RESEARCH SUMMARY

ADVANCES IN ENCEPHALITIS 2024

Encephalitis International

The brain inflammation non-profit

EPIDEMIOLOGY
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Welcome to Encephalitis International's Research Summary 2024

The Research Summary-Advances in Encephalitis 2024 presents a collection of research papers published during the same year.

The year 2024 has continued to see outbreaks of encephalitis across different regions and viral strains. New viral threats have emerged, including the Oropouche virus as an underestimated cause of infections in South America, due in part to a lack of diagnostic tests. Globally, Nipah virus mortality rates have shown a concerning increase to 80.1% in the 2014-2023 decade, representing a 24% increase compared to the previous decade. Powassan virus, an emerging flavivirus associated with neuroinvasive disease, has also been increasingly recognised in North America. In Australia, April saw the Murray Valley virus spreading to a new part of Western Australia, the Pilbara region. In Europe, tick-borne encephalitis virus continues to increase in prevalence, and here we have highlighted two particular reports from Italy and Norway.

Autoimmune encephalitis (AE) research has also expanded in 2024, with new findings on racial and ethnic disparities in anti-NMDAR encephalitis, showing disproportionately higher incidence rates in Black, Hispanic, and Asian/Pacific Island populations. Long-term outcome studies have provided crucial insights, including into less-widely reported as part of postencephalitis neurobehavioural syndrome.

Encephalitis International has continued its mission with global impact. To coincide with World Encephalitis Day 2025, the World Health Organization (WHO) published a Technical Brief on encephalitis to engage policymakers, public health officials, and researchers. This was inspired by a global report written by Encephalitis International, nearly two years of conversations, and input from many global stakeholders and key opinion leaders on encephalitis. To mark the occasion, we hosted a launch event with a panel of experts, including a representative from the WHO, to highlight what future global actions are needed to help reduce death and disability from encephalitis.

Our funding programme continued with two awards of seed funding to recipients in Asia and a second year Academic Clinical Fellowship in Neurology to Dr Abdusshakur Muhammad Auwal on his project to further understand the neurological pathophysiology of COVID-19 using functional magnetic resonance imaging (fMRI).

In our Encephalitis Conference 2025 we look forward to welcoming keynote speakers Dr Nicoline Schiess from the WHO and Prof Romana Höftberger from the Medical University of Vienna, Austria who will be respectively presenting on the WHO Technical Brief on Encephalitis and the contributions of pathology to understanding antibody-mediated neurological diseases. 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. For more information and to book your place, please visit: www.encephalitis.info/encephalitis-conference/

As always, 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, I would like to thank you for your interest in encephalitis and Encephalitis International. My gratitude extends to all those working to improve our understanding of this too-often devasting condition. While the research included here represents significant progress in our understanding of encephalitis, it also highlights the ongoing challenges and critical need for continued research and collaboration.

Dr Ava Easton
Chief Executive, Encephalitis International

Acknowledgements

Encephalitis International would like to thank Gabriela Biernacka, York St John University, UK and Annabel Wallace, Yale University, USA for their contributions to this work.

Contents

Epidemiology of encephalitis

Autoimmune vs infectious encephalitis among acute encephalitis syndrome in India

ABSTRACT: Background & objectives: Acute encephalitic syndrome (AES), encompasses a wide spectrum of potential causes, clinical presentations, and outcomes. While infectious encephalitis is generally considered more prevalent, autoimmune encephalitis is emerging as a significant aetiology. Neuronal autoantibodies have been identified independently or in association with acute viral encephalitis. The primary objective of this study was to ascertain the prevalence and clinical manifestation of autoimmune encephalitis as well as of coexisting viral markers in children with AES. **Methods:** This study was a prospective observational investigation conducted in a hospital setting. It involved enrolling children with AES who were admitted to specific tertiary hospitals. Children were subjected to examinations to detect the presence of viral markers and neuronal autoantibodies in both their blood and cerebrospinal fluid (CSF). All the participants received treatment based on established guidelines and was followed for six months for outcome assessment. **Results:** During the study period, 867 children with AES were examined. Among these cases, 37 children (4.2%) were diagnosed with autoimmune encephalitis, and all of them tested positive for anti-NMDAR (N-methyl-D-aspartate receptor) antibodies. Evidence of viral infection was seen in 409 (47.1%) of cases, out of which nearly 254 (29.2%) children had detectable HSV IgM antibodies. Among the 37 children with autoimmune encephalitis, 25 (67.5%) had evidence of a viral trigger, with eight of them tested positive for HSV IgM antibodies. The clinical presentation of autoimmune-associated AES was similar to those with viral aetiology. I**nterpretation & conclusions:** Autoimmune encephalitis triggered by neurotropic (HSV) viral infection was more prevalent in this study than in the earlier reports. Typically, these children show positive responses to immunosuppressive treatments if administered promptly. It is hence advisable to assess children who exhibit behavioural issues and movement disorders for possible autoimmune encephalitis.

