RESEARCH SUMMARY

ADVANCES IN ENCEPHALITIS 2023

Encephalitis International

The brain inflammation non-profit

EPIDEMIOLOGY
PATHOGENESIS
DIAGNOSIS
TREATMENT
OUTCOMES
RECOVERY

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Welcome to Encephalitis International's Research Summary 2023

The Research Summary-Advances in Encephalitis 2023 presents a collection of research papers published during the same year. The number of papers on encephalitis appears to have increased over the last few decades, reflecting the growing recognition of encephalitis, its importance and complexity in the clinical and research fields. There is a continued increase in papers on autoimmune encephalitis as well as outcomes of encephalitis more generally. However, there is still a lack of papers that have focused on quality of life or rehabilitation after encephalitis.

The last year has seen outbreaks and emerging threats of encephalitis across different regions and viral strains. In 2022, we had reported the emergence of the long-silent genotype 4 of Japanese encephalitis virus in Australia, resulting in a local outbreak of viral encephalitis. This appears to be mirrored in other parts of the world, and in 2023 Japanese encephalitis has been described as an emerging threat in eastern central India, particularly in eastern parts of Madhya Pradesh. In a European study of tick-borne encephalitis from 2012-2020, 19 countries reported over 29,000 cases, with the highest notification rates in Lithuania, Latvia, and Estonia. In 2020, 11.5% more tick-borne encephalitis cases were reported than predicted based on data from 2016 to 2019. These developments underscore the dynamic nature of encephalitis threats and highlight the need for urgent ongoing surveillance, research, and public health preparedness on a global scale.

Neurological complications associated with COVID-19 are also emerging. For example, in a study of 161,239 patients hospitalised with COVID-19 across 1500+ sites worldwide, 20.9% of adults and 6.8% of children had altered consciousness at admission. Indeed, in a systematic review of 113 articles on COVID-19 neurological manifestations, headache and encephalitis/encephalopathy were common central nervous system symptoms. Generally, there has been an increase of reports and papers dealing with the neurological effects and symptoms associated with COVID-19-associated encephalitis.

Encephalitis International itself has had an eventful year. 2023 ended with one of our biggest changes since our inception: our name-change from 'The Encephalitis Society' to 'Encephalitis International'. After extensive collaboration with our key stakeholders, we were thrilled to unveil this significant chapter in our journey; a strategic evolution that mirrors our renewed commitment to saving lives on a global scale. The emergence of novel pathogens and the spread of existing pathogens to new regions, coupled with the increased recognition of autoimmune encephalitis worldwide, has compelled us to recalibrate our focus and expand our horizons. 'Encephalitis International' encapsulates our broader, more inclusive mission.

Plans for our annual conference – Encephalitis 2024 – are underway. Held at the Royal College of Physicians in London and virtually on the 2nd and 3rd of December, this global conference attracting around 500 delegates from over 50 countries, is dedicated exclusively to encephalitis and covers epidemiology, pathogenesis, diagnosis, treatment, and rehabilitation in both children and adults; and covers both infectious and autoimmune aetiologies. There will be cutting-edge insights from global leaders in the field of brain inflammation covering hot topics, critical research questions, and approaches to the key clinical challenges informed by the latest research. We continue to provide a number of free places for medical and healthcare professionals from low-to-middle income countries (LMIC) to attend this year's conference. Overall, the conference is an excellent forum for physicians, scientists, researchers, and healthcare professionals to exchange ideas, knowledge, and clinical experience relating to encephalitis. For more information, and to book your place, please visit: https://www.encephalitis.info/encephalitis-conference/.

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 Encephalitis International. As a member you will have the opportunity to access grants, bursaries, and seed funding for your research. Sign up for a free membership here today www.encephalitis.info/professional-membership.

Finally, thank you for your interest in encephalitis and Encephalitis International. I extend my heartfelt gratitude to all clinicians, scientists, and researchers working so hard to improve our understanding of this too-often devasting condition.

Dr Ava Easton
Chief Executive, Encephalitis International

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We would like to thank Anita Rein, King's College London, for her contributions to this work.

Epidemiology of encephalitis

The burden of encephalitis

Abstract: Encephalitis affects people across the lifespan, has high rates of mortality and morbidity, and results in significant neurological sequelae with long-term consequences to quality of life and wider society. The true incidence is currently unknown due to inaccurate reporting systems. The disease burden of encephalitis is unequally distributed across the globe being highest in low- and middle-income countries where resources are limited. Here countries often lack diagnostic testing, with poor access to essential treatments and neurological services, and limited surveillance and vaccination programs. Many types of encephalitis are vaccine preventable, whereas others are treatable with early diagnosis and appropriate management. In this viewpoint, we provide a narrative review of key aspects of diagnosis, surveillance, treatment, and prevention of encephalitis and highlight priorities for public health, clinical management, and research, to reduce the disease burden.

Granerod J, et al. Global Landscape of Encephalitis: Key Priorities to Reduce Future Disease Burden. Clin Infect Dis. 2023;77(11):1552-1560. doi:10.1093/cid/ciad417.

This team of researchers from Canada investigated causes, comorbidities, costs, and outcomes of encephalitis in a population-based cohort. ICD-10 codes corresponding to encephalitis were used to identify health services records for all adults from 2004 to 2019. Data were cross-validated for identified diagnoses based on laboratory confirmation using univariate and multivariate statistical analyses. Cumulative incidence rates showed increased cerebral spinal fluid (CSF) Varicella-zoster virus (VZV) detection in patients with encephalitis, which predominated in people over 65 years with a higher mean Charlson index. Herpes simplex virus-2 (HSV-2) and VZV were detected more frequently in CSF from encephalitis cases with greater material-social deprivation. The mean costs of care were significantly greater for the HSV-1 group. The researchers conclude that encephalitis remains an important cause of neurological disability and death with a viral aetiology in 54.2% of affected adults accompanied by substantial costs of care and mortality: 'Virus-associated encephalitis is evolving with increased VZV detection, especially in older persons.'

Bakal JA, et al. Evolving etiologies, comorbidities, survival, and costs of care in adult encephalitis. J Neurovirol. 2023;29(5):605-613. doi:10.1007/s13365-023-01165-9.

The spread of Japanese encephalitis

Background & objectives: Emerging zoonotic and vector-borne diseases are posing new challenges to public health authorities. Morbidities and mortalities due to acute encephalitis syndrome (AES) is a serious health problem in paediatric patients. We conducted serological investigations on AES cases from six districts of north eastern Madhya Pradesh (MP), India for Japanese encephalitis (JE).

Methods: The paired serum and CSF samples were collected from paediatric patients having signs and symptoms of encephalitis and admitted at a tertiary care hospital during the study period from August 2020 to October 2021. Demographic and clinical information was collected in predesigned formats. Serum and CSF were subjected to JE IgM specific ELISA.

Results: Samples from 110 patients were collected during the study period of which 28 (25.4%) were reactive for JE IgM antibodies. JE IgM positivity was marginally higher in male children (26.6%) as compared to female children (22.8%). Out of 28 positive cases, 11 (39.2%) deaths were attributed to JE. Four districts of north eastern Madhya Pradesh showed JE activity. Maximum cases were observed in post-monsoon season.

Interpretation & conclusion: Our results show that JEV is an emerging threat in eastern central India and health authorities need to be vigilant. A systematic molecular and serological survey among humans and animals along with xenomonitoring will help in understanding intricacies of JE epidemiology in the region.

Kumar A, et al. "Emergence of Japanese encephalitis in eastern parts of Madhya Pradesh, India." Journal of vector borne diseases vol. 60,2 (2023): 215-219. doi:10.4103/0972-9062.364761.

Abstract: The Japanese encephalitis virus (JEV) is classified into five distinct genotypes, with genotypes 1 and 3 historically showing higher activity. These genotypes are the primary agents of viral encephalitis in the Asian continent. Genotypes 4 and 5 have remained silent in low-latitude tropical regions since their discovery. From 2009, the hidden genotype 5 suddenly emerged simultaneously in mosquitoes from the Tibetan region of China and those from South Korea in East Asia. The detection of genotype 5 of JEV in these mosquitoes was associated with cases of viral encephalitis in the local population. Similarly, in 2022, the long-silent genotype 4 of JEV emerged in Australia, resulting in a local outbreak of viral encephalitis that primarily affected adults and caused fatalities. The emergence and outbreaks of genotypes 4 and 5 of JEV present new challenges for the prevention and control of Japanese encephalitis (JE). This study not only analyzes

the recent emergence of these new genotypes but also discusses their implications in the development of JE vaccines and laboratory tests for newly emerging JEV infections.

Zhang W, et al. "The reemerging and outbreak of genotypes 4 and 5 of Japanese encephalitis virus." Frontiers in cellular and infection microbiology vol. 13 1292693. 16 Nov. 2023, doi:10.3389/fcimb.2023.1292693.

Background and objective: No autochthonous human cases of Japanese encephalitis (JE) have been reported to date in the European Union (EU). In this study, we assess the likelihood of Japanese encephalitis virus (JEV) introduction and transmission within the EU and propose outbreak response measures.

Risk assessment: Given the global geographical distribution of JEV, the probability of virus introduction into the EU is currently very low, with viremic bird migration being the most plausible pathway of introduction. However, this likelihood would significantly increase if the virus were to become established in the Middle East, Caucasus, Central Asia or Africa. Considering the environmental conditions that are expected to be conducive for virus circulation, there is a high likelihood of virus transmission within the EU after its introduction in environmentally suitable areas. The spread of the virus within the EU would likely occur through the movement of wild birds, pigs and mosquitoes.

Mitigation: To mitigate or potentially contain the emergence of JE in the EU, early detection of both human and animal cases will be crucial.

Gossner CM, et al. "Potential for emergence of Japanese encephalitis in the European Union." Zoonoses and public health vol. 71,3 (2024): 274-280. doi:10.1111/zph.13103.

Abstract: Japanese encephalitis virus is a mosquito-borne member of the Flaviviridae family. JEV is the leading cause of viral encephalitis in Asia and is characterized by encephalitis, high lethality, and neurological sequelae in survivors. The virus also causes severe disease in swine, which are an amplifying host in the transmission cycle, and in horses. US agricultural authorities have recently recognized the threat to the swine industry and initiated preparedness activities. Other mosquito-borne viruses exotic to the Western Hemisphere have been introduced and established in recent years, including West Nile, Zika, and chikungunya viruses, and JEV has recently invaded continental Australia for the first time. These events amply illustrate the potential threat of JEV to US health security. Susceptible indigenous mosquito vectors, birds, feral and domestic pigs, and possibly bats, constitute the receptive ecological ingredients for the spread of JEV in the US. Fortunately, unlike the other virus invaders mentioned above, an inactivated whole virus JE vaccine (IXIARO®) has been approved by the US Food and Drug Administration for human use in advance of a public health emergency, but there is no veterinary vaccine. This paper describes the risks and potential consequences of the introduction of JEV into the US, the need to integrate planning for such an event in public health policy, and the requirement for additional countermeasures, including antiviral drugs and an improved single dose vaccine that elicits durable immunity in both humans and livestock.

Monath TP. "Japanese Encephalitis: Risk of Emergence in the United States and the Resulting Impact." Viruses vol. 16,1 54. 28 Dec. 2023, doi:10.3390/v16010054.

Tick-borne encephalitis

Background: Tick-borne encephalitis (TBE) is a vaccine-preventable disease involving the central nervous system. TBE became a notifiable disease on the EU/EEA level in 2012.

Aim: We aimed to provide an updated epidemiological assessment of TBE in the EU/EEA, focusing on spatiotemporal changes.

Methods: We performed a descriptive analysis of case characteristics, time and location using data of human TBE cases reported by EU/EEA countries to the European Centre for Disease Prevention and Control with disease onset in 2012-2020. We analysed data at EU/EEA, national, and subnational levels and calculated notification rates using Eurostat population data. Regression models were used for temporal analysis.

Results: From 2012 to 2020, 19 countries reported 29,974 TBE cases, of which 24,629 (98.6%) were autochthonous. Czechia, Germany, and Lithuania reported 52.9% of all cases. The highest notification rates were recorded in Lithuania, Latvia, and Estonia (16.2, 9.5 and 7.5 cases/100,000 population, respectively). Fifty regions from 10 countries, had a notification rate ≥ 5/100,000. There was an increasing trend in number of cases during the study period with an estimated 0.053 additional TBE cases every week. In 2020, 11.5% more TBE cases were reported than predicted based on data from 2016 to 2019. A geographical spread of cases was observed, particularly in regions situated north-west of known endemic regions.

Conclusion: A close monitoring of ongoing changes to the TBE epidemiological situation in Europe can support the timely adaption of vaccination recommendations. Further analyses to identify populations and geographical areas where vaccination programmes can be of benefit are needed.

Van Heuverswyn J, et al. Spatiotemporal spread of tick-borne encephalitis in the EU/EEA, 2012 to 2020. Euro Surveill. 2023;28(11):2200543. doi:10.2807/1560-7917.ES.2023.28.11.2200543

Encephalitis in elderly patients

Purpose: Data on encephalitis in elderly patients are scarce. We aimed to describe the characteristics, aetiologies, management, and outcome of encephalitis in patients older than 65 years.

Methods: We performed an ancillary study of ENCEIF, a prospective cohort that enrolled all cases of encephalitis managed in 46 clinical sites in France during years 2016-2019. Cases were categorized in three age groups: (1) 18-64; (2) 65-79; (3) ≥ 80 years.

Results: Of the 494 adults with encephalitis enrolled, 258 (52%) were ≥ 65 years, including 74 (15%) ≥ 80 years. Patients ≥ 65 years were more likely to present with coma, impaired consciousness, confusion, aphasia, and rash, but less likely to present with fever, and headache ($P < 0.05$ for each). Median cerebrospinal fluid (CSF) white cells count was 61/mm3[13-220] in 65-79 years, 62 [17-180] in ≥ 80 years, vs. 114 [34-302] in < 65 years ($P = 0.01$). The proportion of cases due to *Listeria monocytogenes* and VZV increased after 65 years ($P < 0.001$), while the proportion of tick-borne encephalitis and Mycobacterium tuberculosis decreased with age ($P < 0.05$ for each). In-hospital mortality was 6/234 (3%) in < 65 years, 18/183 (10%) in 65-79 years, and 13/73 (18%) in ≥ 80 years ($P < 0.001$). Age ≥ 80 years, coma on admission, CSF protein ≥ 0.8 g/L and viral encephalitis were independently predictive of 6 month mortality.

Conclusion: Elderly patients represent > 50% of adults with encephalitis in France, with higher proportion of *L. monocytogenes* and VZV encephalitis, increased risk of death, and sequels. The empirical treatment currently recommended, aciclovir and amoxicillin, is appropriate for this age group.

Petitgas P, et al. Infectious encephalitis in elderly patients: a prospective multicentre observational study in France 2016-2019. Infection. 2023 Aug;51(4):859-867. doi: 10.1007/s15010-022-01927-3. Epub 2022 Sep 24. PMID: 36152225.

