVID-19 associated encephalopathy and encephalitis predict long-term outcome. Front. Immunol. 13: 866153.

Endothelial cell biomarkers in critically ill COVID-19 patients with encephalitis

Altmayer et al. (2022) sought to determine the hallmark of endothelial activation in COVID-19-related encephalitis. In an observational study in an intensive care unit (ICU), they compared vascular biomarkers of critically ill COVID-19 patients with or without encephalitis. Among the 32 critically ill COVID-19 consecutive patients, 21 were categorised in the control group and 11 in the encephalitis group. Encephalitis patients had a longer ICU stay (median length of 52 vs. 20.5 day). Mortality rates in the encephalitis group and the control group were of 27% and 19%, respectively. Encephalitis was associated with significantly higher release of soluble endothelial activation markers (sE-selectin, tumour necrosis factor-α (TNF-α), interleukin 6, placental growth factor, and thrombomodulin), but these increases were correlated with TNF-α plasmatic levels. The hypoxia-inducible protein angiopoietin-like 4 (ANGPTL4) was at significantly higher levels in encephalitis patients compared to control patients ($p = 0.0099$) and, in contrary to the other increased factors, was not correlated with TNF-α levels ($r = 0.2832$, $p = 0.1163$). The authors concluded that COVID-19-related encephalitis is a cytokine-associated acute brain dysfunction.

Altmayer V, Ziveri J, Frère C, et al. (2022) Endothelial cell biomarkers in critically ill COVID-19 patients with encephalitis. J Neurochem; 161(6): 492-505.

Seizures and encephalitis

"Early diagnosis and timely treatment of seizures of autoimmune aetiology are paramount and significantly associated with a better overall clinical outcome." (Matricardi et al., 2022)

Seizures characteristics and outcomes in autoimmune encephalitis (AE)

Kaaden et al. (2022) aimed to assess seizure characteristics in anti-NMDAR, LGI1, and GAD encephalitis via a multicentre nationwide prospective cohort study of the German Network for Research in Autoimmune Encephalitis. In total 320 patients were included: 190 NMDAR+, 89 LGI1+, and 41 GAD+. Seizures were present in 113 (60%) NMDAR+, 69 (78%) LGI1+, and 26 (65%) GAD+ patients and as leading symptoms for diagnosis in 53 (28%) NMDAR+, 47 (53%) LGI+, and 20 (49%) GAD+ patients. Bilateral tonic-clonic seizures occurred with almost equal frequency in NMDAR+ (38/51, 75%) and GAD+ (14/20, 70%) patients, while being less common in LGI1+ patients (27/59, 46%). Focal seizures occurred less frequently in NMDAR+ (67/113; 59%) than in LGI1+ (54/69, 78%) or in GAD+ patients (23/26; 88%). An aura with déjà-vu phenomenon was nearly specific in GAD+ patients (16/20, 80%). Faciobrachial dystonic seizures (FBDS) were uniquely observed in LGI1+ patients (17/59, 29%). Status epilepticus was reported in one-third of NMDAR+ patients, but only rarely in the two other groups. The occurrence of seizures was associated with higher disease severity only in NMDAR+ patients. Seizures are a frequent and diagnostically relevant symptom of ab + AE. Whereas NMDAR+ patients had few localising semiological features, semiology in LGI1+ and GAD+ patients pointed toward a predominant temporal seizure onset.

Li et al. (2022) evaluated long-term seizure outcomes in patients with AE based on a large cohort study with long follow-up from patients with AE mediated by common types of neuronal surface antibodies (anti-NMDAR, anti-LGI1/Caspr2, anti-$GABA_BR$). Of 320 patients with AE, 75.9% had acute seizures, among whom >90% of patients had their last seizure within 12 months of disease onset. During the follow-up, 21 (9.3%) patients experienced seizure recurrence. Patients with anti-$GABA_BR$ encephalitis had a higher cumulative incidence of seizure recurrence than those with anti-NMDAR or anti-LGI1/Caspr2 encephalitis. Among patients with anti-NMDAR encephalitis, women had a significantly higher cumulative incidence of seizure recurrence than men. Interictal epileptiform discharges (IEDs) or seizures captured on continuous electroencephalogram (EEG) in the acute phase were identified as potential risk factors for seizure recurrence. Among 163 patients with ≥24 months of follow-up, five (3.1%) showed persistent seizures and required ongoing antiseizure medications despite aggressive immunotherapy.