Dwibedi, Bhagirathi et al. "Prevalence & clinical outcome of autoimmune encephalitis versus viral encephalitis in children with acute encephalitis syndrome: A prospective observational study." The Indian journal of medical research vol. 160,2 (2024): 217-225. doi:10.25259/ijmr_2332_23

Chikungunya virus and neurological disorders

ABSTRACT: Chikungunya disease typically presents with the fever-arthralgia-rash symptom triad. However, an increase in the number of atypical clinical manifestations, particularly neurological disorders, has occurred. The current evidence regarding the pooled prevalence of Chikungunya virus (CHIKV)-associated neurological cases (CANCs) suspected of having an arboviral aetiology is not well-understood. Therefore, this meta-analysis included 19 studies (n = 7319 patients) and aimed to determine the pooled rate of exposure to CANC. The pooled positivity rate of CANC was 12 % (95 % CI: 6-19), and Brazil was overrepresented (11/19). These estimations varied between 3 and 14 % based on the diagnostic method (real-time PCR vs. ELISA-IgM) and biological samples (cerebrospinal fluid or blood specimens) used for detection of CHIKV. Regarding the frequency of CHIKV in neurological clinical subgroups, the rates were higher among patients with myelitis (27 %), acute disseminated encephalomyelitis (27 %), Guillain-Barré syndrome (15 %), encephalitis (12 %), and meningoencephalitis (7 %). Our analysis highlights the significant burden of CANC. However, the data must be interpreted with caution due to

the heterogeneity of the results, which may be related to the location of the studies covering endemic periods and/or outbreaks of CHIKV. Current surveillance resources should also focus on better characterizing the epidemiology of CHIKV infection in neurological disorders. Additionally, future studies should investigate the interactions between CHIKV and neurological diseases with the aim of gaining deeper insight into the mechanisms underlying the cause-and-effect relationship between these two phenomena.

da Costa, Vivaldo G et al. "A meta-analysis of Chikungunya virus in neurological disorders." Infectious diseases now vol. 54,5 (2024): 104938. doi:10.1016/j.idnow.2024.104938

Increasing mortality rates of Nipah virus

The mortality rate of Nipah virus can vary across different regions and its pattern across timelines is yet to be assessed. Vasudevan et al. aimed to perform a comparative analysis of mortality rates across different timelines and countries. Articles reporting mortality from inception to November 2023 were analysed in PubMed, Ovid Embase, Scopus, and Web of Science databases. The initial search yielded 1213 records. The Global mortality rate of the Nipah virus in the 2014-2023 decade was 80.1% (CI: 68.7-88.1%), indicating a significant 24% increase compared to the preceding decade (2004-2013) with a mortality rate of 54.1% (CI: 35.5-71.6%). Among the countries analysed for overall mortality from 1994-2023, India experienced the highest mortality rate at 82.7% (CI: 74.6-88.6%), followed by Bangladesh at 62.1% (CI: 45.6-76.2%), Philippines at 52.9% (CI: 30-74.5%), Malaysia at 28.9% (CI: 21.4-37.9%), and Singapore at 21% (CI: 8-45%). Subgroup analysis revealed that India consistently had the highest mortality rate for the past two decades (91.7% and 89.3%). The primary complication leading to mortality was encephalitis, accounting for 95% of cases. This review is noteworthy for revealing a surge in mortality rates, particularly in the last decade (2014-2023). The particular escalation in India signifies, according to the researchers, a pressing public health challenge.

Vasudevan, Srivatsa Surya et al. "Global and regional mortality statistics of nipah virus from 1994 to 2023: a comprehensive systematic review and meta-analysis." Pathogens and global health vol. 118,6 (2024): 471-480. doi:10.1080/20477724.2024.2380131

Oropouche virus: underestimated rates in South America

ABSTRACT: Oropouche Virus (OROV; genus of Orthobunyavirus) is the causal agent of Oropouche Fever (OF). Due to the lack of specific signs and symptoms and the limited availability of diagnostic tests, the actual epidemiology of OROV infections and OF has been extensively disputed. In this systematic review with meta-analysis, a literature search was carried out in PubMed, Scopus, EMBASE, and MedRxiv in order to retrieve relevant articles on the documented occurrence of OROV infections. Pooled detection rates were then calculated for anti-OROV antibodies and virus detection (i.e., viral RNA detected by viral cultures and/or real-time polymerase chain reaction [RT-qPCR]). Where available, detection rates for other arboviruses (i.e., Dengue [DENV], Chikungunya [CHKV], and Zika Virus [ZIKV]) were calculated and compared to those for OROV. A total of 47 studies from South America and the Caribbean were retrieved. In individuals affected by febrile illness during OROV outbreaks, a documented prevalence of 0.45% (95% confidence interval [95%CI] 0.16 to 1.12) for virus isolation, 12.21% (95%CI 4.96 to 27.09) for seroprevalence (including both IgM and IgG class antibodies), and 12.45% (95%CI 3.28 to 37.39) for the detection of OROV-targeting IgM class antibodies were eventually documented. In the general population, seroprevalence was estimated to be 24.45% (95%CI 7.83 to 55.21) for IgG class antibodies. The OROV detection rate from the cerebrospinal fluids of suspected cases of viral encephalitis was estimated to be 2.40% (95%CI 1.17 to 5.03). The occurrence of OROV infections was consistently lower than that of DENV, CHKV, and ZIKV during outbreaks (Risk Ratio [RR] 24.82, 95%CI 21.12 to 29.16; RR 2.207, 95%CI 1.427 to 3.412; and RR 7.900, 95%CI 5.386 to 11.578, respectively) and in the general population (RR 23.614, 95%CI 20.584 to 27.129; RR 3.103, 95%CI 2.056 to 4.685; and RR 49.500, 95%CI 12.256 to 199.921, respectively). In conclusion, our study stresses the possibly high underestimation of OROV prevalence in the general population of South America, the potential global threat represented by this arbovirus infection, and the potential preventive role of a comprehensive "One Health approach".