Encephalitis in the intensive care unit (ICU)

This team aimed to characterise the outcomes of patients with severe meningoencephalitis requiring intensive care. The researchers conducted a prospective multicentre international cohort study (2017-2020) in 68 centres across seven countries. Eligible patients were adults admitted to the intensive care unit (ICU) with meningoencephalitis, defined by an acute onset of encephalopathy, a cerebrospinal fluid pleocytosis ≥ 5 cells/mm3, and at least two of the following criteria: fever, seizures, focal neurological deficit, abnormal neuroimaging, and/or electroencephalogram. The researchers conclude meningoencephalitis is a severe neurologic syndrome associated with high mortality and disability rates at three months. Actionable factors for which improvement could be made include time from hospital to ICU admission, early antimicrobial therapy, and detection of respiratory and cardiovascular complications at admission.

Sonneville R, et al. Clinical features, etiologies, and outcomes in adult patients with meningoencephalitis requiring intensive care (EURECA): an international prospective multicenter cohort study. Intensive Care Med. 2023;49(5):517-529. doi:10.1007/s00134-023-07032-9.

Infectious encephalitis (IE) is a severe disease which requires intensive care unit (ICU) admission in around half of cases. Fillatre et al. aimed to describe characteristics, management, and outcomes of IE patients who required ICU admission, drawing on a French observational multicentre study. Their study focussed on the functional

status of patients at the point of their discharge from hospital. In total, they enrolled 198 ICU patients with IE, with herpes simplex virus (HSV) as the primary cause of IE. The authors found that HSV was the main cause of IE that required ICU admission, and those that were admitted in ICU had a poor prognosis. Specifically, there was 11% of in-hospital mortality and 15% of severe disabilities in survivors at their point of discharge.

Fillatre P, et al. Characteristics, management, and outcomes of patients with infectious encephalitis requiring intensive care: A prospective multicentre observational study. J Crit Care. 2023 Oct;77:154300. doi: 10.1016/j.jcrc.2023.154300

Encephalitis in children

In this collaborative study between Italy and Australia, the team sought to describe the characteristics, differential diagnoses, management, and outcomes of severe encephalitis in children. The research was designed as a 10-year retrospective cohort study in children admitted to a tertiary paediatric intensive care unit (ICU) with suspected encephalitis. One to six months' follow-up data were compared between different categories. 175 children with encephalitis required ICU admission over 10 years. The median age was 4.5 months. The leading cause was enterovirus, followed by parechovirus, influenza, herpes simplex virus (HSV), and human herpesvirus-6 (HHV-6). Immune-mediated encephalitis was reported to have had a higher prevalence in females, older age, and patients with longer duration of encephalopathy. 11 patients died (case fatality rate 6.3%): five with HHV-6, two enterovirus, two influenza, one HSV, one human-metapneumovirus. The researchers conclude that encephalitis has a varied aetiology and causes death or severe disability in 1 in every 10 children requiring intensive care.

Palmas G, Duke T. Severe encephalitis: aetiology, management and outcomes over 10 years in a paediatric intensive care unit. Arch Dis Child. 2023;108(11):922-928. doi:10.1136/archdischild-2023-325305.

In this important study, the authors begin by highlighting that prospective studies of encephalitis are rare in regions where encephalitis is prevalent, such as low middle-income Southeast Asian countries. The team sought to compare the diagnostic yield of local and advanced tests in cases of paediatric encephalitis in Myanmar. Children with suspected subacute or acute encephalitis at Yangon Children's Hospital, Yangon, Myanmar, were prospectively recruited from 2016-2018. A total of 20 cases were found to have illnesses other than encephalitis. Of the 52 remaining cases in the first cohort of two, 43 had presumed infectious encephalitis, of which 2 cases had a confirmed infectious aetiology. Of the 31 cases in the second cohort, 23 had presumed infectious encephalitis, of which one had confirmed infectious aetiology using local tests only. Advanced tests confirmed an additional 10 infections, four possible infections, and five cases of anti-NMDAR encephalitis. The team concludes that paediatric encephalitis is prevalent in Myanmar, but advanced technologies can increase identification of treatable infectious and autoimmune causes. Thus, developing affordable advanced tests to use globally is a high clinical and research priority to improve the diagnosis and prognosis of encephalitis.

Galardi MM, et al. Pathogen and Antibody Identification in Children with Encephalitis in Myanmar. Ann Neurol. 2023;93(3):615-628. doi:10.1002/ana.26560.

Objectives: To assess the frequency and types of neuronal and glial (neural) antibodies in children with suspected autoimmune encephalitis (AE).

Methods: Patients younger than 18 years with suspected AE other than acute disseminated encephalomyelitis, whose serum or CSF samples were examined in our center between January 1, 2011, and April 30, 2022, were included in this study. Samples were systematically examined using brain immunohistochemistry; positive immunostaining was further investigated with cell-based assays (CBA), immunoblot, or live neuronal immunofluorescence.

Results: Of 2,750 children, serum or CSF samples of 542 (20%) showed brain immunoreactivity, mostly (>90%) against neural cell surface antigens, and 19 had antibodies only identified by CBA. The most frequent targets were N-methyl-d-aspartate receptor (NMDAR, 76%) and myelin oligodendrocyte glycoprotein (MOG, 5%), followed by glutamic acid decarboxylase 65 (2%) and γ-aminobutyric acid A receptor (2%). Antibodies against other known cell surface or intracellular neural antigens (altogether 6% of positive cases) and unknown antigens (9%) were very infrequent.

Discussion: The repertoire of antibodies in children with AE is different from that of the adults. Except for NMDAR and MOG antibodies, many of the antibodies included in diagnostic panels are rarely positive and their up-front testing in children seems unneeded.

Chen LW, et al. "Antibody Investigations in 2,750 Children With Suspected Autoimmune Encephalitis." Neurology(R) neuroimmunology & neuroinflammation vol. 11,1 e200182. 15 Nov. 2023, doi:10.1212/NXI.0000000000200182.

Autoimmune encephalitis in India and China

In a prospective study, Sharma et al. describe the demographic profile, clinical spectrum, diagnosis, and treatment of 42 patients from a tertiary care centre in Northwestern India with features of autoimmune encephalitis. Patients with suspected autoimmune encephalitis underwent detailed clinical assessment, routine blood tests, magnetic resonance imaging (MRI) brain, electroencephalopathy (EEG), cerebrospinal fluid (CSF) study, and autoimmune profile in blood and CSF. The team found that males and females were almost equally affected, with the mean age of onset at 31 years.

Anti-NMDAR encephalitis was the commonest (57%) followed by anti-LGI-1 encephalitis (11.9%) and anti-CASPR2 encephalitis (4.7%). Seizure was noted in around 72% of patients, the commonest in the anti-NMDAR group. Faciobrachial dystonic seizure (FBDS) was noted in all five anti-LGI-1 encephalitis patients and delta brush was noted in three anti-NMDAR patients. The team concludes that autoimmune encephalitis is a common neurological problem, is a diagnosis for many cases of unexplained encephalitis, and that good clinical acumen and knowledge are required for early diagnosis and treatment of this potentially reversible disorder.

Sharma B, et al. A Prospective Observational Study of Autoimmune Encephalitis in Northwestern India. J Assoc Physicians India. 2023;71(9):39-44. doi:10.59556/japi.71.0312.

Objective: This retrospective observational study primarily aimed to analyse the clinical characteristics of patients with neuronal surface antibody-mediated autoimmune encephalitis (AE) in China and report their prognosis after immunotherapy.

Methods: Clinical characteristics, laboratory or imaging examinations, and treatment outcomes of 103 patients diagnosed with AE between 1 September 2014 and 31 December 2020 were collected. Univariate and multivariate logistic regression analyses were performed to determine the predictors of poor prognosis.

Results: Overall, 103 patients were enrolled in the study. The main clinical symptoms included seizures (74.8%), psychiatric and behavior disorders (66.0%), cognitive deficits (51.5%), disturbances of consciousness (45.6%), and movement disorders/involuntary movements (26.2%). The distribution of clinical syndromes also differed for different AE subtypes. The efficacy rates of first-line immunotherapy for anti-NMDAR, anti-LGI1, anti-$GABA_BR$, and anti-CASPR2 encephalitis were 70.2%, 92.3%, 70%, and 83.3%, respectively, and rituximab was administered to 21 patients as second-line immunotherapy, including 14 patients with anti-NMDAR encephalitis, 4 with anti-LGI1 encephalitis, 2 with anti-$GABA_BR$ encephalitis, and 1 with anti-CASPR2 encephalitis. Five patients with poor effect of the second-line treatment received bortezomib. According to the results of the last follow-up, 78 patients had a good prognosis (mRS 0-2), and 21 patients had a poor prognosis (mRS 3-6). The proportion of patients with a poor prognosis was significantly higher in anti-GABABR encephalitis compared to the other AE subtypes ($p<0.001$). Multivariate analysis indicated that elevated neutrophil-to-lymphocyte ratio (NLR) and tumour presence were independent risk factors for poor prognosis. The regression equation of the model was logit(P)=-3.480 + 0.318 NLR+2.434 with or without tumour (with assignment =1, without assignment =0). The prediction probability generated by the regression model equation was used as the independent variable for receiver operating curve (ROC) analysis. The results showed that the area under the curve (AUC) of the prediction probability was 0.847 (95% CI, 0.733-0.961; $p < 0.001$).

Conclusions: Different AE subtypes demonstrated different clinical symptom spectra throughout the disease stage. Anti-LGI1 encephalitis and anti-CASPR2 encephalitis were more sensitive to first-line and second-line treatments. Anti-$GABA_BR$ encephalitis had the worst prognosis among the abovementioned subtypes. The regression equation constructed using NLR and tumour presence effectively predicted the poor prognosis.

Huang T, et al. Clinical characteristics and prognosis in patients with neuronal surface antibody-mediated autoimmune encephalitis: a single-center cohort study in China. Front Immunol. 2023 Dec 12;14:1213532. doi: 10.3389/fimmu.2023.1213532. PMID: 38152405; PMCID: PMC10751914.

Pathogenesis of encephalitis

Autoantibody-associated neurological diseases

Abstract: In 2015, we wrote a review in The Journal of Neurology summarizing the field of autoantibody-associated neurological diseases. Now, in 2023, we present an update of the subject which reflects the rapid expansion and refinement of associated clinical phenotypes, further autoantibody discoveries, and a more detailed understanding of immunological and neurobiological pathophysiological pathways which mediate these diseases. Increasing awareness around distinctive aspects of their clinical phenotypes has been a key driver in providing clinicians with a better understanding as to how these diseases are best recognized. In clinical practice, this recognition supports the administration of often effective immunotherapies, making these diseases 'not to miss' conditions. In parallel, there is a need to accurately assess patient responses to these drugs, another area of growing interest. Feeding into clinical care are the basic biological underpinnings of the diseases, which offer clear pathways to improved therapies toward enhanced patient outcomes. In this update, we aim to integrate the clinical diagnostic pathway with advances in patient management and biology to provide a cohesive view on how to care for these patients in 2023, and the future.

Varley JA, et al. Autoimmune encephalitis: recent clinical and biological advances. J Neurol. 2023;270(8):4118-4131. doi:10.1007/s00415-023-11685-3.

Inflammatory markers in anti-NMDAR encephalitis

Objectives: To summarize the cytokine/chemokine levels of anti-N-methyl-Daspartate receptor encephalitis (NMDAR-E) and explore the potential role of these molecules and immune cells in the pathogenic mechanism.

Results: A total of 19 articles were included in the systematic review from 260 candidate papers, and cytokine/chemokine levels reported in the CSF/serum were examined in each article. This meta-analysis included 17 eligible studies comprising 579 patients with NMDAR-E, 367 patients with noninflammatory neurological disorders, and 42 healthy controls from China, Spain, South Korea, Australia, Czechia, and Sweden. The results indicated that the levels of different cytokines interleukin (IL)-6, tumor necrosis factor (TNF)-α, IL-10, IL-13, IL-1β, IL-12, and IL-17 and chemokine C-X-C motif ligand (CXCL)10 in the CSF were significantly higher in NMDAR-E patients with a large effect size. In addition, B cell activating factor (BAFF), CXCL13, and interferon (IFN)-γ levels in the CSF were higher in NMDAR-E patients with a middle effect size. In contrast, levels of IL-2 and IL-4 in the CSF and CXCL13 and BAFF in the serum did not show a significant difference between cases and controls.

Conclusions: These analyses showed that the central immune response in NMDAR-E is a process that involves multiple immune cell interactions mediated by cytokines/chemokines, and T cells play an important role in the pathogenesis of immunity.

Ma Y, et al. Cytokine/chemokine levels in the CSF and serum of anti-NMDAR encephalitis: A systematic review and meta-analysis. Front Immunol. 2023 Jan 23;13:1064007. doi:10.3389/fimmu.2022.1064007. PMID: 36761173; PMCID: PMC9903132.

Epigenetics of encephalitis

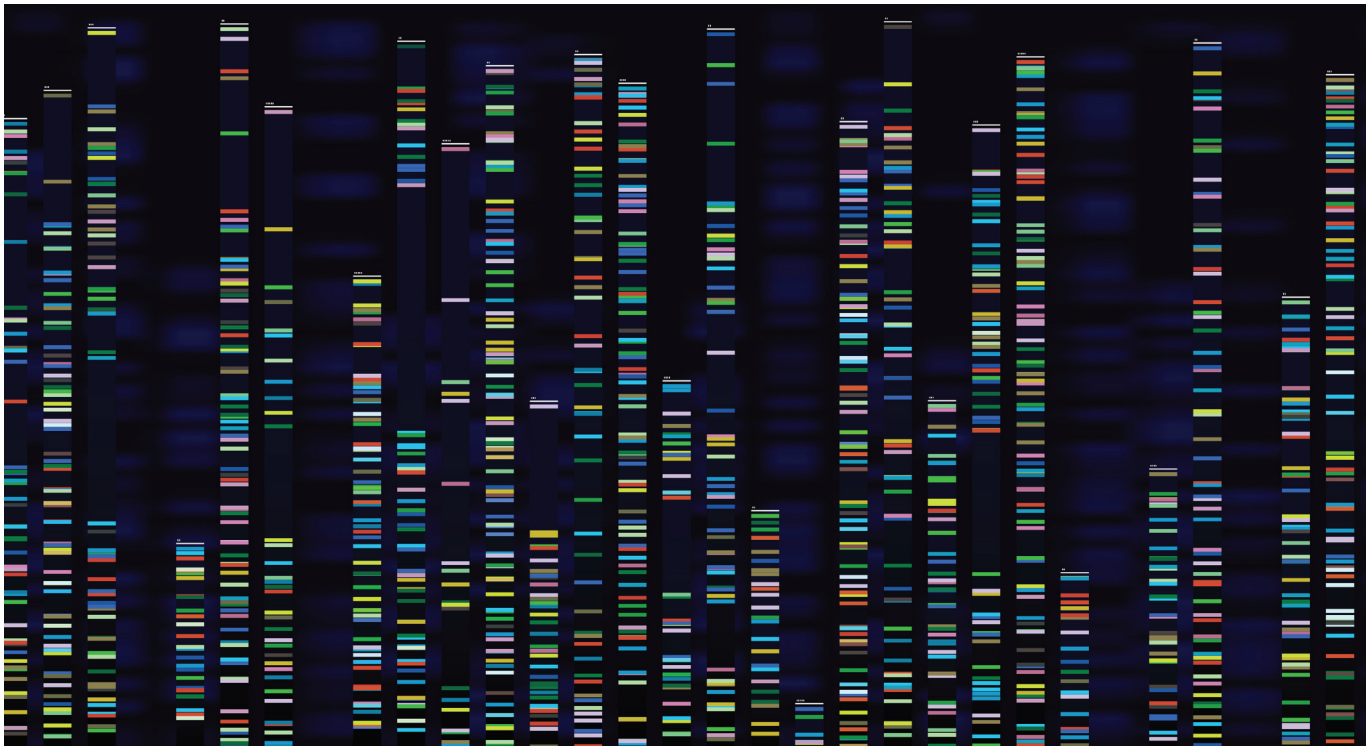
Background: Aberrant DNA methylation occurs commonly during pathogenesis of neuroimmunological diseases and is of clinical value in various encephalitis subtypes. However, knowledge of the impact of DNA methylation changes on pathogenesis of leucine-rich glioma-inactivated 1 (LGI1) antibody encephalitis remains limited.