Matricardi et al. (2022) described the clinical and paraclinical findings, treatment options and long-term outcomes in autoimmune encephalitis (AE), with a close look at epilepsy. Overall, 263 patients (138 females; median age 55 years, range 4–86) were followed up for a median time of 30 months (range 12–120). Autoimmune-associated epilepsy was the long-term sequela in 43.73% of patients and associated with cognitive and psychiatric disturbances in 81.73% of patients.

The recognition of seizures secondary to AE represents a rare chance for aetiology-driven seizure management. Early recognition and treatment at the pathogenic level may reduce the risk of long-term irreversible sequelae. However, the severity of seizures at onset is the major risk factor for the development of chronic epilepsy. This study provides class IV evidence for management recommendations.

Kaaden T., Madlener M., Angstwurm K. et al. (2022) Seizure Semiology in Antibody-Associated Autoimmune Encephalitis. Neurol Nuroimmunol Neuroinflamm; 9: 6 e200034.

Lui X., Guo K., Lin J., et al. (2022) Long-term seizure outcomes in patients with autoimmune encephalitis: A prospective observational registry study update. Epilepsia; 63: 1812-1821.

Matricardi S., Casciato S., Bozzetti S., et al. (2022) Epileptic phenotypes in autoimmune encephalitis: from acute symptomatic seizures to autoimmune-associated epilepsy. J Neruol Neurosurg Psychiatry; 0: 1-8.

Acute seizure risk in patients with encephalitis

Wood et al. (2022) determined the factors associated with seizures in encephalitis and developed a clinical prediction model by analysing 203 patients from 24 English hospitals (2005–2008) (Cohort 1 Development cohort) and an additional 233 patients from 31 UK hospitals (2013–2016) (Cohort 2 Validation cohort).

In Cohort 1, 121 (60%) patients had a seizure including 103 (51%) patients with inpatient seizures. Admission Glasgow Coma Scale (GCS) ≤8/15 was predictive of subsequent inpatient seizures, including in those without a history of prior seizures at presentation.

A clinical model of overall seizure risk identified admission GCS along with aetiology (autoantibody-associated OR 11.99 (95% CI 2.09 to 68.86) and herpes simplex virus 3.58 (95% CI 1.06 to 12.12). The same model was externally validated in Cohort 2 (AUROC=0.744 (95% CI 0.677 to 0.811), p<0.001). A clinical scoring system for stratifying inpatient seizure risk by decile demonstrated good discrimination using variables available on admission; age, GCS and fever and once probable aetiology established. Age, GCS, fever and aetiology can effectively stratify acute seizure risk in patients with encephalitis. These findings can support the development of targeted interventions and aid clinical trial design for antiseizure medication prophylaxis.

Wood G. K., Babar R., Ellul M. A., et al. (2022) Acute seizure risk in patients with encephalitis: development and validation of clinical prediction models from two independent prospective multicentre cohorts. BMJ Neurol Open; 4: e000323.

Diagnosis and treatment of encephalitis

"Our study emphasizes the importance of respiratory viruses in the aetiology of unexplained child encephalitis and suggests that non-central-nervous-system sampling in encephalitis clinical guidelines and protocols could improve the diagnostic yield." (Li et al., 2022)

Challenges for nurses in caring for patients with acute encephalitis

Gill et al. (2022) investigated nurses' challenges in caring for patients with acute encephalitis. Their study, published in the British Journal of Nursing, included in-depth, semi-structured interviews with eight registered nurses from a teaching hospital. The key findings of the study were that the nurses lacked knowledge of encephalitis and patients' needs to enable them to care for these patients confidently; lacked time to give patients the level of care that they required; and experienced a lack of access to specialist neuro-rehabilitation for patients. The authors summarised the main four themes as being: managing confusion, supporting relatives, frustration and rehabilitation. The authors argue that this study provides evidence for the need of a new theory on nursing care of patients with encephalitis. This theory should be considered within the bigger picture of neurological conditions.

Gill C., Griffiths M., Easton A., Solomon T. (2022) Challenges for nurses in caring for patients with acute encephalitis: lack of knowledge, time and rehabilitation. British Journal of Nursing; 31(1).