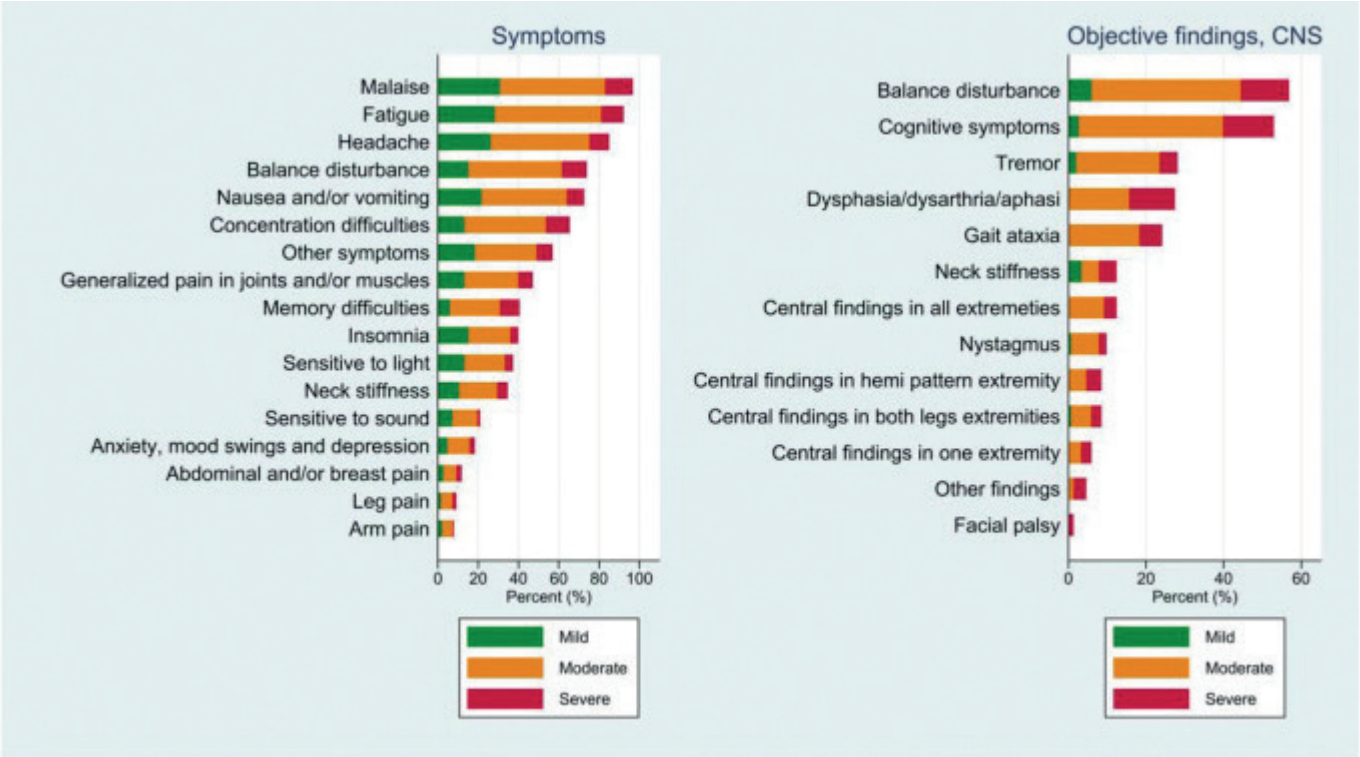
Riccò, Matteo et al. "(Re-)Emergence of Oropouche Virus (OROV) Infections: Systematic Review and Meta-Analysis of Observational Studies." Viruses vol. 16,9 1498. 22 Sep. 2024, doi:10.3390/v16091498

Tick-borne encephalitis in Europe

ABSTRACT: Skudal et al. aimed to describe the clinical characteristics and factors associated with disease severity in a Norwegian cohort of hospitalized patients with tick-borne encephalitis (TBE).

Methods: This observational multicenter study included hospitalized patients with TBE in the endemic area in the southeastern region of Norway from 2018 to 2022. Clinical signs and findings from laboratory tests, EEG, CT and MRI scans were recorded. Patient characteristics were compared among those with mild, moderate, and severe TBE, and factors associated with disease severity were identified.

Results: Nearly all eligible patients were included in the final cohort (153/189 participants, 81%). The median age was 56 years, 63% were men, and 7% were vaccinated against TBE; no participants were fully vaccinated. TBE presented as mild (meningeal) disease in 31% of patients and as moderate or severe (encephalitic) disease in 54% and 14% of patients, respectively. We found that 46% of the patients had a monophasic course, 64% had hyponatremia, and 7%



Symptoms and findings stratified by TBE disease severity in the CNS phase. Each bar represents the total percentage of symptoms or objective findings. The colors show the percentages for each severity group: mild, moderate and severe. The following symptoms were recorded as "other symptoms": diarrhoea n=27 (18%); dizziness, n=23 (15%); reduced appetite, n=23 (15%); diplopia, n=11 (7%); weight loss>5 kg, n=16 (11%); and dysesthesia, n=15 10%. [Source: Skudal et al., 2024]

presented with central nervous system (CNS) symptoms without pleocytosis in cerebrospinal fluid (CSF). Dysesthesia, a symptom previously not described, was reported in 10% of the patients. Most objective findings were related to the CNS. Preexisting comorbidities, CRP and CSF protein levels were predictors of more severe disease.