Methods: A total of 44 cytokines and 10 immune checkpoint moleculars (ICMs) in the serum of patients with LGI1 encephalitis and healthy donors (HDs) were measured to evaluate the association of them with clinical parameters. Genome-wide DNA methylation profiles were performed in peripheral blood mononuclear cell (PBMC) from LGI1 encephalitis patients and HDs using reduced representation bisulfite sequencing (RRBS) and validated for the methylation status by pyrosequencing. MicroRNA profiles were acquired in serum exosome by small RNA sequencing. Targeted cytokines expression was assessed at the presence or absence of miR-2467-5p in PBMCs and the culture media, and the binding of miR-2467-5p and its targeted genes was validated by luciferase assay.

Results: There existed significant difference in 22 cytokines/chemokines and 6 ICMs between LGI1 encephalitis patients and HDs. Decreased PDCD1 with increased ICAM1 could predict unfavorable prognosis in one-year follow-up for LGI1 encephalitis patients. 15 of cytokines/chemokines and ICMs presented DNA-methylated changes in the promoter and gene body using RRBS in which five were verified as methylation status by pyrosequencing, and the methylation level of CSF3, CCL2, and ICAM1 was conversely associated with their expression in PBMCs. By combining RRBS data with exosome-derived microRNA sequencing, we found that hypomethylated-driven hsa-miR-2467-5p presented elevated expression in serum exosomes and PBMCs in LGI1 encephalitis. Mechanically, miR-2467-5p significantly induced reduced expression of CSF3 and PDCD1 by binding with their 3`UTR while enhanced CCL15 expression, but not significantly correlated with peripheral blood CD19+B cell proportion of LGI1 encephalitis patients.

Conclusions: Our results provided convincing evidence for DNA methylation changes, microRNA profiles in serum exosome for LGI1 encephalitis, and we also identified several novel cytokines related to clinical features in which some represented epigenetic modification of methylated-driven pattern and microRNA modulation. Our study contributed to develop treatment for epigenetic pathogenesis in LGI1 encephalitis.

Qiao S, et al. Abnormal DNA methylation analysis of leucine-rich glioma-inactivated 1 antibody encephalitis reveals novel methylation-driven genes related to prognostic and clinical features. Clin Epigenetics. 2023;15(1):139. Published 2023 Aug 29. doi:10.1186/s13148-023-01550-5.



Infectious encephalitis

Herpes simplex virus encephalitis

It has been reported that herpes simplex virus-1 (HSV-1), a neurotropic DNA virus with neural latency and stereotypic viral encephalitis, conceals underlying glioblastoma (GBM). To better describe the pathophysiology of HSV-1 superinfections in GBM, the team performed a comprehensive review of GBM cases with superimposed HSV-1. A comprehensive literature search of six electronic databases was performed to identify eligible cases of GBM with HSV-1. The team identified 20 cases of HSE in GBM with an overall survival (OS) of 8.0 months. The median age of presentation was 63 years and the median interval between GBE or HSE diagnosis was 2 months. HSE diagnosis before GBM diagnosis was a predictor for improved survival. There is a significant reduction in OS in patients with concomitant HSE and GBM compared to the cancer genome atlas (GCGA) cohort. Finally, HSV does not directly infect GBM cells but indirectly activates a local immune response in the tumour microenvironment. The researchers conclude that superimposed HSE in GBM may contribute to a significant reduction in OS compared to uninfected controls, potentially activating proto-oncogenes during active infection and latency. Pre-op HSE may induce an antiviral immune response, which may serve as a positive prognostic factor. Prompt antiviral treatment upon co-occurrence is necessary.

Mendez Valdez MJ, et al. Outcomes of HSV-1 encephalitis infection in glioblastoma: An integrated systematic analysis. Microb Pathog. 2023;181:106211. doi:10.1016/j.micpath.2023.106211.

Influenza and encephalitis

Influenza virus is generally characterised by fever, myalgia, and respiratory symptoms. Neurological entities have already been described, such as acute necrotising encephalitis (ANE). Goetz et al. aimed to highlight the non-exceptional nature and explore the clinical spectrum and evolution of neurological features related to influenza virus in children. This monocentric observational study included patients under 18 years of age, positive for influenza virus, admitted to a paediatric university hospital between January 2017 and April 2019. Patients were classified into two groups: those with or without a previous significant neurological or metabolic disorder. 289 children were identified with influenza infection. 37 had a neurological manifestation: 14 patients who had previous significant neurological or metabolic disorder and 23 patients with no medical history. The team identified several clinical patterns: 22 patients had seizures, seven behaviour disorders, five disturbances of consciousness, and three motor deficits. Four were diagnosed with a known influenza-associated neurological syndrome: one ANE, one cytotoxic lesion of the corpus callosum, one hemiconvulsion-hemiplegia-epilepsia syndrome, and one recurrent encephalitis in the context of a RANBP2 mutation. The neurological outcome was favourable in most cases. None of the patients with previous significant disorder retained sequelae or had a recurrence. Two patients had a fatal outcome, and both had a predisposing disorder.

Goetz V, et al. Neurological features related to influenza virus in the pediatric population: a 3-year monocentric retrospective study. Eur J Pediatr. 2023;182(6):2615-2624. doi:10.1007/s00431-023-04901-9.

Japanese encephalitis

A team reports a case of new onset refractory status epilepticus (NORSE) triggered by Japanese encephalitis (JE) in an unvaccinated US adult traveller. NORSE is a rare but critical condition characterised by refractory status epilepticus (RSE) in an individual without prior history of epilepsy or known structural, toxic or metabolic cause. The team refer to another study by Wickstrom et al. (2022) which strongly recommends early testing for autoimmune antibodies. Cerebral spinal fluid (CSF) from the traveller later revealed positive anti-N-methyl-d-aspartate (NMDA)-receptor antibody. The patient responded well to first-line immunotherapy with a favourable functional outcome. This case, the researchers conclude, highlights the diagnostic and treatment challenges in this rare presentation.

Osbourn SR, et al. "A case of new onset refractory status epilepticus in a U.S. traveler with Japanese encephalitis." Journal of neuroimmunology vol. 383 (2023): 578193. doi:10.1016/j.jneuroim.2023.578193.

A team of researchers report a child from Southern Australia (New South Wales) who presented encephalopathy and acute flaccid paralysis. MRI suggested Japanese encephalitis (JE). Steroids and intravenous immunoglobin did not improve symptoms. Therapeutic plasma exchange (TPE) resulted in rapid improvement and tracheostomy decannulation. This case, the researchers contend, illustrates the complex pathophysiology of JE, its geographic expansion into Southern Australia and potential use of TPE for neuroinflammatory sequelae.

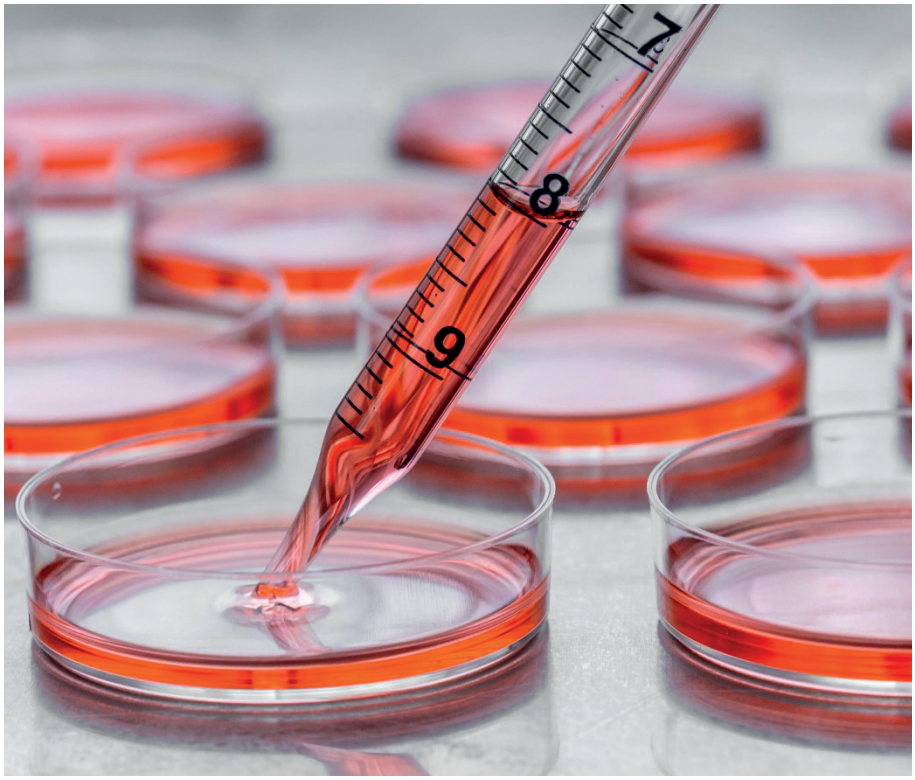
Cole E, et al. "Geographic Expansion of Japanese Encephalitis Virus to Australia: Neuroinflammatory Sequelae and Consideration of Immunomodulation." The Pediatric infectious disease journal vol. 42,5 (2023): e173-e176. doi:10.1097/INF.0000000000003861.

Varicella-zoster virus encephalitis

Le et al. presented an extremely rare case of varicella-zoster virus (VZV) encephalitis in an immunocompetent male 15-year-old patient, despite being vaccinated against VZV.

He presented with altered mental status, no rash, no fever, no seizures, confusion, headache, and memory loss. VZV encephalitis diagnosis was discerned after lumbar puncture and cerebrospinal fluid assessment. He was treated with intravenous acyclovir, symptoms subsided. Usually, VZV encephalitis predominantly affects immunocompromised adults and elderly patients; thus, this case is exceptionally rare and highlights a necessity for VZV encephalitis' efficient and early diagnosis especially in rarer manifestations.

Le N, et al. (2023). A Rare Case of Varicella-Zoster Virus Encephalitis Presenting With Lost Ability to Play the Piano in an Immunocompetent Pediatric Patient. Cureus, 15(7), e41383. https://doi.org/10.7759/cureus.41383



Bacterial encephalitis

Abstract: Scrub typhus is an established cause of acute encephalitis syndrome (AES) in northern states of India. We systematically investigated 376 children with AES in southern India, using a stepwise diagnostic strategy for the causative agent of scrub typhus, Orientia tsutsugamushi, including IgM and PCR testing of blood and cerebrospinal fluid (CSF) to grade its association with AES. We diagnosed scrub typhus in 87 (23%) children; of those, association with AES was confirmed in 16 (18%) cases, probable in 55 (63%), and possible in 16 (18%). IgM detection in CSF had a sensitivity of 93% and specificity of 82% compared with PCR. Our findings suggest scrub typhus as an emerging common treatable cause of AES in children in southern India and highlight the importance of routine testing for scrub typhus in diagnostic algorithms. Our results also suggest the potential promise of IgM screening of CSF for diagnosis of AES resulting from scrub typhus.

Damodar T, et al. Association of Scrub Typhus in Children with Acute Encephalitis Syndrome and Meningoencephalitis, Southern India. Emerg Infect Dis. 2023;29(4):711-722. doi:10.3201/eid2904.221157.

Introduction: To date, few studies have explored the specific risk factors of patients with listeriosis who develop rhombencephalitis, and there is insufficient information regarding imaging findings and clinical symptoms in patients with this disease. This work aimed to analyze the imaging findings associated with *L. monocytogenes* rhombencephalitis in a cohort of patients with listeriosis.

Materials and methods: We conducted a retrospective observational study of all declared cases of listeriosis in a tertiary hospital from Granada, Spain, from 2008 to 2021. Risk factors, comorbidities, and clinical outcomes were collected for all patients. In addition, clinical symptoms, and magnetic resonance imaging (MRI) findings were included for those patients who developed rhombencephalitis. Descriptive and bivariate analyses were performed using SPSS statistical software (IBM SPSS, version 21).

Results: Our cohort comprised 120 patients with listeriosis (41.7% women, mean age: 58.6 $\pm$ 23.8 years), of which 10 (8.3%) had rhombencephalitis. The most frequent MRI findings in patients with confirmed rhombencephalitis were T2-FLAIR hyperintensity (100%), T1 hypointensity (80%), scattered parenchymal enhancement (80%), and cranial nerve enhancement (70%), while the most frequent anatomical involvement were pons, medulla oblongata, and cerebellum. Complications occurred in 6 patients (abscess in 4, hemorrhage in 2, hydrocephalus in 1).

Conclusions: Rhombencephalitis is associated with an increased in-hospital mortality in patients with listeriosis. The anatomical distribution and imaging characteristics of neurolisteriosis could be useful to suggest the diagnosis. Future studies with greater sample size should explore the association between anatomical location, imaging patterns, and associated complications (e.g., hydrocephalus, hemorrhage), and clinical outcomes.

Láinez-Ramos Bossini AJ, et al. "Epidemiology, clinical and imaging features of rhombencephalitis caused by L. monocytogenes. A retrospective observational study." "Epidemiología, clínica y resultados de imagen de rombencefalitis causada por L. monocytogenes. Un estudio observacional." Revista de neurologia vol. 76,12 (2023): 385-390. doi:10.33588/rn.7612.2023020.

COVID-19 and encephalitis

Abstract: The current pandemic caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is accompanied with a rapid increase of reports and papers detailing its neurological effects and symptoms. The virus infection causes respiratory illness named by the world health organization as corona virus 19 (COVID-19). This systematic review aims to study and summarize the different neurological manifestations of this virus. All articles published and indexed via Pubmed, Medline and Google Scholar databases between January 1st 2020 and February 28th 2021 that reported neurological symptoms of SARS-CoV-2 are reviewed following the Preferred Reporting Items for Systemic review and Meta-Analysis (PRISMA) guidelines. We included data from 113 articles: eight prospective studies, 25 retrospective studies and the rest were case reports/series. COVID-19 can present with central nervous system manifestations, such as headache, encephalitis and encephalopathy, peripheral nervous system manifestations, such as anosmia, ageusia and Guillian Barre syndrome, and skeletal muscle manifestations, such as myalgia and myasthenia gravis. Our systematic review showed that COVID-19 can be manifested by a wide spectrum of neurological symptoms reported either in the early stage or within the course of the disease. However, a detailed comprehension of these manifestations is required and more studies are needed in order to improve our scientific knowledge and to develop preventive and therapeutic measures to control this pandemic.