Infectious or autoimmune aetiology in encephalitis

Hoang et al. (2022) aimed to identify routine laboratory markers that are associated with infectious or autoimmune encephalitis (AE). Overall 333 individuals with confirmed acute meningoencephalitis were included. An infectious-nonbacterial (NB) pathogen was identified in 151/333 (45.40%), bacterial pathogen in 95/333 (28.50%) and autoantibody in 87/333 (26.10%). NB encephalitis was differentiated from AE by the presence of fever (NB 62.25%, AE 24.10%), higher CSF white blood cell (WBC)(median 78 cells/lL, 8.00 cells/lL), higher CSF protein (76.50 mg/dL, 40.90 mg/d), lower CSF glucose (58.00 mg/dL, 69.00 mg/dL), lower serum WBC (7.80 cells/lL, 9.72 cells/lL), higher erythrocyte sedimentation rate (19.50 mm/HR, 13.00 mm/HR), higher C-reactive protein (6.40 mg/L, 1.25 mg/L), and lack of antinuclear antibody titers (>1:40; NB 11.54%, AE 32.73%). CSF-to serum WBC ratio was significantly higher in NB compared to AE (NB 11.3, AE 0.99). From these findings, the association of presenting with fever, CSF WBC ≥50 cells/lL, and CSF protein ≥75 mg/dL was explored in ruling-out AE. When all three criteria are present, an AE was found to be highly unlikely (sensitivity 92%, specificity 75%, negative predictive value 95%, and positive predictive value 64%).

Hoang H.E., Robinson-Papp J., Mu L., et al. (2022) Determining an infectious or autoimmune aetiology in encephalitis. Ann Clin Transl Neurol; 9(8): 1125-1135.

Unexplained cases of childhood encephalitis in Australia

Li et al. (2022) investigated the clinical characteristics and potential aetiological agents of unexplained encephalitis through metagenomic sequencing of residual clinical samples from multiple tissue types. Forty-three specimens were collected from 18 encephalitis cases with no cause identified by the Australian Childhood Encephalitis study. Samples were subjected to total RNA sequencing ('metatranscriptomics') to determine the presence and abundance of potential pathogens, and to describe the possible aetiologies of unexplained encephalitis. Using this protocol, the authors identified five RNA and two DNA viruses associated with human infection from both non-sterile and sterile sites, which were confirmed by PCR. These comprised two human rhinoviruses, two human seasonal coronaviruses, two polyomaviruses and one picobirnavirus.

Human rhinovirus and seasonal coronaviruses may be responsible for five of the encephalitis cases. Immune-mediated encephalitis was considered likely in six cases and metatranscriptomics did not identify a possible pathogen in these cases. The aetiology remained unknown in nine cases. The study emphasises the importance of respiratory viruses in the aetiology of unexplained child encephalitis and suggests that non-central-nervous-system sampling in encephalitis clinical guidelines and protocols could improve diagnostic yield.

Li C.X., Burrell R., Dale R.C., et al. (2022) Diagnosis and analysis of unexplained cases of childhood encephalitis in Australia using metatranscriptomic sequencing. J Gen Virol; 103(4).

Intravenous immunoglobulin (IVIG) in autoimmune encephalitis (AE) and Japanese encephalitis

Lee et al. (2022) performed a prospective clinical trial of IVIG for functional recovery in autoimmune encephalitis. Overall, 23 patients received IVIG (ITT) and 18 patients completed the study according to the protocol (PP). mRS improved significantly at days eight and 29 compared to baseline in both the ITT and PP populations. Other secondary outcomes also improved significantly at day eight, 15, and 29 versus baseline. In the PP population, 6/18 patients achieved favourable outcomes with IVIG alone (mRS = 0~2 at day 8), and 12/18 patients received rescue immunotherapy. Five adverse events were reported in relation to IVIG, all of which were mild. The conclusion of the study is that IVIG improved neurological functional outcomes, and the improvement was evident by day eight. Adverse effects were tolerable.

Chen et al. (2022) investigated the efficacy and safety of intravenous immunoglobulin (IVIG) in the treatment of severe

Japanese encephalitis (JE). Their prospective study included 124 children with severe JE. Half of the children were in the IVIG group and half in the control group. The children were evaluated at three days; one, two, and three weeks; and six months after IVIG. There were four deaths during hospitalisation (one death in the IVIG group and three in the control group). Of the children who were followed up (98), 85 cases had a good prognosis, 12 cases had a poor prognosis, and one case died. At six months, in the IVIG group, 53 cases were followed up, eight cases were lost to follow-up, three cases had serious sequelae (including consciousness disturbance, complete paralysis), and 50 cases had a good prognosis. At six months, in the control group, 45 cases were followed up, 14 cases were lost to follow-up, one patient died, nine cases had serious sequelae, and 35 cases had a good prognosis. The authors concluded that IVIG showed good efficacy, safety, and tolerance for treatment of the severe form of JE. The age and imaging abnormalities of patients affect the efficacy of IVIG treatment.