Conclusion: This novel presentation of a large Norwegian cohort supports TBE as a serious disease in the southeastern region of Norway. The majority of hospitalized patients presented with encephalitis, and fewer presented with meningitis. Comorbidities, CRP and CSF protein levels were associated with more severe disease.

ABSTRACT: Scaggiante et al conducted a study to assess the incidence trends and healthcare resource utilization of hospitalizations for Tick-Borne Encephalitis (TBE) and associated costs in Italy in order to improve public awareness and preventive measures.

Methods: This retrospective observational study was based on the Italian Ministry of Health's Hospital Discharge Record (HDR) database. Data were gathered across Italy from 2015 to 2019, selecting hospitalizations with ICD-9 code 063 related to TBE, both in primary and secondary diagnoses. For each year, we collected the following variables: number of hospitalizations, hospitalization rate, mortality rate, mean length of hospital stay, hospital ward, and cost of hospitalization.

Results: There were a total of 237 hospitalizations from 2015 to 2019; 62 % of those were male. The lowest number of TBE hospitalizations was in 2015 (21 cases, corresponding to 0.35 per million inhabitants), the highest in 2019 (64 cases, 1.04 per million inhabitants). The summer months saw a greater than average number of hospitalizations. For the years analyzed, the cumulative number of cases peaked in June (54 cases), July (46 cases), and August (35 cases). There were only two deaths registered in our study sample. TBE cases were mostly localized in the North-Eastern regions of Italy. TBE incidence during the study period in the most affected areas were: Autonomous Province of Trento, ranging from 11.2 to 42.3 per million inhabitants, Autonomous Province of South Tyrol, from 0 to 21.1 per million inhabitants, and Veneto Region, from 2.6 to 4.5 per million inhabitants. In the study period, the average length of hospital stay was largely stable ranging from 10.6 days to 12.8 days, with related costs ranging from 5,813.7 € to 7,352.5 €.

Conclusions: According to our data, the majority of TBE hospitalizations occur in North-East Italy with an increasing trend over the analyzed period. Even though Italy has fewer TBE cases than other neighboring European countries, the health and economic impact can be high in the affected areas.

Skudal, Hilde et al. "Clinical characteristics and factors affecting disease severity in hospitalized tick-borne encephalitis patients in Norway from 2018 to 2022." European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology vol. 43,7 (2024): 1355-1366. doi:10.1007/s10096-024-04855-2

Scaggiante, Renzo et al. "Incidence, healthcare resource utilization and costs of hospitalized patients with tick-borne encephalitis (TBE) in Italy." Ticks and tick-borne diseases vol. 15,6 (2024): 102372. doi:10.1016/j.ttbdis.2024.102372

Jamestown Canyon virus in North America

ABSTRACT: Jamestown Canyon virus (JCV) is a mosquito borne orthobunyavirus in the California serogroup that circulates throughout Canada and the United States. Most JCV exposures result in asymptomatic infection or a mild febrile illness, but JCV can also cause neurologic diseases, such as meningitis and encephalitis. We describe a case series of confirmed JCV-mediated neuroinvasive disease among persons from the provinces of British Columbia, Alberta, Quebec, and Nova Scotia, Canada, during 2011-2016. We highlight the case definitions, epidemiology, unique features and clinical manifestations, disease seasonality, and outcomes for those cases. Two of the patients (from Quebec and Nova Scotia) might have acquired JCV infections during travel to the northeastern region of the United States. This case series collectively demonstrates JCV's wide distribution and indicates the need for increased awareness of JCV as the underlying cause of meningitis/meningoencephalitis during mosquito season.

Meier-Stephenson, Vanessa et al. "Case Series of Jamestown Canyon Virus Infections with Neurologic Outcomes, Canada, 2011-2016." Emerging infectious diseases vol. 30,5 (2024): 874-881. doi:10.3201/eid3005.221258

Racial and ethnic disparities in anti-NMDAR encephalitis

ABSTRACT: Objectives: To estimate the incidence of anti-N-methyl-d-aspartate receptor (NMDAR) encephalitis.

Methods: We conducted a retrospective cohort study of >10 million person-years of observation from members of Kaiser Permanente Southern California, 2011-2022. The electronic health record of individuals with text-string mention of NMDA and encephalitis were reviewed to identify persons who met diagnostic criteria for anti-NMDAR encephalitis. Age-standardized and sex-standardized incidences stratified by race and ethnicity were estimated according to the 2020 US Census population.

Results: We identified 70 patients who met diagnostic criteria for anti-NMDAR encephalitis. The median age at onset was 23.7 years (IQR = 14.2-31.0 years), and 45 (64%) were female patients. The age-standardized and sex-standardized incidence of anti-NMDAR encephalitis per 1 million person-years was significantly higher in Black (2.94, 95% CI 1.27-4.61), Hispanic (2.17, 95% CI 1.51-2.83), and Asian/Pacific Island persons (2.02, 95% CI 0.77-3.28) compared with White persons (0.40, 95% CI 0.08-0.72). Ovarian teratomas were found in 58.3% of Black female individuals and 10%-28.6% in other groups.

Discussion: Anti-NMDA receptor encephalitis disproportionately affected Black, Hispanic, or Asian/Pacific Island persons. Ovarian teratomas were a particularly common trigger in Black female individuals. Future research should seek to identify environmental and biological risk factors that disproportionately affect minoritized individuals residing in the United States.