Ousseiran ZH, et al. Neurological manifestations of COVID-19: a systematic review and detailed comprehension. Int J Neurosci. 2023 Jul;133(7):754-769. doi: 10.1080/00207454.2021.1973000. Epub 2021 Sep 27. PMID: 34433369; PMCID: PMC8506813.

Objective: To investigate the clinical manifestations, treatment and prognosis of COVID-19-associated central nervous system (CNS) complications.

Methods: In this single-centre observation study, we recruited patients with COVID-19-associated CNS complications at the neurology inpatient department of the Eighth Affiliated Hospital, Sun Yat-Sen University (Futian, Shenzhen) from Dec 2022 to Feb 2023. Patients were analysed for demographics, clinical manifestations, cerebrospinal fluid properties, electroencephalographic features, neuroimaging characteristics, and treatment outcome. All patients were followed-up at one and two months after discharge until Apr 2023.

Results: Of the 12 patients with COVID-19-associated CNS complications, the CNS symptoms occur between 0 days and four weeks after SARS-CoV-2 infection. The most common CNS symptoms were memory deficits (4/12, 33%), unresponsiveness (4/12, 33%), mental and behavioural disorders (4/12, 33%). Seven of 12 cases can be categorized as probable SARS-CoV-2 encephalitis, and five cases can be described as brainstem encephalitis, acute disseminated encephalomyelitis, optic neuritis, multiple sclerosis or tremor probably associated with SARS-CoV-2 infection. Six patients received antiviral therapy, and 11 patients received glucocorticoid therapy, of which 3 patients received human immunoglobulin synchronously. Nine patients recovered well, two patients had residual neurological dysfunction, and one patient passed away from complications associated with tumor.

Conclusion: In this observational study, we found that the inflammatory or immune-related complications were relatively common manifestations of COVID-19-associated CNS complications, including different phenotypes of encephalitis and CNS inflammatory demyelinating diseases. Most patients recovered well, but a few patients had significant neurological dysfunctions remaining.

Li Z, et al. Central nervous system complications in SARS-CoV-2-infected patients. J Neurol. 2023 Oct;270(10):4617-4631. doi: 10.1007/s00415-023-11912-x. Epub 2023 Aug 13. PMID: 37573554; PMCID: PMC10511589.

Anti-NMDAR encephalitis

Anti-NMDAR encephalitis in children

Background: Rates of sleep problems in children with anti-NMDA receptor encephalitis (NMDARE) are unknown.

Methods: We used a retrospective observational cohort database of children with a diagnosis of NMDARE at a single freestanding institution. One-year outcomes were assessed with the pediatric modified Rankin score (mRS), with 0-2 as good and three or greater as poor outcome.

Results: 95 percent (39/41) of children with NMDARE had sleep dysfunction at onset; 34 percent (11/32) reported sleep problems at one year. Sleep problems at onset and propofol use were not associated with poor outcomes at one year. Poor sleep at one year correlated with mRS scores (range 2-5) at one year.

Discussion: High rates of sleep dysfunction occur in children with NMDARE. Persistent sleep problems at one year may correlate with outcomes as assessed by mRS at one year. Further studies comparing the relationship of poor sleep with outcomes in NMDARE are needed.

Gombolay G, et al. Sleep Characteristics in Pediatric Anti-methyl-d-aspartate (NMDA) Receptor Encephalitis: A Retrospective Cohort Study. J Child Neurol. 2023 Apr;38(5):298-306. doi: 10.1177/08830738231173603. Epub 2023 May 18. PMID:37203168; PMCID: PMC10524468.

Herpes simplex virus (HSV) type 1 is a frequent form of infectious encephalitis. Early treatment with intravenous acyclovir has led to a significant decrease in mortality. However, particularly in children, deterioration during or after HSVE may occur without any evidence of HSV reactivation or improvement following repeated treatment with antivirals. In this study, it is reported that 15 patients who suffered from autoimmune encephalitis with autoantibodies to NMDAR1 following Herpes encephalitis presented with movement abnormalities or neuropsychiatric symptoms as major complaints respectively. The diagnosis was based on positive cerebrospinal fluid (CSF) and/or serum anti-NMDAR-antibodies with two children showing only positive CSF antibody findings. After immunotherapy, no patients relapsed with HSVE. Early diagnosis and treatment of autoimmune encephalitis after HSVE may be associated, the authors conclude, with a better outcome so that high clinical awareness and routine testing for anti-NMDAR-antibodies after HSVE seems advisable. If autoimmune encephalitis is suspected, antibody testing should also be performed on CSF if negative in serum.

Quade A, et al. Autoimmune Encephalitis with Autoantibodies to NMDAR1 following Herpes Encephalitis in Children and Adolescents. Neuropediatrics. 2023;54(1):14-19. doi:10.1055/s-0042-1757706.

Background and Objectives: Anti-N-methyl-D-aspartate receptor encephalitis (NMDARE) is the most common form of autoimmune encephalitis in children and adults. Although our understanding of the disease mechanisms has progressed, little is known about estimating patient outcomes. Therefore, the NEOS (anti-NMDAR Encephalitis One-Year Functional Status) score was introduced as a tool to predict disease progression in NMDARE. Developed in a mixed-age cohort, it currently remains unclear whether NEOS can be optimized for pediatric NMDARE.

Methods: This retrospective observational study aimed to validate NEOS in a large pediatric-only cohort of 59 patients (median age of 8 years). We reconstructed the original score, adapted it, evaluated additional variables, and assessed its predictive power (median follow-up of 20 months). Generalized linear regression models were used to examine predictability of binary outcomes based on the modified Rankin Scale (mRS). In addition, neuropsychological test results were investigated as alternative cognitive outcome.

Results: The NEOS score reliably predicted poor clinical outcome (mRS $\geq$3) in children in the first year after diagnosis ($p = 0.0014$) and beyond ($p = 0.036$, 16 months after diagnosis). A score adapted to the pediatric cohort by adjusting the cutoffs of the 5 NEOS components did not improve predictive power. In addition to these 5 variables, further patient characteristics such as the "Herpes simplex virus encephalitis (HSE) status" and "age at disease onset" influenced predictability and could potentially be useful to define risk groups. NEOS also predicted cognitive outcome with higher scores associated with deficits of executive function ($p = 0.048$) and memory ($p = 0.043$).

Discussion: Our data support the applicability of the NEOS score in children with NMDARE. Although not yet validated in prospective studies, NEOS also predicted cognitive impairment in our cohort. Consequently, the score could help identify patients at risk of poor overall clinical outcome and poor cognitive outcome and thus aid in selecting not only optimized initial therapies for these patients but also cognitive rehabilitation to improve long-term outcomes.

Nikolaus M, et al. Retrospective Pediatric Cohort Study Validates NEOS Score and Demonstrates Applicability in Children With Anti-NMDAR Encephalitis. Neurol Neuroimmunol Neuroinflamm. 2023;10(3):e200102. Published 2023 Mar 22. doi:10.1212/NXI.0000000000200102

Manifestations in anti-NMDAR encephalitis: suicidal thoughts and catatonia

Tellez-Martinez et al. addressed the gap in literature for suicidal thoughts and its behavioural manifestations in

the acute stage of anti-N-methyl-D-aspartate receptor encephalitis (ANMDARE) from a Mexican cohort. The longitudinal study measured patient suicidal thoughts and behaviour with a caregiver/relative's clinical interview and patient assessment. From the preliminary cohort, suicidal thoughts, and behaviours in the acute phase (15%), suicidal ideation with intention and psychosis (100%), preparatory behaviours, self-harm, depression, and impulsivity were documented. Immunotherapy was successful in alleviating suicidal manifestations, most of which sustained remission (93.3%). The researchers highlighted the importance of considering suicide in ANMDARE psychiatric assessment.

Tellez-Martinez A, et al. "Suicidal Thoughts and Behaviors in Anti-NMDA Receptor Encephalitis: Psychopathological Features and Clinical Outcomes." The Journal of neuropsychiatry and clinical neurosciences vol. 35,4 (2023): 368-373. doi:10.1176/appi.neuropsych.20220200.

Background: Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is one of the most prevalent autoimmune encephalitis and is closely related to catatonia. This study aimed to investigate the clinical features and disease outcomes of adult catatonic anti-NMDAR encephalitis patients.

Methods: Adult patients diagnosed with anti-NMDAR encephalitis between January 2013 and October 2021 were retrospectively enrolled in this study. According to the Bush Francis Catatonia screening instrument (BFCSI), patients were divided into two groups: those with catatonia and those without catatonia. The modified Rankin scale (mRS), Clinical Assessment Scale for Autoimmune Encephalitis (CASE), Neuropsychiatric Inventory (NPI), Patient Health Questionnaire-9 (PHQ-9) and 7-item Generalized Anxiety Disorder Questionnaire (GAD-7) scores were assessed at follow-up. The Mann–Whitney U test (nonparametric), Student's t test (parametric), and chi-squared test were used to analyse the differences between the two groups.

Results: 84 patients were recruited, including 25 catatonic patients and 59 noncatatonic patients. Among them, 28 had positive antibody only in cerebrospinal fluid (CSF), four had positive antibody only in serum and 52 had positive antibody both in CSF and serum. Catatonic patients experienced more disturbance of consciousness (p=0.01), aggression (p=0.046) and affective disorders (p=0.043) than noncatatonic patients. The mRS scores of the catatonia group assessed at admission (p=0.045) were worse than those of the non-catatonia group. Catatonic patients were more inclined to develop deep vein thrombosis (p=0.003), decubitus (p=0.046), pneumonia (p=0.025), and to be admitted to the intensive care unit (ICU) (p=0.011) than noncatatonic patients. All patients in the catatonia group received first-line immunotherapy. At the 24-month follow-up, two patients in the catatonia group did not achieve good outcomes. At the last follow-up, the catatonia group had more relapses (p=0.014) and more neuropsychiatric problems (p=0.035).

Conclusions: Adult anti-NMDAR encephalitis patients with catatonia present distinct clinical features in disease course and are prone to experience more relapses and long-term neuropsychiatric problems than those without catatonia.

Wu H, et al. Catatonia in adult anti-NMDAR encephalitis: an observational cohort study. BMC Psychiatry. 2023 Feb 7;23(1):94. doi: 10.1186/s12888-022-04505-x. PMID: 36750806; PMCID: PMC9903498.

Prognosis

Purpose: Anti–N-methyl-d-aspartate receptor (anti-NMDAR) encephalitis is a form of autoimmune encephalitis associated with EEG abnormalities. In view of the potentially severe outcomes, there is a need to develop prognostic tools to inform clinical management. The authors explored whether quantitative EEG was able to predict outcomes in patients with suspected anti-NMDAR encephalitis.

Methods: A retrospective, observational study was conducted of patients admitted to a tertiary clinical neuroscience center with suspected anti-NMDAR encephalitis. Peak power and peak frequency within delta (<4 Hz), theta (4–8 Hz), alpha (8 - 13 Hz), and beta (13–30 Hz) frequency bands were calculated for the first clinical EEG recording. Outcome was based on the modified Rankin Scale (mRS) score at 1 year after hospital discharge. Binomial logistic regression using backward elimination was performed with peak frequency and power, anti-NMDAR Encephalitis One-Year Functional Status score, age, and interval from symptom onset to EEG entered as predictors.

Results: 20 patients were included (mean age 48.6 years, 70% female), of which seven (35%) had a poor clinical outcome (mRS 2–6) at one year. There was no association between reported EEG abnormalities and outcome. The final logistic regression model was significant ($\chi 2(1) = 6.35$, $P < 0.012$) with peak frequency in the delta range (<4 Hz) the only retained predictor. The model explained 38% of the variance (Nagelkerke R2) and correctly classified 85% of cases. Higher peak frequency in the delta range was significantly associated ($P = 0.04$) with an increased likelihood of poor outcome.

Conclusions: In this exploratory study, it was found that quantitative EEG on routinely collected EEG recordings in patients with suspected anti-NMDAR encephalitis was feasible. A higher peak frequency within the delta range was associated with poorer clinical outcome and may indicate anti-NMDAR-mediated synaptic dysfunction. Quantitative EEG may have clinical utility in predicting outcomes in patients with suspected NMDAR antibody encephalitis, thereby serving as a useful adjunct to qualitative EEG assessment; however, given the small sample size, replication in a larger scale is indicated.

Blackman G, et al. Quantitative EEG as a Prognostic Tool in Suspected Anti-N-Methyl- d -Aspartate Receptor Antibody Encephalitis. J Clin Neurophysiol. 2023 Feb 1;40(2):160-164. doi: 10.1097/WNP.0000000000000877. Epub 2021 Jul 2. PMID: 34238869; PMCID: PMC9886530.

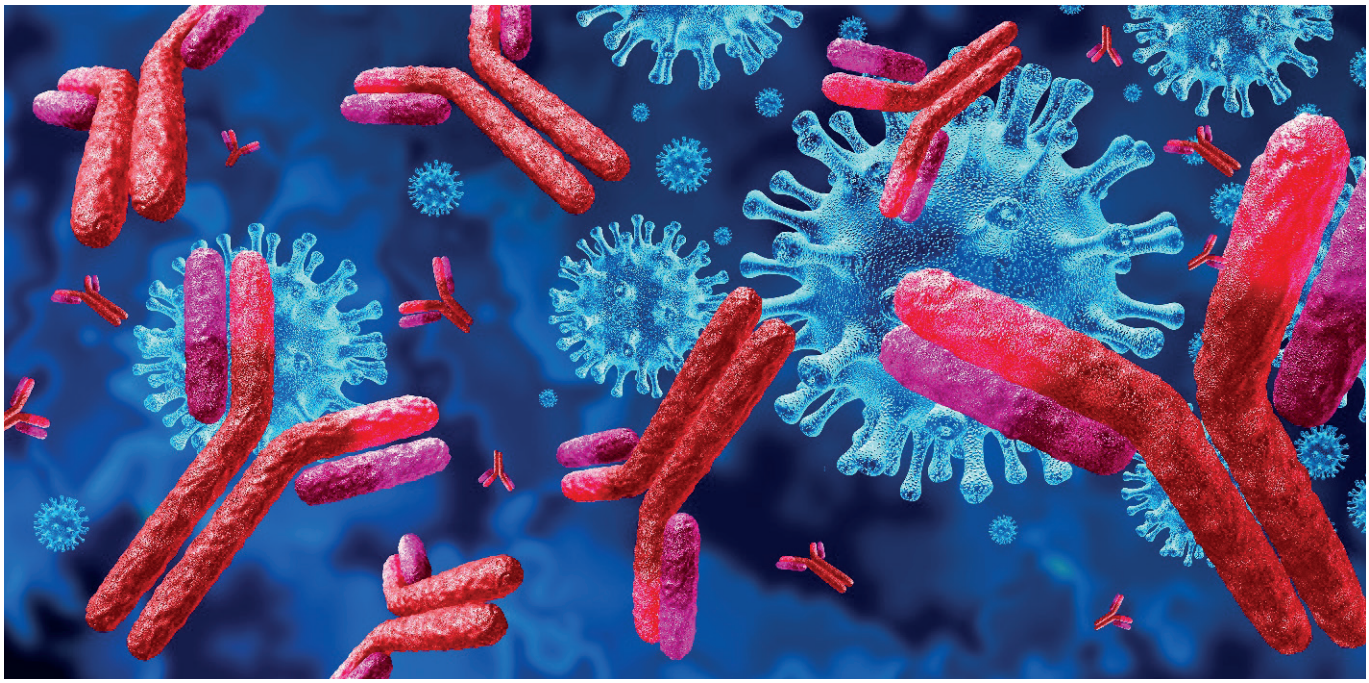
Background and Objectives: Anti-NMDA receptor (NMDAR) encephalitis is defined by the presence of antibodies (Abs) targeting the NMDAR in the CSF. This study aimed to determine the prognostic value of persistent CSF NMDAR-Abs during follow-up.