Chen D., Peng X., Zhan Y., et al. (2022) Efficacy and safety of intravenous high-dose immunoglobulin in treatment of the severe form of Japanese encephalitis Neurological Sciences; 43:3911–3918.

Lee S.T., Lee H.S., Lee W.J., et al. (2022) The safety and efficacy of intravenous immunoglobulin in autoimmune encephalitis. Ann Clin Transl Neurol; 9(5):610-621.

Immunotherapy in autoimmune encephalitis

Dinoto et al. (2022) summarised the current evidence and related methodological issues in the use of treatments for refractory autoimmune encephalitis. The study's key points were:

- A minority of patients with autoimmune encephalitis may remain refractory even to second-line therapies and they represent a major clinical challenge. In these cases, treatment strategies are controversial, and no guidelines exist.
- Treatments proposed for refractory autoimmune encephalitis include cytokine-based drugs, plasma cell-depleting agents, and treatments targeting intrathecal immune cells or their trafficking through the blood–brain barrier.
- The evidence of efficacy of these treatments is mostly based on case reports or small case series; controlled studies and systematic reviews are rare.

Currently, the guidelines for treatment of autoimmune encephalitis (AE) recommend first line therapies – steroids, intravenous immunoglobulin and/or plasma exchange which should be prescribed as soon as a diagnosis of possible autoimmune encephalitis is established. For patients who do not respond to first-line therapy, second line (rituximab and cyclophosphamide) and additional therapies (tocilizumab, bortezomib) have been reported. Trewin et al. (2022) evaluated recent studies on larger

cohorts, registries and meta-analyses to highlight existing evidence for contemporary therapeutic approaches in AE. They highlight the role of early first-line immunotherapies in improving outcomes and of second-line immunotherapies in reducing relapses rate. However the best time to immunotherapy escalation is still unclear. They suggest that routine reporting of outcome measures which incorporate cognitive impairment, fatigue, pain, and mental health will permit more accurate quantification of residual disability and comprehensive comparisons between international multicentre cohorts and enable future meta-analyses with the aim of developing evidence-based therapeutic guidelines.

Considering some clinicians' preference for monoclonal antibodies directed at B cells, against second line therapies (due to their side effects), Smets and Titulaer (2022) reviewed the use of monoclonal antibodies (mAbs) targeting B cells, IL-6, the neonatal Fc receptor (FCRn) and the complement cascade. Although they have favourable side effects, anti-CD20 mAb do not deplete long-lived plasma cells which might underlie treatment-refractory cases and the occurrence of (early) relapses. The authors also described the emerging mAb that aim to directly (inebulizumab, daratumumab) or indirectly (tocilizumab, sartralizumab) target long-lasting plasmablasts or plasma cells with or without additional B cell depletion and the mAb targeting the FcRn (efgartigimod, rozanolixizumab). The authors concluded that future trials are needed to understand whether these third line treatments are effective, when they need to be initiated and whether they have an acceptable safety profile in combination with previous rituximab administration.

Dinoto A, Ferrari S, Mariotto S.(2022) Treatment Options in Refractory Autoimmune Encephalitis. CNS Drugs; 36(9):919-931

Trewin B.P., Freeman I., Ramanathan S., Irani S.R. (2022) Immunotherapy in autoimmune encephalitis. Curr Opin Neurol; 35(3): 399-414.

Smets I., Titulaer M.J. (2022) Antibody therapies in autoimmune encephalitis. Neurotherapeutics; 19(3):823-831.