Alsalek, Samir et al. "Racial and Ethnic Disparities in the Incidence of Anti-NMDA Receptor Encephalitis." Neurology(R) neuroimmunology & neuroinflammation vol. 11,4 (2024): e200255. doi:10.1212/NXI.0000000000200255

Powassan virus

ABSTRACT: Background: Powassan virus (POWV) is an emerging arthropod-borne flavivirus, transmitted by Ixodes spp. ticks, which has been associated with neuroinvasive disease and poor outcomes.

Methods: A retrospective study was conducted at Mayo Clinic from 2013 to 2022. We included clinical and epidemiologic data of probable and confirmed neuroinvasive POWV cases.

Results: Sixteen patients with neuroinvasive POWV were identified; their median age was 63.2 years, and 62.5% were male. Six patients presented with rhombencephalitis, 4 with isolated meningitis, 3 with meningoencephalitis, 2 with meningoencephalomyelitis, and 1 with opsoclonus myoclonus syndrome. A median time of 18 days was observed between symptom onset and diagnosis. Cerebrospinal fluid analysis showed lymphocytic pleocytosis with elevated protein and normal glucose in the majority of patients. Death occurred within 90 days in 3 patients (18.8%), and residual neurologic deficits were seen in 8 survivors (72.7%).

Conclusions: To our knowledge, this is the largest case series of patients with neuroinvasive POWV infection. We highlight the importance of a high clinical suspicion among patients who live in or travel to high-risk areas during the spring to fall months. Our data show high morbidity and mortality rates among patients with neuroinvasive disease.

Mendoza, Maria Alejandra et al. "Powassan Virus Encephalitis: A Tertiary Center Experience." Clinical infectious diseases : an official publication of the Infectious Diseases Society of America vol. 78,1 (2024): 80-89. doi:10.1093/cid/ciad454

Impact of climate change on global West Nile virus dynamics

ABSTRACT: Background: West Nile virus (WNV), the most widely distributed flavivirus causing encephalitis globally, is a vector-borne pathogen of global importance. The changing climate is poised to reshape the landscape of various infectious diseases, particularly vector-borne ones like WNV. Understanding the anticipated geographical and range shifts in disease transmission due to climate change, alongside effective adaptation strategies, is critical for mitigating future public health impacts. This scoping review aims to consolidate evidence on the impact of climate change on WNV and to identify a spectrum of applicable adaptation strategies.

Main body: We systematically analyzed research articles from PubMed, Web of Science, Scopus, and EBSCOhost. Our criteria included English-language research articles published between 2007 and 2023, focusing on the impacts of climate change on WNV and related adaptation strategies. We extracted data concerning study objectives, populations, geographical focus, and specific findings. Literature was categorized into two primary themes: 1) climate-WNV associations, and 2) climate change impacts on WNV transmission, providing a clear understanding. Out of 2168 articles reviewed, 120 met our criteria. Most evidence originated from North America (59.2%) and Europe (28.3%), with a primary focus on human cases (31.7%). Studies on climate-WNV correlations (n = 83) highlighted temperature (67.5%) as a pivotal climate factor. In the analysis of climate change impacts on WNV (n = 37), most evidence suggested that climate change may affect the transmission and distribution of WNV, with the extent of the impact depending on local and regional conditions. Although few studies directly addressed the implementation of adaptation strategies for climate-induced disease transmission, the proposed strategies (n = 49) fell into six categories: 1) surveillance and monitoring (38.8%), 2) predictive modeling (18.4%), 3) cross-disciplinary collaboration (16.3%), 4) environmental management (12.2%), 5) public education (8.2%), and 6) health system readiness (6.1%). Additionally, we developed an accessible online platform to summarize the evidence on climate change impacts on WNV transmission (https://2xzl2o-neaop.shinyapps.io/WNVScopingReview/).

Conclusions: This review reveals that climate change may affect the transmission and distribution of WNV, but the literature reflects only a small share of the global WNV dynamics. There is an urgent need for adaptive responses to anticipate and respond to the climate-driven spread of WNV. Nevertheless, studies focusing on these adaptation responses are sparse compared to those examining the impacts of climate change. Further research on the impacts of climate change and adaptation strategies for vector-borne diseases, along with more comprehensive evidence synthesis, is needed to inform effective policy responses tailored to local contexts.

Wang, Hao-Ran et al. "Impact of climate change on the global circulation of West Nile virus and adaptation responses: a scoping review." Infectious diseases of poverty vol. 13,1 38. 24 May. 2024, doi:10.1186/s40249-024-01207-2

Chandipura encephalitis in India

ABSTRACT: Chandipura vesiculovirus (CHPV) is an emerging neurotropic virus primarily affecting children and causing acute encephalitis syndrome (AES) in India. The virus, transmitted mainly by sand flies, has led to multiple outbreaks with high mortality rates, particularly in rural and resource-limited settings. CHPV infection is characterized by rapid disease progression, with symptoms ranging from fever and seizures to coma and death, often within 24 to 48 h of onset. The current management of CHPV is limited to supportive care due to the lack of specific antiviral therapies. Diagnosis relies on laboratory methods such as RT-PCR, serology, and immunofluorescence, though these face challenges due to the rapid progression of the disease and the need for timely sample collection and analysis. Prevention strategies are focused on vector control through insecticide use and public health interventions, including community education and early detection programs. Despite some progress in understanding CHPV, significant research gaps remain, particularly in developing effective antiviral treatments and vaccines, understanding transmission dynamics, and improving diagnostic capabilities. The potential for the virus to spread globally due to factors like climate change and increased human movement underscores the need for international collaboration in surveillance and response efforts. Strengthening public health infrastructure, enhancing vector control measures, and fostering global partnerships are crucial steps toward mitigating the impact of CHPV and preventing future outbreaks. Continued research and proactive public health strategies are essential to protect vulnerable populations and control the spread of this potentially deadly virus.