Methods: This retrospective observational study included patients diagnosed with anti-NMDAR encephalitis in the French Reference Center for Paraneoplastic Neurological Syndromes and Autoimmune Encephalitis and for whom CSF samples were obtained at diagnosis and >4 months of follow-up to evaluate CSF NMDAR-Ab persistence. Because patients were tested for CSF NMDAR-Abs at different time points, samples were stratified into different periods of follow-up (i.e., 12 months was considered for the 9- to 16-month follow-up period).

Results: Among the 501 patients diagnosed with anti-NMDAR encephalitis between January 2007 and June 2020, 89 (17%) were tested between 4 and 120 months for CSF NMDAR-Abs after clinical improvement and included in the study (75/89 women, 84%; median age 20 years, interquartile range [IQR] 16–26). During follow-up, 21 of 89 (23%) patients had a relapse after a median time of 29 months (IQR 18–47), and 20 of 89 (22%) had a poor outcome (mRS ≥3) after a median last follow-up of 36 months (IQR 19–64). Most patients (69/89, 77%) were tested at the 12-month follow-up period, and 42 of 69 (60%) of them had persistent CSF NMDAR-Abs. When comparing patients with persistent or absent CSF NMDAR-Abs at 12 months, poor outcome at the last follow-up was more frequent in the former (38% vs 8%, p = 0.01), who had relapses more often (23% vs 7%), which also appeared earlier in the course of the disease (90% during the following four years of follow-up vs 20%), although no significant difference was observed at long-term follow-up (p = 0.15). In addition, patients with persistent CSF NMDAR-Abs at 12 months had higher titers of CSF NMDAR-Abs at diagnosis.

Discussion: In this study, patients with persistent CSF NMDAR-Abs at 12 months were more likely to have subsequent relapses and a poor long-term outcome. However, these findings should be interpreted with caution because of the variability in the time of sampling of this study. Future prospective studies are required to validate these results in larger cohorts.

Ciano-Petersen NL, et al. "Prognostic Value of Persistent CSF Antibodies at 12 Months in Anti-NMDAR Encephalitis." Neurology(R) neuroimmunology & neuroinflammation vol. 10,4 e200108. 5 May. 2023, doi:10.1212/NXI.0000000000200108.



Anti-LGI1 encephalitis

Background and Objectives: Longitudinal outcome studies in leucine-rich glioma inactivated-1 (LGI-1) immunoglobulin G (IgG) autoimmune encephalitis (AE) are needed to inform clinical management and prognostication. This study aims to evaluate longitudinal predictors of disability and disease severity in LGI-1-IgG AE.

Methods: This retrospective observational study of patients with LGI-1-IgG AE was conducted between 2013-2022. Disability and disease severity were defined by scores on the modified Rankin Scale (mRS) and the clinical assessment scale in AE (CASE), respectively. Demographic variables, clinical/paraclinical data, brain MRI, and Montreal Cognitive Assessment (MOCA) scores were examined as predictors of mRS and CASE scores in logistic and linear regression models, respectively.

Results: 30 patients (60% male, median age = 68.5; interquartile range (IQR) = 63.0–75.0) were included, with a median follow-up time of 19.1 months (IQR = 5.3–47.1) The majority developed seizures (29, [97%]) and/or cognitive impairment (30, [100%]) and received acute (27, [90%]) and maintenance (23 [77%]) immunotherapy. The median initial MOCA was 23/30 (IQR = 21.0–25.0). Baseline mRS (median = 2.0, IQR = 2.0–3.0) and CASE (mean = 4.3, SD = 3.7) correlated with one another ($r = 0.58$, $p < 0.001$) and with initial MOCA score (mRS $r = -0.60$, $p = 0.012$; CASE $r = -0.56$, $p = 0.021$) After 12 months from symptom onset, mRS (OR = 0.88, [95% CI = 0.82–0.94], $p < 0.001$) and CASE ($\beta = -0.03$, [SE = 0.01], $p < 0.001$) improved significantly. Lower initial MOCA score (OR = 0.68, 95% CI = 0.47–0.98, $p = 0.041$) and temporal lobe(s) T2 hyperintensity (OR = 16.50, 95% CI = 2.29–119.16, $p = 0.006$) were associated with higher mRS longitudinally. At last follow-up, most patients had persistent memory dysfunction (25, [83%]) while few had ongoing seizure activity (3, [10%]).

Discussion: Overall, there was a high degree of correlation between mRS and CASE scores in patients with LGI-1-IgG AE, with both scores improving significantly after 12 months. Memory dysfunction and psychiatric disturbance were the most prevalent longitudinal symptoms. Cognitive impairment and temporal lobe T2 hyperintensity at baseline were both associated with greater disability at long-term follow-up, underscoring these as important determinants of disability outcomes in LGI-1-IgG AE.

Aboseif A, et al. Clinical Determinants of Longitudinal Disability in LGI-1-IgG Autoimmune Encephalitis. Neurol Neuroimmunol Neuroinflamm. 2023 Nov 10;11(1):e200178. doi:10.1212/NXI.0000000000200178. PMID: 37949667; PMCID: PMC10691218.

Objectives: Anti-leucine glioma-inactivated protein 1 (anti-LGI1) autoimmune encephalitis (AE) presents as subacute memory loss, behavioral changes, and seizures. Diagnosis and treatment delays can result in long term sequelae, including cognitive impairment. 18F-FDG PET/CT may be more sensitive than MRI in patients with AE. Our objective was to determine if anti-LGI1 is associated with a distinct pattern of FDG uptake and whether this pattern persists following treatment.

Methods: Nineteen18F-FDG PET/CT brain scans (13 pre-treatment, 6 convalescent phase) for 13 patients with anti-LGI1 were studied using NeuroQ™ and CortexID™. The sensitivity of the PET images was compared to MRI. The Z scores of 47 brain regions between the pre-treatment and next available follow-up images during convalescence were compared.

Results: All 18F-FDG PET/CT scans demonstrated abnormal FDG uptake, while only 6 (42.9%) pre-treatment brain MRIs were abnormal. The pre-treatment scans demonstrated hypermetabolism in the bilateral medial temporal cortices, basal ganglia, brain stem, and cerebellum and hypometabolism in bilateral medial and mid frontal, cingulate, and parietotemporal cortices. Overall, the brain uptake during convalescence showed improvement of the Z scores towards 0 or normalization of previous hypometabolic activity in medial frontal cortex, inferior frontal cortex, Broca's region, parietotemporal cortex, and posterior cingulate cortex and previous hypermetabolic activity in medial temporal cortices, caudate, midbrain, pons and cerebellum.

Conclusions: Brain FDG uptake was more commonly abnormal than MRI in the pre-treatment phase of anti-LGI1, and patterns of dysmetabolism differed in the pre-treatment and convalescent phases. These findings may expedite the diagnosis, treatment, and monitoring of anti-LGI1 patients.

Sadaghiani MS, et al. Comparison of quantitative FDG-PET and MRI in anti-LGI1 autoimmune encephalitis. Neuroradiology. 2023;65(8):1225-1238. doi:10.1007/s00234-023-03165-2.

Objective: To assess the efficacy and safety of immunotherapy for LGI1 antibody encephalitis, and consider the predictors of poor outcomes following immunotherapy.

Methods: We searched PubMed and Embase for articles reporting the immunotherapy data of anti-LGI1 encephalitis patients. The proportions of patients with poor outcomes (modified Rankin Scale [mRS] score>2) at 3months, 12months, and the last follow-up, as well as the odds ratio [OR] of predictors were pooled.

Results: The review included 162 articles with 1066 patients. The proportion of patients with poor functional outcomes was 21% at 3months, 14% at 12months, and 14% at the last follow-up after receiving immunotherapy. The proportion of patients with reported relapse was 16.6%. The mean duration from onset to the first relapse was 15.6months. Predictors significantly associated with poor outcomes were age (increase of 1year), the presence of cognitive impairment, and CSF LGI1 antibody positive. We did not find a statistically significant association between the worst mRS score in the acute phase, the presence of faciobrachial dystonic seizures (FBDS), days from symptom onset to immunotherapy, second-line treatment, maintenance immunotherapy, or follow-up time and outcomes.

Interpretation: Although most patients respond to immunotherapy, a minority of patients still have poor outcomes. Advanced age, cognitive impairment, and CSF LGI1 antibody positive are associated with an increased risk of poor outcomes. However, due to the insufficiency of the data, these conclusions need to be interpreted with caution.

Kong X, et al. Efficacy of immunotherapy and prognosis in anti-LGI1 encephalitis patients: A meta-analysis. Ann Clin Transl Neurol. 2023 Sep;10(9):1578-1589. doi: 10.1002/acn3.51847. Epub 2023 Jul 13. PMID: 37443415; PMCID: PMC10502619.

Background and Objectives: Antileucine-rich glioma-inactivated 1 (anti-LGI1) autoimmune encephalitis was first described in 2010 and is today the most common type of limbic encephalitis. During the course of the disease, 60%–88% of the patients develop hyponatremia. The etiology of the sodium disorder is unclear, often presumed to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Other electrolyte abnormalities have not been reported in association with anti-LGI1 antibody encephalitis. Due to the presence of hypomagnesemia and hypophosphatemia in our patients, we set out to try to find the expression of LGI1 protein in the kidney as an explanation for these abnormalities.

Methods: We reviewed the medical files of all patients diagnosed with anti-LGI1 antibody encephalitis, at the Department of Neurology in the Tel Aviv Medical Center between January 2011 and December 2020, exploring for electrolyte abnormalities. Using tissue staining, Western blot, mass spectrometry, and RNA expression techniques, we tried to demonstrate the expression of LGI1 protein in the human kidney.

Results: We identified 15 patients diagnosed with anti-LGI1 antibody encephalitis. Their average age was 65 years (44–80), and 9 were male individuals. Thirteen of the 15 patients (87%) developed varying degrees of hyponatremia. Laboratory studies demonstrated low serum osmolality, low serum blood urea nitrogen, and low uric acid, with a high urinary sodium and inappropriately high urine osmolality, supporting the presumable diagnosis of SIADH. One patient with hyponatremia that was tested, had high levels of copeptin, supporting the diagnosis of SIADH. In addition to hyponatremia, 7 patients (47%) exhibited other electrolyte abnormalities; 5 patients (33%) had overt hypophosphatemia, 4 patients (27%) had overt hypomagnesemia, and 2 other patients (13%) had borderline low magnesium levels. Western blot analysis of human kidney lysate, mass spectrometry, and qRT-PCR failed to demonstrate the expression of LGI1 protein in the kidney.

Discussion: Hyponatremia in patients with anti-LGI1 antibody encephalitis is due to SIADH as previously assumed. Other electrolyte abnormalities such as hypomagnesemia and hypophosphatemia occur in at least 40% of patients and may be another clue for the diagnosis of anti-LGI1 antibody encephalitis. Because we failed to demonstrate LGI1 expression in the kidney, the results of our study suggest that renal losses lead to these disturbances, most probably due to SIADH.

Gadoth A, et al. Electrolyte Imbalance in Anti-LGI1 Encephalitis: It Is Not All in Your Head. Neurol Neuroimmunol Neuroinflamm. 2023;10(6):e200155. Published 2023 Aug 17. doi:10.1212/NXI.0000000000200155.

Other autoimmune encephalitis

Anti-Ma2 encephalitis

Abstract: Antibodies against the neuronal protein Ma2 have been reported in a peculiar form of paraneoplastic encephalitis with prominent involvement of the limbic, brainstem, and diencephalic structures and usually associated with germ cell testicular, lung, or breast cancer. The diagnosis is frequently challenged by atypical clinical manifestations including parkinsonism, sleep disturbances, hypothalamic-pituitary dysfunctions, and motor neuron-like syndrome. In recent years, the advent of monoclonal antibodies targeting immune checkpoints has deeply changed the treatment of different tumors, especially melanoma and lung cancer. However, given their nature, an increasing number of neurological immune-related adverse events, including ocular motor abnormalities, have been described. Here, we report a woman with advanced non-small cell lung cancer treated with anti-PD-L1 durvalumab, presenting with an isolated pendular torsional nystagmus, in association with anti-Ma2 antibodies. This peculiar case widens our knowledge on the clinical presentation of anti-Ma2 encephalitis associated with checkpoint inhibitors.

Vaghi G, et al. A Case of Anti-Ma2 Encephalitis Presenting with Pendular Torsional Nystagmus. Cerebellum. 2024;23(3):1249-1253. doi:10.1007/s12311-023-01601-w

Cerebral cortical encephalitis

Abstract: Cerebral cortical encephalitis (CCE) is a recently described myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) phenotype. In this observational retrospective study, we characterized 19 CCE patients (6.7% of our MOGAD cohort). Headache (n = 15, 79%), seizures (n = 13, 68%), and encephalopathy (n = 12, 63%) were frequent. Magnetic resonance imaging revealed unilateral (n = 12, 63%) or bilateral (n = 7, 37%) cortical T2 hyperintensity and leptomeningeal enhancement (n = 17, 89%). N-Methyl-D-aspartate receptor autoantibodies coexisted in two of 15 tested (13%). CCE pathology (n = 2) showed extensive subpial cortical demyelination (n = 2), microglial reactivity (n = 2), and inflammatory infiltrates (perivascular, n = 1; meningeal, n = 1). Most received high-dose steroids (n = 17, 89%), and all improved, but three had CCE relapses. This study highlights the CCE spectrum and provides insight into its pathogenesis.

Valencia-Sanchez C, et al. "Cerebral Cortical Encephalitis in Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease." Annals of neurology vol. 93,2 (2023): 297-302. doi:10.1002/ana.26549.