Outcomes of encephalitis

"The treating neuropsychologist will often need to do family and staff education regarding the disorder, possible unusual pattern of recovery and discuss the risk of relapse. Additionally, staff may need help with behavior management and the potential need for a behavior management plan." (Perna and Arenivas, 2022)

Defining outcomes in encephalitis

Tooren et al. (2022) performed a systematic literature review to explore outcome measures used for patients with encephalitis. The authors found that 37 outcome measures were used for 3,133 patients of which, only one was developed for encephalitis (Liverpool Outcome Score). The most used outcome measures were the Glasgow Outcome Score used in 46%, Barthel Index used in 37%, Euro-QoL-5D used in 35% and modified Rankin Scale used in 33%. However, most of the outcome's measures used assessed a single category of sequelae (physical) using 5–8-point scales and were not validated for use in encephalitis. The authors highlight that encephalitis can affect multiple aspects of one's life and some of these effects, such as those on personal and professional relationships, are not included in any of the outcome's measures reported. The authors conclude that research is needed to develop a composite outcome measure for use in clinical practice and a core outcome set for use in clinical trials.

Tooren H.V.D., Easton A., Hooper C., et al. (2022) How should we define a 'good' outcome from encephalitis? A systematic review of the range of outcome measures used in the long-term follow-up of patients with encephalitis. Clin Med (Lond); 22(2): 145-148.

Outcomes in autoimmune encephalitis (AE)

In a study conducted at the Cleveland Medical Center in the USA, Abboud et al. (2022) aimed to assess residual symptoms in patients with AE in an outpatient setting and compare long-term outcomes. The study found that despite the initial severity of AE, it generally carries a good prognosis, which aligns with previous research findings. The study's novel contribution lies in the detailed evaluation of residual symptoms and their respective improvement rates. Additionally, the authors validated the CASE (clinical assessment scale for autoimmune encephalitis) score, confirming its usefulness in quantifying AE symptoms, monitoring patient progress, and evaluating treatment response. The authors suggested that future studies should focus on identifying predictors of AE relapses and comparing objective improvements between neuropsychological rehabilitation and standard care. Despite its limitations, the data presented in this study serve as an essential reference for estimating long-term outcomes in future AE clinical trials, covering a wide range of causative antibodies and clinical syndromes.

Griffith et al. (2022) conducted a retrospective observational study which included 59 patients with AE across six secondary and tertiary referral centres in Victoria, Australia between January 2008 and July 2019 to characterise psychometric outcomes in this population. The most common difficulties reported in this population were deficits in psychometric markers of executive dysfunction followed by deficits on tasks sensitive to memory. Psychometric impairments across at least two cognitive domains were reported in half of the patients (54.2%) with 29 patterns observed. None of the demographic and clinical features or auxiliary examinations data were predictive of psychometric outcomes. The authors concluded that cognitive outcomes in autoimmune encephalitis are complex. Further detailed and standardised cognitive testing, inclusion of behavioural and psychopathology outcomes combined with magnetic resonance imaging (MRI) volumetrics and serum/cerebrospinal fluid (CSF) biomarkers are required to enable rigorous assessment of this disease outcomes.

Abboud H., Briggs F., Buerki R., et al. (2022) Residual symptoms and long-term outcomes after all-cause autoimmune encephalitis in adults. J Neurol Sci; 434: 120124.

Griffith S., Wesselingh R., Broadley J., et al. (2022) Psychometric deficits in autoimmune encephalitis: A retrospective study from the Australian Autoimmune Encephalitis Consortium. Eur J Neurol; 29: 2355–2366.

Neurological and cognitive outcomes after antibody-negative autoimmune encephalitis (AE) in children

In a study by Gadian et al. (2022) using contemporary consensus diagnostic criteria modified for children, the varying disease course and outcomes after Ab-negative AE were compared with outcomes in children with NMDAR encephalitis. The study made two key observations. Firstly, children with Ab-negative AE had poor cognitive outcomes compared to those with NMDAR encephalitis (NMDARE). The majority of NMDARE children had normal cognitive function, while Ab-negative AE children had lower IQ scores and persistent behavioural or cognitive problems. Secondly, the frequency of postencephalitic epilepsy was significantly higher in Ab-negative AE children compared to NMDARE children. The study emphasised the need for standardised assessment, larger cohorts, and biomarker identification to improve diagnosis, prognosis, and treatment decisions for AE.

Gadian J., Eyre M., Konstantoulaki E., et al. (2022) Neurological and cognitive outcomes after antibody-negative autoimmune encephalitis in children. Dev Med Child Neurol; 64(5): 649-653.