Padhi, Abhishek et al. "Re-emerging Chandipura vesiculovirus: A cause of concern for global health." Virusdisease vol. 35,3 (2024): 385-399. doi:10.1007/s13337-024-00896-5

Pathogenesis of encephalitis

Herpes simplex virus infection pathogenesis

ABSTARCT: Most cases of herpes simplex virus 1 (HSV-1) encephalitis (HSE) remain unexplained. Chan et al report on two unrelated people who had HSE as children and are homozygous for rare deleterious variants of TMEFF1, which encodes a cell membrane protein that is preferentially expressed by brain cortical neurons. TMEFF1 interacts with the cell-surface HSV-1 receptor NECTIN-1, impairing HSV-1 glycoprotein D- and NECTIN-1-mediated fusion of the virus and the cell membrane, blocking viral entry. Genetic TMEFF1 deficiency allows HSV-1 to rapidly enter cortical neurons that are either patient specific or derived from CRISPR-Cas9-engineered human pluripotent stem cells, thereby enhancing HSV-1 translocation to the nucleus and subsequent replication. This cellular phenotype can be rescued by pretreatment with type I interferon (IFN) or the expression of exogenous wild-type TMEFF1. Moreover, ectopic expression of full-length TMEFF1 or its amino-terminal extracellular domain, but not its carboxy-terminal intracellular domain, impairs HSV-1 entry into NECTIN-1-expressing cells other than neurons, increasing their resistance to HSV-1 infection. Human TMEFF1 is therefore a host restriction factor for HSV-1 entry into cortical neurons. Its constitutively high abundance in cortical neurons protects these cells from HSV-1 infection, whereas inherited TMEFF1 deficiency renders them susceptible to this virus and can therefore underlie HSE.

ABSTRACT: Encephalitis is a rare and potentially fatal manifestation of herpes simplex type 1 infection. Following genome-wide genetic analyses, Bibert et al identified a previously uncharacterized and very rare heterozygous variant in the E3 ubiquitin ligase WWP2, in a 14-month-old girl with herpes simplex encephalitis. The p.R841H variant (NM_007014.4:c.2522G > A) impaired TLR3 mediated signaling in inducible pluripotent stem cells-derived neural precursor cells and neurons; cells bearing this mutation were also more susceptible to HSV-1 infection compared to control cells. The p.R841H variant increased TRIF ubiquitination in vitro. Antiviral immunity was rescued following the correction of p.R841H by CRISPR-Cas9 technology. Moreover, the introduction of p.R841H in wild type cells reduced such immunity, suggesting that this mutation is linked to the observed phenotypes.

Bibert, Stéphanie et al. "Herpes simplex encephalitis due to a mutation in an E3 ubiquitin ligase." Nature communications vol. 15,1 3969. 10 May. 2024, doi:10.1038/s41467-024-48287-0

Chan, Yi-Hao et al. "Human TMEFF1 is a restriction factor for herpes simplex virus in the brain." Nature vol. 632,8024 (2024): 390-400. doi:10.1038/s41586-024-07745-x

Anti-NMDAR encephalitis – genetic predisposition

ABSTRACT: **Introduction:** Genetic predisposition to autoimmune encephalitis with antibodies against N-methyl-D-aspartate receptor (NMDAR) is poorly understood. Given the diversity of associated environmental factors (tumors, infections), we hypothesized that human leukocyte antigen (HLA) and killer-cell immunoglobulin-like receptors (KIR), two extremely polymorphic gene complexes key to the immune system, might be relevant for the genetic predisposition to anti-NMDAR encephalitis. Notably, KIR are chiefly expressed by Natural Killer (NK) cells, recognize distinct HLA class I allotypes and play a major role in anti-tumor and anti-infection responses. **Methods:** We conducted a Genome Wide Association Study (GWAS) with subsequent control-matching using Principal Component Analysis (PCA) and HLA imputation, in a multi-ethnic cohort of anti-NMDAR encephalitis (n=479); KIR and HLA were further sequenced in a large subsample (n=323). PCA-controlled logistic regression was then conducted for carrier frequencies (HLA and KIR) and copy number variation (KIR). HLA-KIR interaction associations were also modeled. Additionally, single cell sequencing was conducted in peripheral blood mononuclear cells from 16 cases and 16 controls, NK cells were sorted and phenotyped. **Results:** Anti-NMDAR encephalitis showed a weak HLA association with DRB1*01:01~DQA1*01:01~DQB1*05:01 (OR=1.57, 1.51, 1.45; respectively), and DRB1*11:01 (OR=1.60); these effects were stronger in European descendants and in patients without an underlying ovarian teratoma. More interestingly, we found increased copy number variation of KIR2DL5B (OR=1.72), principally due to an overrepresentation of KIR2DL5B*00201. Further, we identified two allele associations in framework genes, KIR2DL4*00103 (25.4% vs. 12.5% in controls, OR=1.98) and KIR3DL3*00302 (5.3% vs. 1.3%, OR=4.44). Notably, the ligands of these KIR2DL4 and KIR3DL3, respectively, HLA-G and HHLA2, are known to act as immune checkpoint with immunosuppressive functions. However, we did not find differences in specific KIR-HLA ligand interactions or HLA-G polymorphisms between cases and controls. Similarly, gene expression of CD56dim or CD56bright NK cells did not differ between cases and controls. **Discussion:** Our observations for the first time suggest that the HLA-KIR axis might be involved in anti-NMDAR encephalitis. While the genetic risk conferred by the identified polymorphisms appears small, a role of this axis in the pathophysiology of this disease appears highly plausible and should be analyzed in future studies.