Autoimmune encephalitis during pregnancy

Abstract: Several reports have described the autoimmune encephalitis' (AE) possible onset during pregnancy. In this systematic review, we summarize the available data on the diagnostic and therapeutic approach to AE during pregnancy, highlighting the associated maternal and fetal clinical outcomes. A systematic search of the literature was performed. The following databases were used: PubMed, Google Scholar, EMBASE, and CrossRef. The revision was registered on the PROSPERO platform (CRD42022336357). Forty-nine patients were included. AE onset was mainly observed during the first and the second trimester of pregnancy with psychiatric manifestations and seizures as main onset symptoms. CSF analysis showed AE-specific autoantibody positivity in 33 patients (anti-NMDA receptor as the most frequent). EEG generally showed normal findings. MRI revealed pathological findings in less than half of patients. Tumor screening was positive in 14 cases. First-line immunotherapy (single or combined) was generally employed while second line was administered in a minority of patients. Levetiracetam was the most used antiseizure medication. Cesarean section was performed in 18 women. Most of the women had an excellent early outcome after delivery but 22 showed persistent neurological deficits in long-term follow-up. Fetal outcome was positive in 33 cases, whereas 12 cases of fetal death were reported. A logistic regression showed that no variable significantly influenced the odds of good/bad maternal and fetal clinical outcome. Diagnosis and treatment of AE during pregnancy is challenging. The rate of miscarriage in women with AE seems to be higher than the general population. In addition, mothers may show long-term neurological deficits.

Dono F, et al. "Autoimmune encephalitis during pregnancy: A diagnostic and therapeutic challenge-A systematic review with individual patients' analysis and clinical recommendations." Epilepsia open vol. 8,4 (2023): 1221-1240. doi:10.1002/epi4.12806.

Autoimmune encephalitis with anti-amphiphysin antibodies

Objective: An analysis of the clinical features of autoimmune encephalitis accompanied by anti-amphiphysin antibodies.

Methods: The data of encephalitis patients with anti-amphiphysin antibodies were retrospectively evaluated, including demographics, neurological and laboratory findings, imaging, treatment, and prognostic predictions.

Results: Ten patients aged between 29 and 78 years (median age 52 years) were included. The male: female ratio was 4:6. Limbic encephalitis was found in nine patients while epileptic seizures were present in seven patients. All patients showed anti-amphiphysin antibody positivity in sera while one

ninth was positive for CSF antibody. The EEG findings were abnormal, including reductions in background activity, and the presence of diffuse slow waves, sharp waves, and spikes and waves. Five patients showed signs of increased T2 signals in the medial temporal lobe on MRI while PET showed either hyper- or hypo-metabolic changes in several brain regions, including the temporal lobe, hippocampus, basal ganglia, frontal and parietal cortices. Nine of ten patients were treated with immunotherapy, with improvements of varying degrees. There was a significant reduction in seizure frequency, and all patients were seizure-free at last follow-up.

Conclusion: Autoimmune encephalitis with anti-amphiphysin antibodies has a variety of clinical manifestations. The most common symptom is limbic encephalitis. Although relief from seizures can be achieved relatively easily, many patients suffer psychiatric, cognitive, and sleep sequelae. The disease was found to be associated with a lower incidence of cancer than has been previously reported for paraneoplastic neurologic syndromes.

Sun Y, et al. "Anti-amphiphysin encephalitis: Expanding the clinical spectrum." Frontiers in immunology vol. 14 1084883. 5 Apr. 2023, doi:10.3389/fimmu.2023.1084883.

Anti-GABA$_B$ receptor encephalitis

Background and Objectives: Existing evidence indicates anti-GABA$_B$ receptor encephalitis (GABA$_B$R-E) seems to occur more commonly later in life, yet the age-associated differences in clinical features and outcomes are not well determined. This study aims to explore the demographic, clinical characteristics, and prognostic differences between late-onset and early-onset GABA$_B$R-E and identify predictors of favorable long-term outcomes.

Methods: This is an observational retrospective study conducted in 19 centers from China. Data from 62 patients with GABA$_B$R-E were compared between late-onset (aged 50 years or older) and early-onset (younger than 50 years) groups and between groups with favorable outcomes (modified Rankin scale (mRS) ≤ 2) and poor outcomes (mRS >2). Logistic regression analyses were applied to identify factors affecting long-term outcomes.

Results: Forty-one (66.1%) patients experienced late-onset GABABR-E. A greater proportion of males, a higher mRS score at onset, higher frequencies of ICU admission and tumors, and a higher risk of death were demonstrated in the late-onset group than in the early-onset group. Compared with poor outcomes, patients with favorable outcomes had a younger onset age, a lower mRS score at onset, lower frequencies of ICU admission and tumors, and a greater proportion with immunotherapy maintenance for at least six months. On multivariate regression analysis, age at onset (OR, 0.849, 95% CI 0.739–0.974, p = 0.020) and the presence of underlying tumors (OR, 0.095, 95% CI 0.015–0.613, p = 0.013) were associated with poorer long-term outcomes, whereas immunotherapy maintenance for at least six months was associated with favorable outcomes (OR, 10.958, 95% CI 1.469–81.742, p = 0.020).

Discussion: These results demonstrate the importance of risk stratification of $GABA_B$R-E according to age at onset. More attention should be paid to older patients especially with underlying tumors, and immunotherapy maintenance for at least six months is recommended to achieve a favorable outcome.

Sun T, et al. Late-Onset Anti-GABA B Receptor Encephalitis: Clinical Characteristics and Outcomes Differing From Early-Onset Patients. Neurol Neuroimmunol Neuroinflamm. 2023 May 25;10(4):e200131. doi: 10.1212/NXI.0000000000200131. PMID: 37230544; PMCID: PMC10211328.

Thymoma-associated autoimmune encephalitis

Song et al. discusses thymoma-associated autoimmune encephalitis (AE) with a systematic review of 2013-2023 thymoma-associated AE case reports for its therapeutic approaches and factors affecting its prognosis. Of the 68 patients involved, several clinical features dominated: cognitive changes (70.6%), epilepsy (50%), mental disorders (57.4%), motor disorders (29.4%), language disorders (25%), altered consciousness (29.4%), autonomic dysregulation (19.1%), sleep conditions (13.2%), fever (4.4%), headaches (4.44%), and dizziness (4.4%). Most patients tested positive for amino-3-hydroxy-5-methyl-4-isoazole propionic acid receptor (AMPAR) (28%), and of the 81% with magnetic resonance imaging (MRI) abnormalities, lesions were focal to the hippocampus and temporal lobe. Abnormal electroencephalogram (EEG) showed slow wave and sharp wave emissions at the frontotemporal lobe (69.8%). Most patients were treated with hormone, gamma globulin, or plasmapheresis immunotherapy (82%), and 79.7% displayed improvement in presentations after treatment. Prevalence in specific clinical features led researchers to conclude that thymoma-associated AE is a separate AE classification. Researchers also called for a needed focus in future research on the consequences of specific symptoms, comorbid conditions, and surgical cognitions on recurrence and the course of treatment.

Song W, et al. Thymoma-associated autoimmune encephalitis: Analysis of factors determining prognosis. CNS Neurosci Ther. 2023;29(5):1213-1221. doi:10.1111/cns.14166

Autoimmune limbic encephalitis (ALE)

Objectives: It is assumed that autoimmune limbic encephalitis (ALE) demonstrates distinct neuropsychological manifestations with differential responses to immunotherapy according to which associated autoantibody (AAB), if any, is identified. Towards investigating whether this is the case, this study aims to summarize respective findings from the primary literature on ALE with AABs binding to cell surface neural antigens and ALE with AABs against intracellular neural antigens.

Methods: We chose ALE with AABs against leucine-rich, glioma inactivated protein 1 (LGI1) and contactin-associated protein-like 2 (CASPR2) as the most frequent cell surface membrane antigens, and ALE with AABs to Embryonic Lethal, Abnormal Vision, Like 1 (ELAVL) proteins (anti-Hu) and glutamic acid decarboxylase 65 (GAD65) as the most frequent intracellular neural antigens. The PubMed and Scopus databases were searched on March 1st, 2021 for neuropsychological test and -screening data from patients with ALE of these AAB-types. Findings were reviewed according to AAB-type and immunotherapy status and are presented in a review section and are further statistically evaluated and presented in a meta-analysis section in this publication.

Results: Of the 1304 initial hits, 32 studies on ALE with AABs against LGI1, CASPR2, and GAD65 reporting cognitive screening data could be included in a review. In ALE with AABs against LGI1, CASPR2 and GAD65, memory deficits are the most frequently reported deficits. However, deficits in attention and executive functions including working memory, fluency, and psychological function have also been reported. This review shows that ALE patients with AABs against both LGI1 and CASPR2 show higher percentages of neuropsychological deficits compared to ALE patients with AABs against GAD65 before and after initiation of immunotherapy. However, the methodologies used in these studies were heterogenous, and longitudinal studies were not comparable. Moreover, 21 studies including ALE patients with AABs against LGI1 and GAD65 were also suitable for meta-analysis. No suitable study on ALE with AABs against ELAVL proteins could be identified. Meta-Analyses could be executed for cognitive screening data and only partially, due to the small number of studies. However, in statistical analysis no consistent effect of AAB or immunotherapy on performance in cognitive screening tests could be found.

Conclusion: Currently, there is no definite evidence supporting the notion that different AAB-types of ALE exhibit distinct neuropsychological manifestations and respond differently to immunotherapy. Overall, we could not identify evidence for any effect of immunotherapy on cognition in ALE. More systematic, in-depth and longitudinal neuropsychological assessments of patients with different AAB-types of ALE are required in the future to investigate these aspects.

Mueller C, et al. Review and meta-analysis of neuropsychological findings in autoimmune limbic encephalitis with autoantibodies against LGI1, CASPR2, and GAD65 and their response to immunotherapy. Clin Neurol Neurosurg. 2023 Jan;224:107559. doi:10.1016/j.clineuro.2022.107559. Epub 2022 Dec 11. PMID: 36549220.

Sleep disturbances in autoimmune encephalitis

Koo et al reported the clinical importance of sleep disturbances in autoimmune encephalitis (AE), specifically anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis, Morvan syndrome, and anti-immunoglobulin-like cell adhesion molecule 5 (anti-lgLON5) disease. The research summated the types of sleep disorders prevalent in autoimmune encephalitis. Hypersomnia, characteristic of excessive daytime sleepiness, is present in the recovery phase of anti-NMDA receptor encephalitis, anti-amino-3-hydroxy-3-methyl-4-isoxa`olepropionic acid receptor encephalitis, anti-dipeptidyl-peptidase-like protein 6 (DPPX) encephalitis, and anti-IgLON5 disease. Narcolepsy with cataplexy is present in cases of anti-Ma2 encephalitis and narcolepsy alone reported in autoimmune encephalitis with anti-aquaporin-4 IgG antibody. Insomnia is common in anti-NMDA receptor, anti-contactin-associated protein-like 2 (anti-Caspr2), and anti-leucine-rich glioma inactivated 1 (LGH1) autoimmune encephalitis; it is often concurrent with hallucinations and irregular behaviour. Obstructive sleep apnoea (OSA) disorders have been noted in anti-DPPX, anti-LGI1, and anti-IgLON5 encephalitis, and REM sleep behaviour disorder, presenting with parasomnia, has been found in anti-DPPX, anti-LGI1, anti-Caspr2, anti-Ma2, and anti-IgLON5. Periodic limb movements during sleep (PLMS) is reportedly associated with anti-IgLON5, anti-DPPX, anti0LGH, and anti-Ma1/Ma2 encephalitis. Finally, restless legs syndrome is linked to anti-LGH and anti-Ma1/Ma2 encephalitis. The researchers discussed sleep disorders' crucial manifestation in autoimmune encephalitis and the importance of its understanding in assessment, diagnosis, and treatment to enhance AE intervention outcomes.

Koo DL. Sleep disturbances in autoimmune encephalitis. Encephalitis. 2023;3(1):1-6. doi:10.47936/encephalitis.2022.00073

Autoimmune encephalitis antibodies with presumed dementia

Background & Objectives: Autoimmune encephalitis (AIE) may present with prominent cognitive disturbances without overt inflammatory changes in MRI and CSF. Identification of these neurodegenerative dementia diagnosis mimics is important because patients generally respond to immunotherapy. The objective of this study was to determine the frequency of neuronal antibodies in patients with presumed neurodegenerative dementia and describe the clinical characteristics of the patients with neuronal antibodies.

Methods: In this retrospective cohort study, 920 patients were included with neurodegenerative dementia diagnosis from established cohorts at 2 large Dutch academic memory clinics. In total, 1,398 samples were tested (both CSF and serum in 478 patients) using immunohistochemistry (IHC), cell-based assays (CBA), and live hippocampal cell cultures (LN). To ascertain specificity and prevent false positive results, samples had to test positive by at least 2 different research techniques. Clinical data were retrieved from patient files.

Results: Neuronal antibodies were detected in 7 patients (0.8%), including anti-IgLON5 (n = 3), anti-LGI1 (n = 2), anti-DPPX, and anti-NMDAR. Clinical symptoms atypical for neurodegenerative diseases were identified in all 7 and included subacute deterioration (n = 3), myoclonus (n = 2), a history of autoimmune disease (n = 2), a fluctuating disease course (n = 1), and epileptic seizures (n = 1). In this cohort, no patients with antibodies fulfilled the criteria for rapidly progressive dementia (RPD), yet a subacute deterioration was reported in 3 patients later in the disease course. Brain MRI of none of the patients demonstrated abnormalities suggestive for AIE. CSF pleocytosis was found in 1 patient, considered as an atypical sign for neurodegenerative diseases. Compared with patients without neuronal antibodies (4 per antibody-positive patient), atypical clinical signs for neurodegenerative diseases were seen more frequently among the patients with antibodies (100% vs 21%, p = 0.0003), especially a subacute deterioration or fluctuating course (57% vs 7%, p = 0.009).

Discussion: A small, but clinically relevant proportion of patients suspected to have neurodegenerative dementias have neuronal antibodies indicative of AIE and might benefit from immunotherapy. In patients with atypical signs for neurodegenerative diseases, clinicians should consider neuronal antibody testing. Physicians should keep in mind the clinical phenotype and confirmation of positive test results to avoid false positive results and administration of potential harmful therapy for the wrong indication.

Bastiaansen AEM, et al. "Antibodies Associated With Autoimmune Encephalitis in Patients With Presumed Neurodegenerative Dementia." Neurology(R) neuroimmunology & neuroinflammation vol. 10,5 e200137. 13 Jun. 2023, doi:10.1212/NXI.0000000000200137.

Seizures and encephalitis

Paediatric autoimmune encephalitis

This study aimed to characterise seizure incidence and outcomes in paediatric autoimmune encephalitis (AE). Among 110 paediatric patients with AE, the team compared seizure characteristics and outcomes in 68 patients with seizure who satisfied the proposed criteria of paediatric AE. Seizure incidence in the anti-NMDAR (88.9%) and Ab-negative (71.1%) groups differed from anti-MOG group (37.8%). Median seizure frequency within six months was higher in the Ab-negative group (6.0, interquartile range [IQR] 3.0 to 13.0) than in the anti-NMDAR group (3.0, IQR 2.0 to 4.5) and anti-MOG group (2.0, IQR 1.0 to 5.0). Patients in the Ab-negative group tended to develop postencephalitic seizures more frequently and have a lower seizure freedom rate than those in the anti-NMDAR and anti-MOG groups. Ab-negative status, high seizure frequency within six months, and the presence of status epilepticus were associated with the development of postencephalitic seizures on univariate analysis. On multivariate analysis, Ab-negative status remained the only significant variable linked with postencephalitic seizure (odds ratio, 4.17; 95% confidence interval, 1.02 to 18.05). The team concluded that Ab-negative statis is predictive of higher seizure burden, more frequent development of postencephalitic seizures, and less favourable seizure outcome than anti-NMDAR and anti-MOG Ab-positive status.