Neuropsychological outcomes in children and adolescents with anti-NMDAR encephalitis

A 2022 study by Wilkinson-Smith et al. (2022) aimed to assess areas of impairment and characterise neuropsychological outcomes in paediatric patients through a retrospective chart review. Twenty-three patients (average 18.5 months post-diagnosis) underwent comprehensive neuropsychological assessments measuring intellectual functioning, memory, reading, verbal fluency, visuomotor skills, attention, and working memory. Caregiver ratings and resource utilisation information were collected, and neuropsychological impairment index (NPI) scores were calculated, revealing variable outcomes across individuals. Memory and fine motor dexterity were particularly affected. Nearly 90% of caregivers reported concerns in emotional-behavioural, adaptive, or executive functioning. Over two-thirds of the sample showed impairment based on NPI scores in performance measures. The majority received outpatient interventions, primarily school-based services. These findings provide quantitative evidence of ongoing cognitive concerns in paediatric patients, emphasising the need for long-term monitoring and support, despite significant recoveries achieved through diagnosis and treatment. Previous studies using neuropsychological assessments have consistently shown persistent deficits in areas such as memory, fine motor skills, executive functioning, language, and adaptive functioning. The authors suggest a framework is needed to guide recovery expectations and ensure ongoing monitoring by neuropsychologists in the long-term management of paediatric patients with anti-NMDAR encephalitis.

A similar study by Hageboutros et al. (2023) sought to examine the neuropsychological functioning and medical features of paediatric patients with anti-NMDAR encephalitis. Retrospective data were collected from medical records and neuropsychological reports of 15 children and adolescents, aged 7-21 years, who had confirmed anti-NMDARE through cerebral spinal fluid antibodies. The median time between treatment initiation and neuropsychological testing was 228 days. The results indicated that while the patients generally had average IQ scores, they showed lower scores in verbal and visual memory, executive functioning (set shifting and phonemic verbal fluency), visuo-constructional ability, and reading comprehension. Further prospective studies are needed to validate these findings and explore disease and treatment factors that may affect the risk of neuropsychological impairments. Longitudinal analyses are also necessary to understand the academic, vocational, and social outcomes in these patients.

Flet-Berliac et al. (2022) studied the long-term clinical and cognitive outcomes of paediatric patients with anti-NMDAR encephalitis. Significant cognitive disorders were present at least two years after diagnosis in 45% of patients, involving impairment of attention, language, memory, executive functions, praxis, or psychomotor ability. Academic difficulties persisted after at least two years of follow-up, and most children still needed rehabilitation and/or psychological/psychiatric care requiring appropriate management by a psychologist/psychiatrist. These results reinforce the importance of multidisciplinary management for long-term rehabilitation and may suggest the need for earlier aggressive and long-term treatment.

Wilkinson-Smith A., Blackwell L.S., Howarth R.A. (2022) Neuropsychological outcomes in children and adolescents following anti-NMDA receptor encephalitis. Child Neuropsychol; 28(2): 212-223.

Hageboutros K., Hattiangadi Thomas N., Hutchinson M, et al. (2023) Neuropsychological functioning in children and adolescents with anti-NMDA receptor encephalitis (anti-NMDARE). J Neurol; 270(1): 402-412.

Flet-Berliac L., Tchitchek N., Lépine A., et al. (2023) Long-term outcome of paediatric anti-N-methyl-D-aspartate receptor encephalitis. Dev Med Child Neurol; 65(5): 691-700.