Peris Sempere, Vicente et al. "HLA and KIR genetic association and NK cells in anti-NMDAR encephalitis." Frontiers in immunology vol. 15 1423149. 10 Jul. 2024, doi:10.3389/fimmu.2024.1423149

Immune signalling in varicella zoster virus infection

ABSTRACT: Varicella zoster virus (VZV) is a neurotropic alphaherpesvirus exclusively infecting humans, causing two distinct pathologies: varicella (chickenpox) upon primary infection and herpes zoster (shingles) following reactivation. In susceptible individuals, VZV can give rise to more severe clinical manifestations, including disseminated infection, pneumonitis, encephalitis, and vasculopathy with stroke. Here, we describe a 3-year-old boy in whom varicella followed a complicated course with thrombocytopenia, hemorrhagic and necrotic lesions, pneumonitis, and intermittent encephalopathy. Hemophagocytic lymphohistiocytosis (HLH) was strongly suspected and as the condition deteriorated, HLH therapy was initiated. Although the clinical condition improved, longstanding hemophagocytosis followed despite therapy. We found that the patient carries a rare monoallelic variant in autocrine motility factor receptor (AMFR), encoding a ubiquitin ligase involved in innate cytosolic DNA sensing and interferon (IFN) production through the cyclic GMP-AMP synthase-stimulator of IFN genes (cGAS-STING) pathway. Peripheral blood mononuclear cells (PBMCs) from the patient exhibited impaired signaling downstream of STING in response dsDNA and 2′3′-cGAMP, agonists of cGAS and STING, respectively, and fibroblasts from the patient showed impaired type I IFN responses and significantly increased VZV replication. Overexpression of the variant AMFR R594C resulted in decreased K27-linked STING ubiquitination compared to WT AMFR. Moreover, ImageStream technology revealed reduced STING trafficking from ER to Golgi in cells expressing the patient AMFR R594C variant. This was supported by a dose-dependent dominant negative effect of expression of the patient AMFR variant as measured by IFN-β reporter gene assay. Finally, lentiviral transduction with WT AMFR partially reconstituted 2′3′-cGAMP-induced STING-mediated signaling and ISG expression in patient PBMCs. This work links defective AMFR-STING signaling to severe VZV disease and hyperinflammation and suggests a direct role for cGAS-STING in the control of viral infections in humans. In conclusion, we describe a novel genetic etiology of severe VZV disease in childhood, also representing the first inborn error of immunity related to a defect in the cGAS-STING pathway.

Thomsen, Michelle Mølgaard et al. "Impaired STING Activation Due to a Variant in the E3 Ubiquitin Ligase AMFR in a Patient with Severe VZV Infection and Hemophagocytic Lymphohistiocytosis." Journal of clinical immunology vol. 44,2 56. 26 Jan. 2024, doi:10.1007/s10875-024-01653-5

Rasmussen's encephalitis progression

ABSTRACT: Rasmussen's encephalitis (RE) stands as a rare neurological disorder marked by progressive cerebral hemiatrophy and epilepsy resistant to medical treatment. Despite extensive study, the primary cause of RE remains elusive, while its histopathological features encompass cortical inflammation, neuronal degeneration, and gliosis. The underlying molecular mechanisms driving disease progression remain largely unexplored. In this case study, we present a patient with RE who underwent hemispherotomy and has remained seizure-free for over six months, experiencing gradual motor improvement. Furthermore, we conducted molecular analysis on the excised brain tissue, unveiling a decrease in the expression of cell-cycle-associated genes coupled with elevated levels of BDNF and TNF-α proteins. These findings suggest the potential involvement of cell cycle regulators in the progression of RE.

Gonçalves, João Ismael Budelon et al. "Case Report: Molecular Analyses of Cell-Cycle-Related Genes in Cortical Brain Tissue of a Patient with Rasmussen Encephalitis." International journal of molecular sciences vol. 25,15 8487. 3 Aug. 2024, doi:10.3390/ijms25158487

DBR1 deficiency and SARS-CoV-2 brainstem encephalitis

ABSTRACT: Inherited deficiency of the RNA lariat-debranching enzyme 1 (DBR1) is a rare etiology of brainstem viral encephalitis. The cellular basis of disease and the range of viral predisposition are unclear. We report inherited DBR1 deficiency in a 14-year-old boy who suffered from isolated SARS-CoV-2 brainstem encephalitis. The patient is homozygous for a previously reported hypomorphic and pathogenic DBR1 variant (I120T). Consistently, DBR1 I120T/I120T fibroblasts from affected individuals from this and another unrelated kindred have similarly low levels of DBR1 protein and high levels of RNA lariats. DBR1 I120T/I120T human pluripotent stem cell (hPSC)-derived hindbrain neurons are highly susceptible to SARS-CoV-2 infection. Exogenous WT DBR1 expression in DBR1 I120T/I120T fibroblasts and hindbrain neurons rescued the RNA lariat accumulation phenotype. Moreover, expression of exogenous RNA lariats, mimicking DBR1 deficiency, increased the susceptibility of WT hindbrain neurons to SARS-CoV-2 infection. Inborn errors of DBR1 impair hindbrain neuron-intrinsic antiviral immunity, predisposing to viral infections of the brainstem, including that by SARS-CoV-2.