Woo H, et al. "Seizure Evolution and Outcome in Pediatric Autoimmune Encephalitis." Pediatric neurology vol. 139 (2023): 35-42. doi:10.1016/j.pediatrneurol.2022.11.008.

Viral encephalitis

Objective: To systematically evaluate the risk factors of post-encephalitis epilepsy (PEE).

Methods: Systematic computerized searches of databases such as Cochrane Library, PubMed and EMBASE were performed. The meta-analysis of pooled odds ratios and 95% confidence intervals for PEE risk were calculated.

Results: Sixteen studies with 2504 patients were included for meta-analysis. The results showed that PEE was associated with coma, seizure, status epilepticus, cranial MRI abnormality, focal EEG abnormality, and positive herpes simplex virus (HSV) in cerebrospinal fluid (CSF).

Conclusion: Coma, seizures or status epilepticus, abnormal MRI and focal EEG, and HSV in CSF were the risk factors of PEE.

Yang Q, Wei B. Risk factors of epilepsy secondary to viral encephalitis: A meta-analysis. J Neuroimmunol. 2023 May 15;378:578089. doi:10.1016/j.jneuroim.2023.578089. Epub 2023 Apr 11. PMID: 37094438.

Diagnosis and treatment of encephalitis

Severe autoimmune encephalitis

Background and purpose: To investigate severe autoimmune encephalitis (AE) in the intensive care unit (ICU) with regard to standard treatment in responsive patients and additional escalation therapies for treatment-refractory cases.

Methods: This retrospective, single-center study analyzed medical records of ICU-dependent AE patients for clinical characteristics, treatments, prognostic factors, and neurological outcome as quantified by modified Rankin Scale (mRS) and Clinical Assessment Scale for Autoimmune Encephalitis (CASE).

Results: From 40 enrolled patients (median age = 52 years; range = 16-89 years) with AE mediated by neuronal surface antibodies (nsAb; 90%) and AE with onconeuronal antibodies (10%), 98% received first-line therapy. Of those, 62% obtained additional second-line therapy, and 33% received escalation therapy with bortezomib and/or daratumumab. Good neurological outcome, defined as mRS = 0-2, was observed in 47% of AE with nsAb (CASE = 5), 77% of anti-N-methyl D-aspartate receptor encephalitis patients (CASE = 1), whereas AE patients with onconeuronal antibodies had the poorest outcome (mRS = 6, 100%). Treatment-refractory AE patients with nsAb requiring escalation therapy achieved similarly good recovery (mRS = 0-2, 39%, CASE = 3) as patients improving without (mRS = 0-2, 54%, CASE = 4), although they presented a higher disease severity at disease maximum (mRS = 5 100% versus 68%, CASE = 24 versus 17; p = 0.0036), had longer ICU stays (97 versus 23 days; p = 0.0002), and a higher survival propability during follow-up (p = 0.0203). Prognostic factors for good recovery were younger age (p = 0.025) and lack of preexisting comorbidities (p = 0.011).

Conclusions: Our findings suggest that treatment-refractory AE patients with nsAb in the ICU can reach similarly good outcomes after plasma cell-depleting escalation therapy as patients already responding to standard first- and/or second-line therapies.

Schwarz L, et al. "Clinical characteristics, treatments, outcome, and prognostic factors of severe autoimmune encephalitis in the intensive care unit: Standard treatment and the value of additional plasma cell-depleting escalation therapies for treatment-refractory patients." European journal of neurology vol. 30,2 (2023): 474-489. doi:10.1111/ene.15585.

Steroids and IV immunoglobulin for the treatment of encephalitis

Background: Specific antiviral treatment is only available for a small subset of viral encephalitis (VE). Adjunctive steroids are used, but there is scant evidence evaluating its utility. We present a systematic review and meta-analysis on the outcome of steroid use in VE.

Methods: We conducted a systematic literature review and reported it according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards. Two observational studies from unpublished or partially published data were added. For the meta-analysis, we employed the metaphor package of the statistical software R-4.3.1.

Results: We screened 378 studies and included 50. 155 patients were added from the Houston and Linz cohorts. Individual data were available for 281 persons, 120 (43%) of whom received steroids. The most common pathogens were herpes simplex virus 1, West Nile virus, and measles. Study designs and patient outcomes were heterogeneous. Only three of the trials report an advantage of steroid therapy. Steroid-induced side effects were scarce. Ten cohorts were included into the meta-analysis. For the pooled data, the null hypothesis could not be rejected (p=0.245) using a random effects model, i.e., a benefit of steroid treatment on survival in VE could not be shown.

Conclusions: Steroids as potent anti-inflammatory agents may act through a reduction of secondary inflammation-mediated damage. Our data do not support the use of steroids in VE. However, multiple shortcomings apply. Standardized controlled trials are needed to investigate optimal dosing and timing of steroid administration and to explore potential subgroups that could benefit.

Hodzic E, et al. Steroids for the treatment of viral encephalitis: a systematic literature review and meta-analysis. J Neurol. 2023 Jul;270(7):3603-3615. doi:10.1007/s00415-023-11715-0. Epub 2023 Apr 15. PMID: 37060361; PMCID: PMC10105360.

Objective: To investigate whether intravenous immunoglobulin (IVIG) improves neurological outcomes in children with encephalitis when administered early in the illness.

Design: Phase 3b multicentre, double-blind, randomised placebo-controlled trial.

Setting: Twenty-one hospitals in the UK.

Participants: Children aged 6 months to 16 years with a diagnosis of acute or subacute encephalitis, with a planned sample size of 308.

Intervention: Two doses (1 g/kg/dose) of either IVIG or matching placebo given 24-36 hours apart, in addition to standard treatment.

Main outcome measure: The primary outcome was a 'good recovery' at 12 months after randomisation, defined as a score of≤2 on the Paediatric Glasgow Outcome Score Extended.

Secondary outcome measures: The secondary outcomes were clinical, neurological, neuroimaging and neuropsychological results, identification of the proportion of children with immune-mediated encephalitis, and IVIG safety data.

Results: 18 participants were recruited from 12 hospitals and randomised to receive either IVIG (n=10) or placebo (n=8) between 23 December 2015 and 26 September 2017. The study was terminated early following withdrawal of funding due to slower than anticipated recruitment, and therefore did not reach the predetermined sample size required to achieve the primary study objective; thus, the results are descriptive. At 12 months after randomisation, 9 of the 18 participants (IVIG n=5/10 (50%), placebo n=4/8 (50%)) made a good recovery and 5 participants (IVIG n=3/10 (30%), placebo n=2/8 (25%)) made a poor recovery. Three participants (IVIG n=1/10 (10%), placebo n=2/8 (25%)) had a new diagnosis of epilepsy during the study period. Two participants were found to have specific autoantibodies associated with autoimmune encephalitis. No serious adverse events were reported in participants receiving IVIG.

Conclusions: The IgNiTE (ImmunoglobuliN in the Treatment of Encephalitis) study findings support existing evidence of poor neurological outcomes in children with encephalitis. However, the study was halted prematurely and was therefore underpowered to evaluate the effect of early IVIG treatment compared with placebo in childhood encephalitis.

Iro MA, et al. "ImmunoglobuliN in the Treatment of Encephalitis (IgNiTE): protocol for a multicentre randomised controlled trial." BMJ open vol. 6,11 e012356. 3 Nov. 2016, doi:10.1136/bmjopen-2016-012356.

Misdiagnosis and mimics of autoimmune encephalitis (AE)

The diagnosis of autoimmune encephalitis (AE) requires reasonable exclusion of other conditions. The aim of this study was to characterise mimickers and misdiagnoses of AE. To this end, the researchers performed an independent PubMed search for mimickers of AEs or patients with alternative neurological disorders misdiagnosed as AE. The team found that lack of fulfilment of diagnostic criteria for AE, atypical neuroimaging findings, non-inflammatory CSF findings, non-specific autoantibody specificities, and partial response to immunotherapy were major confounding factors.

Dinoto A, et al. "Autoimmune encephalitis misdiagnosis and mimics." Journal of neuroimmunology vol. 378 (2023): 578071. doi:10.1016/j.jneuroim.2023.578071.

Objective: To determine the diseases misdiagnosed as autoimmune encephalitis and potential reasons for misdiagnosis. Design, Setting, and Participants: This retrospective multicenter study took place from January 1, 2014, to December 31, 2020, at autoimmune encephalitis subspecialty outpatient clinics including Mayo Clinic (n=44), University of Oxford (n=18), University of Texas Southwestern (n=18), University of California, San Francisco (n=17), Washington University in St Louis (n=6), and University of Utah (n=4). Inclusion criteria were adults (age ≥18 years) with a prior autoimmune encephalitis diagnosis at a participating center or other medical facility and a subsequent alternative diagnosis at a participating center. A total of 393 patients were referred with an autoimmune encephalitis diagnosis, and of those, 286 patients with true autoimmune encephalitis were excluded.

Main Outcomes and Measures: Data were collected on clinical features, investigations, fulfillment of autoimmune encephalitis criteria, alternative diagnoses, potential contributors to misdiagnosis, and immunotherapy adverse reactions.

Results: A total of 107 patients were misdiagnosed with autoimmune encephalitis, and 77 (72%) did not fulfill diagnostic criteria for autoimmune encephalitis. The median (IQR) age was 48 (35.5-60.5) years and 65 (61%) were female. Correct diagnoses included functional neurologic disorder (27 [25%]), neurodegenerative disease (22 [20.5%]), primary psychiatric disease (19 [18%]), cognitive deficits from comorbidities (11 [10%]), cerebral neoplasm (10 [9.5%]), and other (18 [17%]). Onset was acute/subacute in 56 (52%) or insidious (>3 months) in 51 (48%). Magnetic resonance imaging of the brain was suggestive of encephalitis in 19 of 104 patients (18%) and cerebrospinal fluid (CSF) pleocytosis occurred in 16 of 84 patients (19%). Thyroid peroxidase antibodies were elevated in 24 of 62 patients (39%). Positive neural autoantibodies were more frequent in serum than CSF (48 of 105 [46%] vs 7 of 91 [8%]) and included 1 or more of GAD65 (n=14), voltage-gated potassium channel complex (LGI1 and CASPR2 negative) (n=10), N-methyl-d-aspartate receptor by cell-based assay only (n=10; 6 negative in CSF), and other (n=18). Adverse reactions from immunotherapies occurred in 17 of 84 patients (20%). Potential contributors to misdiagnosis included overinterpretation of positive serum antibodies (53 [50%]), misinterpretation of functional/psychiatric, or nonspecific cognitive dysfunction as encephalopathy (41 [38%]).

Conclusions and Relevance: When evaluating for autoimmune encephalitis, a broad differential diagnosis should be considered and misdiagnosis occurs in many settings including at specialized centers. In this study,

red flags suggesting alternative diagnoses included an insidious onset, positive nonspecific serum antibody, and failure to fulfill autoimmune encephalitis diagnostic criteria. Autoimmune encephalitis misdiagnosis leads to morbidity from unnecessary immunotherapies and delayed treatment of the correct diagnosis.

Flanagan EP, et al. Autoimmune Encephalitis Misdiagnosis in Adults. JAMA Neurol. 2023;80(1):30-39. doi:10.1001/jamaneurol.2022.4251.

Background and objectives: The clinical criteria for autoimmune encephalitis (AE) were proposed by Graus et al. in 2016. In this study, the AE criteria were validated in the real world, and common AE mimics were described. In addition, criteria for probable anti-LGI1 encephalitis were proposed and validated.

Methods: In this retrospective cohort study, patients referred to our national referral center with suspicion of AE and specific neuroinflammatory disorders with similar clinical presentations were included from July 2016 to December 2019. Exclusion criteria were pure cerebellar or peripheral nerve system disorders. All patients were evaluated according to the AE criteria.

Results: In total, 239 patients were included (56% female; median age 42 years, range 1-85). AE was diagnosed in 104 patients (44%) and AE mimics in 109 patients (46%). The most common AE mimics and misdiagnoses were neuroinflammatory CNS disorders (26%), psychiatric disorders (19%), epilepsy with a noninflammatory cause (13%), CNS infections (7%), neurodegenerative diseases (7%), and CNS neoplasms (6%). Common confounding factors were mesiotemporal lesions on brain MRI (17%) and false-positive antibodies in serum (12%). Additional mesiotemporal features (involvement extralimbic structures, enhancement, diffusion restriction) were observed more frequently in AE mimics compared with AE (61% vs 24%; p = 0.005). AE criteria showed the following sensitivity and specificity: possible AE, 83% (95% CI 74-89) and 27% (95% CI 20-36); definite autoimmune limbic encephalitis (LE), 10% (95% CI 5-17) and 98% (95% CI 94-100); and probable anti-NMDAR encephalitis, 50% (95% CI 26-74) and 96% (95% CI 92-98), respectively. Specificity of the criteria for probable seronegative AE was 99% (95% CI 96-100). The newly proposed criteria for probable anti-LGI1 encephalitis showed a sensitivity of 66% (95% CI 47-81) and specificity of 96% (95% CI 93-98).

Discussion: AE mimics occur frequently. Common pitfalls in AE misdiagnosis are mesiotemporal lesions (predominantly with atypical features) and false-positive serum antibodies. As expected, the specificity of the criteria for possible AE is low because these criteria represent the minimal requirements for entry in the diagnostic algorithm for AE. Criteria for probable AE (-LGI1, -NMDAR, seronegative) and definite autoimmune LE are applicable for decisions on immunotherapy in early disease stage, as specificity is high.

Van Steenhoven RW, et al. "Mimics of Autoimmune Encephalitis: Validation of the 2016 Clinical Autoimmune Encephalitis Criteria." Neurology(R) neuroimmunology & neuroinflammation vol. 10,6 e200148. 15 Aug. 2023, doi:10.1212/NXI.0000000000200148.

In this study the researchers highlight increasing awareness of autoimmune encephalitis has led to two unintended consequences: high frequency of misdiagnoses and inappropriate use of diagnostic criteria for antibody-negative disease. The authors contend that misdiagnoses typically occur for three reasons: non-adherence to reported clinical requirements for considering a disorder as possible autoimmune encephalitis; inadequate assessment of inflammatory changes in brain MRI and CSF; and absent or limited use of brain tissue assays. Accurate diagnosis of purported antibody-negative autoimmune encephalitis will identify patients with similar syndromes and biomarkers which will provide homogenous populations for future assessments of treatment response and outcome.