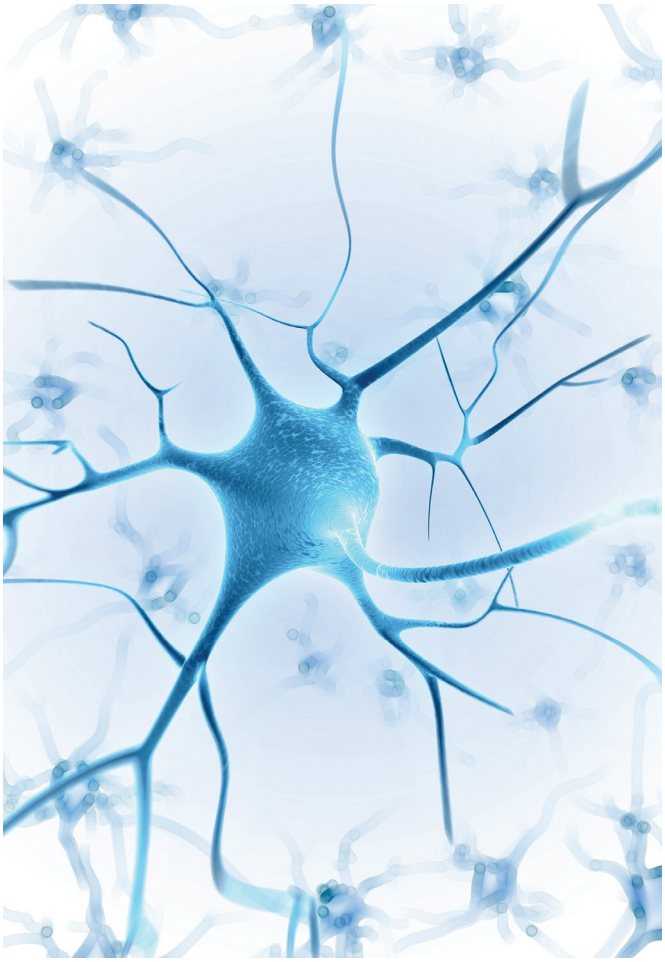
Post-acute neurological rehabilitation in limbic encephalitis

Perna and Arenivas et al. (2022) presented a review of the complex issues people recovering from limbic encephalitis (LE) experience during post-acute rehabilitation. Limbic encephalitis is a complex condition with a severe course of illness in most of the cases. Patients may require various treatments from immunotherapy to a mix of anticonvulsants and psychotropics. They may experience relapses or breakthrough seizures when treatment is reduced or discontinued or during their rehabilitations. They may require readmission to acute settings and follow-up immune-based treatments.

The authors also described five adults diagnosed with LE who experienced complications while receiving post-acute rehabilitative care. Four of them required re-admission to acute care. Three of these individuals required frequent neuropsychology involvement and re-initiation of treatment. Only one person exhibited significant improvement in function and made a full functional recovery including a return to work. Each case required more family education than traumatic brain injury cases. The authors reported that the individuals were often too amnestic to be treated with a typical cognitive behaviour therapy approach.

The authors concluded that LE is complex and appears to require a high level of involvement from the neuropsychologist. Both the treatment team and family need to have the appropriate expectations and the team should be observant of any signs of exacerbated symptoms. Future research should include longitudinal and prospective research on the treatment of LE in the post-acute setting. This will help with the management of the expectations of the treatment team as well as the neuropsychologists.

Perna R., Arenivas A. (2022) Limbic encephalitis and post-acute neuropsychology rehabilitation: A review and case examples. Appl Neuropsychol Adult; 29(4):874-880.



Improving outcomes in viral encephalitis

Sonneville et al. (2022) summarised the practical aspects of managing patients with suspected encephalitis of viral origins. Despite several advances such as faster and more accurate etiological diagnosis (polymerase chain reaction, metagenomics), intravenous acyclovir therapy and supportive care, a vast number of patients still have a dramatic course of the illness: prolonged intensive care stay and long-term disability for the survivors. The authors noted that randomised clinical trials focusing on symptomatic measures or adjunctive immunomodulatory therapies to improve neurologic outcomes have not been conducted in the intensive care unit setting. Large prospective multicenter studies combining clinical, electrophysiological, and neuroimaging data are needed to improve current knowledge on care pathways, long term outcomes, and prognostication.

Sonneville R., Jaquet P., Vellieux G., et al. (2022) Intensive care management of patients with viral encephalitis. Rev Neurol (Paris); 178(1-2): 48-56.

About the Encephalitis Society

How we can help you and your patients

We are 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 worldwide
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  support@encephalitis.info
  (language line available on request)
- Producing high quality, evidence-based and peer-reviewed information about encephalitis.
  www.encephalitis.info/patient-resources
  (Google translate available on our website)
- Organising face-to-face, virtual and hybrid events for those affected by encephalitis and their families worldwide
  www.encephalitis.info/events-and-activities
- Raising awareness about encephalitis, its consequences and the need for improved services worldwide.
  World Encephalitis Day 22nd February
  www.worldencephalitisday.org
- Funding research (seed funding, PhDs), collaborating and working in partnership with other researchers
  www.encephalitis.info/grants
- Recruiting research participants and contributing to patient participation involvement
  www.encephalitis.info/research-currently-recruiting
- Providing networking and educational opportunities: the international go-to conference in encephalitis and webinar masterclasses
  www.encephalitis.info/conference

Become a FREE member of the Encephalitis Society

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Sponsorship packages for events organised by the Encephalitis Society come in different forms and can be tailored to suit your business objectives. Sponsorship can help your company to reach a defined target audience, improve brand perception and raise your profile among our membership.