Dalmau J, et al. "Diagnostic criteria for autoimmune encephalitis: utility and pitfalls for antibody-negative disease." The Lancet. Neurology vol. 22,6 (2023): 529-540. doi:10.1016/S1474-4422(23)00083-2.

Clinical predictors and imaging in encephalitis

Objectives: Encephalitis, brain inflammation and swelling, most often caused by an infection or the body's immune defences, can have devastating consequences, especially if diagnosed late. We looked for clinical predictors of different types of encephalitis to help clinicians consider earlier treatment.

Methods: We conducted a multicentre prospective observational cohort study (ENCEPH-UK) of adults (> 16 years) with suspected encephalitis at 31 UK hospitals. We evaluated clinical features and investigated for infectious and autoimmune causes.

Results: 341 patients were enrolled between December 2012 and December 2015 and followed up for 12 months. 233 had encephalitis, of whom 65 (28%) had HSV, 38 (16%) had confirmed or probable autoimmune encephalitis, and 87 (37%) had no cause found. The median time from admission to 1st dose of aciclovir for those with HSV was 14 hours (IQR 5-50); time to 1st dose of immunosuppressant for the autoimmune group was 125 hours (IQR 45-250). Compared to non-HSV encephalitis, patients with HSV more often had fever, lower serum sodium and lacked a rash. Those with probable or confirmed autoimmune encephalitis were more likely to be female, have abnormal movements, normal serum sodium levels and a cerebrospinal fluid white cell count < 20 cells x106/L, but they were less likely to have a febrile illness.

Conclusions: Initiation of treatment for autoimmune encephalitis is delayed considerably compared with HSV encephalitis. Clinical features can help identify patients with autoimmune disease and could be used to initiate earlier presumptive therapy.

Defres S, et al. Clinical predictors of encephalitis in UK adults-A multi-centre prospective observational cohort study. PLoS One. 2023;18(8):e0282645. Published 2023 Aug 23. doi:10.1371/journal.pone.0282645.

Bai et al. argue that the predictive power of conventional MRI requires improvement as conventional imaging characteristics are only present in a limited subset of patients with Autoimmune Encephalitis (AE). The researchers hypothesized that the identification of a universal pattern of facilitate the identification of AE, a pattern which is yet to be understood. They analysed the PET images of 42 AE patients and 45 healthy controls (HCs) performed between January 2015 and October 2022. They found no significant difference in age (p = 0.33) or sex (p = 0.84) between the AE and HC groups. The researchers found that there was a universal abnormal pattern. Using these findings, they proposed a novel classification model that facilitates the diagnosis of acute/subacute seropositive the team's findings cast new light on brain metabolism characteristics and optimise the methods for AE diagnosis with the PET technique.

Bai S, et al. A novel classification model based on cerebral 18F-FDG uptake pattern facilitates the diagnosis of acute/subacute seropositive autoimmune encephalitis. J Neuroradiol. 2023 Sep;50(5):492-501. doi: 10.1016/j.neurad.2023.05.001. Epub 2023 May 2. PMID: 37142216.

Toxoplasmic encephalitis

Background: Toxoplasmic encephalitis (TE) is an opportunistic infection of people with human immunodeficiency virus (HIV) or other causes of immunosuppression. Guideline-recommended treatments for TE are pyrimethamine and sulfadiazine (P-S) or pyrimethamine and clindamycin (P-C); however, a substantial price increase has limited access to pyrimethamine. Consequently, some centers have transitioned to trimethoprim-sulfamethoxazole (TMP-SMX), an inexpensive alternative treatment. We aimed to review the evidence on the efficacy and safety of pyrimethamine-containing therapies vs TMP-SMX.

Methods: We searched for and included randomized controlled trials (RCTs) and observational studies of TE treatments, regardless of HIV status. Data for each therapy were pooled by meta-analysis to assess the proportions of patients who experienced clinical and radiologic responses to treatment, all-cause mortality, and discontinuation due to toxicity. Sensitivity analyses limited to RCTs directly compared therapies.

Results: We identified 6 RCTs/dose-escalation studies and 26 single-arm/observational studies. Identified studies included only persons with HIV, and most predated modern antiretroviral treatment. Pooled proportions of clinical and radiologic response and mortality were not significantly different between TMP-SMX and pyrimethamine-containing regimens (P > .05). Treatment discontinuation due to toxicity was significantly lower in TMP-SMX (7.3%; 95% confidence interval [CI], 4.7-11.4; I2 = 0.0%) vs P-S (30.5%; 95% CI, 27.1-34.2; I2 = 0.0%; P < .01) or P-C (13.7%; 95% CI, 9.8-18.8; I2 = 32.0%; P = .031). These results were consistent in analyses restricted to RCT data.

Conclusions: TMP-SMX appears to be as effective and safer than pyrimethamine-containing regimens for TE. These findings support modern RCTs comparing TMP-SMX to pyrimethamine-based therapies and a revisiting of the guidelines.

Prosty C, et al. Revisiting the Evidence Base for Modern-Day Practice of the Treatment of Toxoplasmic Encephalitis: A Systematic Review and Meta-Analysis. Clin Infect Dis. 2023 Feb 8;76(3):e1302-e1319. doi: 10.1093/cid/ciac645. PMID: 35944134.

Outcomes of encephalitis

Tick-borne encephalitis

Purpose: Despite being vaccine-preventable, tick-borne encephalitis (TBE) continues to cause considerable morbidity in Germany. Limited insight into potentially debilitating consequences of TBE may partially underly low (~ 20%) TBE vaccine uptake. We aimed to systematically assess TBE sequelae and other consequences.

Methods: Routinely notified TBE patients from 2018 to 2020 from Southern Germany were invited to telephone interviews acutely and again after 18 months. Duration of acute symptoms was prospectively assessed. Recovery was defined as score 0 on the modified RANKIN scale. Determinants of time to recovery were analysed with cox regression, adjusted for covariates identified using directed acyclic graphs, yielding hazard ratios (HR) and 95% confidence intervals (CI).

Results: Of 558 cases, 523 (93.7%) completed follow-up. Full recovery was reported by 67.3% (children: 94.9%, adults: 63.8%). Sequelae included fatigue (17.0%), weakness (13.4%), concentration deficit (13.0%), and impaired balance (12.0%). Compared with 18-39-year-olds, recovery rates were 44% lower in ≥ 50-year-olds (HR: 0.56, 95%CI 0.42-0.75) and 79% higher in children (HR: 1.79, 95%CI 1.25-2.56). The recovery rate was 64% lower after severe TBE (compared to mild; HR: 0.36, 95%CI 0.25-0.52) and 22% lower with comorbidities (HR: 0.78, 95%CI 0.62-0.99). Substantial health-care use was reported (90.1% hospitalisation, 39.8% rehabilitation). Of employed cases, 88.4% required sick leave; 10.3% planned/reported premature retirement due to sequelae.

Conclusion: Half the adult and 5% of paediatric patients reported persisting sequelae after 18 months. Improved prevention could alleviate both individual (morbidity) and societal TBE burden (health-care costs, productivity losses). Insights into sequelae can help guide at-risk populations towards tick-avoidant strategies and encourage TBE vaccination.

Nygren TM, et al. "Recovery and sequelae in 523 adults and children with tick-borne encephalitis in Germany." Infection vol. 51,5 (2023): 1503-1511. doi:10.1007/s15010-023-02023-w.

Anti-NMDAR encephalitis

Aim: To study long-term clinical and cognitive outcomes of patients with anti-N-methyl-d- aspartate receptor encephalitis (NMDAR-E), an acute autoimmune neuro-logical disease with severe acute presentations.

Method: In this French multicentre retrospective observational cohort study, patients no older than 18 years with a follow-up of at least 2 years were included. Data from clinical and cognitive assessments were collected.

Results: Eighty-one patients were included (57 females, 24 males; median age 10 years 7 months [range 1–18 years], median follow-up 40 months [range 25–53 months]). At last follow-up, 35 patients (45%) had cognitive impairment, 48 (70%) had academic difficulties, and 65 (92%) needed rehabilitation. Seventy-one patients (88%) had amodified Rankin Scale score of no more than 2. A higher number of symptoms at diagnosis was associated with cognitive impairment (p = 0.01), while an abnormal electroencephalogram at diagnosis increased the risk of academic difficulties (p = 0.03).

Interpretation: Although most children with NMDAR-E seemed to recover from motor disabilities, more than 45% had cognitive and academic difficulties. The initial severity of symptoms seems to have an impact on cognition and academic performances.

Flet-Berliac L, et al. "Long-term outcome of paediatric anti-N-methyl-D-aspartate receptor encephalitis." Developmental medicine and child neurology vol. 65,5 (2023): 691-700. doi:10.1111/dmcn.15429.

Autoimmune encephalitis

This study by Yokota et al. investigated patient-oriented long-term outcomes and assessed the HRQOL of patients with autoimmune encephalitis (AE), to urgently evaluate the long-term effects of AE on patients' health-related quality of life (HRQOL). AE subacutely causes severe and multiple symptoms; however, most patients achieve neurologically favorable outcomes. Despite the substantial recovery in motor function, persistent impairments in mental/social aspects lasting for several years have been recognized, and its potential effect on HRQOL has been argued. Data of patients who were diagnosed with probable/definite AE, defined by Graus AE criteria 2016, and treated at their hospital between January 2011 and October 2020 were retrospectively retrieved. Their long-term (≥2 years)

outcomes, which included various sequelae and handicaps in social activities such as returning to previous work/school life through structured interview forms, were evaluated, and the HRQOL was assessed using Neuro-QOL battery. They identified 32 patients who met the Graus AE criteria 2016 and eventually enrolled 21 patients in the study. The median interval between disease onset and survey period was 63 (25–156) months, and 43% of the patients had persistent neuropsychiatric symptoms, including memory disorders, personality changes, and seizures. No more than 71% returned to their previous work/school life. Although most of the patients had global QOL within normal limits, 48% had social QOL under normal limits. Patients with sequelae were significantly less likely to return to previous work/school and had worse global/social quality of life than patients without sequelae. In conclusion, nearly half of patients with AE had social QOL under normal limits five years after onset. The difficulty in returning to work/school and a worse HRQOL were notable in patients with sequelae.

Yokota Y, et al. Long-term outcomes and health-related quality of life in patients with autoimmune encephalitis: An observational study. Medicine (Baltimore). 2023 Oct 6;102(40):e35162. doi:10.1097/MD.0000000000035162. PMID: 37800792; PMCID: PMC10553085.

Herpes simplex virus encephalitis

The objective of the study by Rocha et al. was to assess the general prevalence and types of neurological sequelae in children after a case of acute viral encephalitis caused by herpes simplex virus (HSV). Encephalitis is an inflammation of the cerebral parenchyma manifested by acute symptoms such as fever, headaches, and other neurological disorders. Its etiology is mostly viral, with HSV being a frequent etiological agent in children. The development of neurological sequelae is a serious outcome associated with this infection. This systematic review and meta-analysis was developed following the PRISMA guidelines. The literature search was carried out in the MEDLINE, Embase, SciELO, LILACS, Cochrane, CINAHL, PsycINFO, and Web of Science databases. Studies were included of children with confrmed HSV infection and that presented a description of neurological sequelae associated with that infection. For the meta-analysis of general prevalence and of the types of neurological sequelae a random effects model was used. Of the 2827 articles chosen in the initial search, nine studies were included in the systematic review and meta-analysis. The general prevalence of neurological sequelae was 50.7% (95% CI 39.2–62.2). The most frequent sequelae were related to mental disability, with a 42.1% prevalence (95% CI 30–55.2); on the other hand, the least frequent sequelae were those related with visual impairment, with a 5.9% prevalence (95% CI 2.2–14.6). The included studies presented regular quality and substantial heterogeneity. The authors concluded that, even with antiviral therapy, half of patients will develop some type of disability.

Rocha ND, et al. Neurological sequelae after encephalitis associated with herpes simplex virus in children: systematic review and meta-analysis. BMC Infect Dis. 2023 Jan 26;23(1):55. doi:10.1186/s12879-023-08007-3. PMID: 36703115; PMCID: PMC9878875.

Mental health problems following encephalitis

Background and purpose: Acute encephalitis is associated with psychiatric symptoms. Despite this, the extent of mental health problems following encephalitis has not been systematically reported.

Methods: We recruited adults who had been diagnosed with encephalitis of any aetiology to complete a web-based questionnaire.

Results: In total, 445 respondents from 31 countries (55.1% UK, 23.1% USA) responded. Infectious encephalitis constituted 65.4% of cases, autoimmune 29.7%. Mean age was 50.1 years, 65.8% were female, and median time since encephalitis diagnosis was seven years. The most common self-reported psychiatric symptoms were anxiety (75.2%), sleep problems (64.4%), mood problems (62.2%), and unexpected crying (35.2%). Self-reported psychiatric diagnoses were common: anxiety (44.0%), depression (38.6%), panic disorder (15.7%), and posttraumatic stress disorder (PTSD; 21.3%). Severe mental illnesses such as psychosis (3.3%) and bipolar affective disorder (3.1%) were reported. Self-reported diagnosis rates were broadly consistent with results from the Psychiatric Diagnostic Screening Questionnaire. Many respondents also reported they had symptoms of anxiety (37.5%), depression (28.1%), PTSD (26.8%), or panic disorder (20.9%) that had not been diagnosed. Rates of psychiatric symptoms did not differ between autoimmune and infectious encephalitis. In total, 37.5% respondents had thought about suicide, and 4.4% had attempted suicide, since their encephalitis diagnosis. More than half of respondents (53.5%) reported they had no, or substandard, access to appropriate mental health care. High rates of sensory hypersensitivities (>75%) suggest a previously unreported association.

Conclusions: This large international survey indicates that psychiatric symptoms following encephalitis are common and that mental health care provision may be inadequate. We highlight a need for proactive psychiatric input.

Butler M, et al. Mental health outcomes of encephalitis: An international web-based study. Eur J Neurol. 2024;31(1):e16083. doi:10.1111/ene.16083.

Help us to help the global encephalitis community

Encephalitis International is the only resource of its kind providing direct support and information to people affected by all types of encephalitis, raising awareness about the condition, and furthering our understanding of encephalitis through promoting and collaborating on research.

As a non-profit we are funded entirely by the support of our community, philanthropic organisations, trusts and foundations and our team of global fundraisers – every day people like you who are committed to supporting us.

Encephalitis International's fundraising team is determined to ensure our services are funded so we can continue to support people around the world who are facing the impact of encephalitis. There are many ways you can support us, both directly and indirectly.

- Could you take part in a challenge event?
- Do you know, or work for, an organisation that supports charities?
- Do you know a trust or foundation we can apply for funding from?
- Do you know an individual who may like to join our Changemakers community?

We are fortunate to have a global community of fundraisers undertaking a range of challenges for us, from sponsored walks and swims through to gaming marathons and birthday fundraisers. We also receive support from corporate partners, trusts, foundations and philanthropists across the world, who ensure the continuation of our support service, sponsor our events and campaigns, and support our appeals and initiatives like Changemakers – which aims to raise £100,000 a year to fund life-saving encephalitis research.

However you may be able to help, wherever you live in the world, it would be amazing to hear from you. Please get in touch!

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Get in touch!

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