We can also ensure exposure to an unprecedented number of multi-disciplinary delegates who work in the fields of infectious and autoimmune encephalitis, neurology, diagnostics and associated fields from across the globe.

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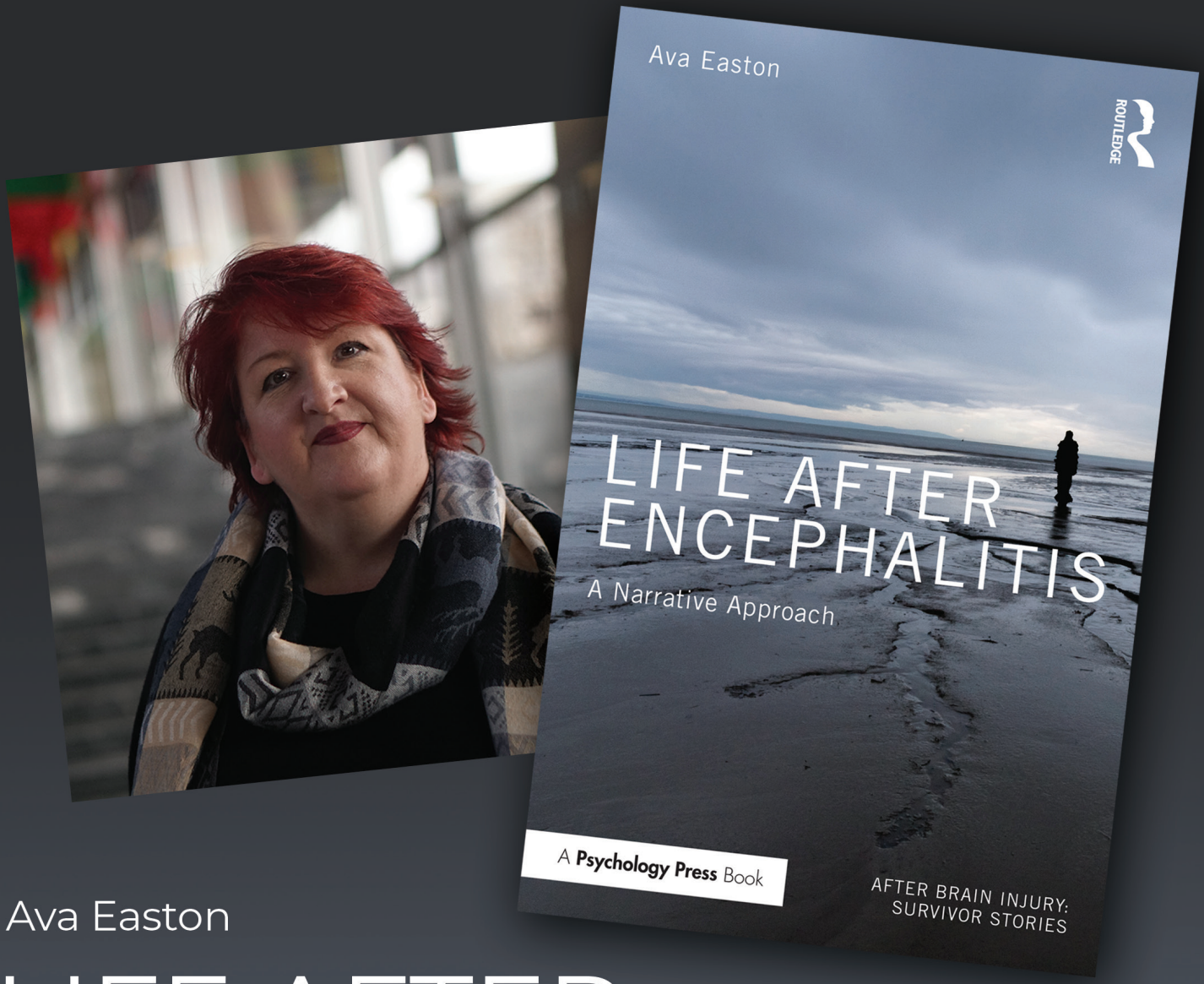

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