Chan, Yi-Hao et al. "SARS-CoV-2 brainstem encephalitis in human inherited DBR1 deficiency." The Journal of experimental medicine vol. 221,9 (2024): e20231725. doi:10.1084/jem.20231725

Infectious encephalitis

Herpes simplex virus: delayed positive PCR

Herpes simplex encephalitis (HSE) is a severe HSV infection with significant morbidity and mortality. Diagnosis relies on neuroimaging (MRI, CT) and HSV DNA PCR analysis of cerebrospinal fluid or brain biopsy. In this case study, HSV-1 was detected via PCR testing four days after presentation, confirming HSE diagnosis. This case highlights the importance of comprehensive diagnostic approaches rather than relying on initial test results, as HSV may not be immediately detectable in CSF or neuroimaging. It emphasises initiating empirical antiviral therapy based on clinical suspicion when initial studies are negative. Prompt diagnosis and treatment are crucial to prevent permanent neurological damage. Ultimately, this case reinforces the need for comprehensive diagnostic strategies and timely intervention in HSE management. Initial CSF analysis and MRI may be normal early in infection, requiring clinical vigilance. HSV PCR remains the gold standard for HSE diagnosis.

Ahmed, Waleed Amasaib et al. "Herpes simplex encephalitis with normal brain magnetic resonance imaging and normocellular initial cerebrospinal fluid." The International journal of neuroscience vol. 134,12 (2024): 1647-1651. doi:10.1080/00207454.2023.2279501

Japanese encephalitis among adults

ABSTRACT: Background and objectives: Japanese encephalitis (JE) is fatal endemic viral encephalitis and is common in India and other parts of the world. It has a mortality rate of around 20-30%, and most of the survivors are left with neurological deficits. Studies related to JE in India, including Jharkhand, are focused on the pediatric population. This study aims to evaluate the presentation and prognosis of JE among adults.

Materials and methods: In this observational and prospective study, 116 patients aged 18 years or above with features of encephalitis were investigated. JE was confirmed in 32 adults by detection of immunoglobulin M (IgM) antibody in cerebrospinal fluid (CSF) through the National Institute of Virology (NIV) Pune kit. Detailed demographic profile, clinical picture, fatality rate, and prognosis were evaluated.

Results: Out of the 32 patients we enrolled for the study, 75% (24) were male and 75% (24) were between 18 and 40 years of age. The mean age of presentation was 29.81 $\pm$ 14.14. Most of the patients (87.5%) belonged to rural areas; also, most of them presented between August and November. In

our study, the most common symptom was fever, seen in all patients, followed by altered sensorium in 24 (75%), seizure in 10 (31.25%), and headache in 8 (25%). Around 14 (43.75%) patients succumbed to death, and out of all patients who were discharged, 88.88% had neurological deficits and 11.11% of patients were healthy. The most common neurological deficit among discharged patients was an inability to speak (44.44%).

Conclusion: We found high mortality and neurological deficits among adults. Detailed epidemiological surveys, awareness programs, and targeted use of vaccination can be helpful.

Lahre, Yuvraj et al. "A Study of 32 Adult Patients of Japanese Encephalitis in Jharkhand." The Journal of the Association of Physicians of India. vol. 72,9 (2024): 19-21. doi:10.59556/japi.72.0625

Eastern equine encephalitis presentation

ABSTRACT: Rationale: This case series aims to describe the clinical and radiographic findings associated with eastern equine encephalitis (EEE) virus.

Patient concerns: Patients in this series presented with a variety of neurological symptoms, including altered mental status, seizures, and focal neurological deficits. Common initial concerns included confusion, hemiparesis, fever, and flu-like symptoms. In all cases, the progression of neurological symptoms prompted urgent medical evaluation and hospitalization.

Diagnoses: Diagnosis of EEE was confirmed in all 4 patients by detection of EEE-specific IgM antibodies in cerebrospinal fluid. Cerebrospinal fluid studies also showed elevated protein, red blood cells, normal or high glucose, and elevated white blood cells with lymphocytic or neutrophil predominance. Magnetic resonance imaging showed T2 hyperintensities in the basal ganglia, thalamus, and cortical regions. Two cases showed encapsulation as evidence by a hyperintense ring around the basal ganglia or thalamus. Electroencephalogram findings ranged from normal, focal irritability, and spikes to nonconvulsive status epilepticus. Clinical and/or electrographic evidence of seizure was seen in all 4 cases.

Interventions: All patients received supportive care, including anticonvulsant therapy, often using levetiracetam. Two patients were treated with high-dose intravenous methylprednisolone and one with intravenous immunoglobulin (IVIG) to modulate the immune response. Empiric antibiotics and antivirals were initiated in most cases until the diagnosis of EEE was confirmed. Two patients required intubation and mechanical ventilation, one of which was due to seizure activity and nonconvulsive status epilepticus.

Outcomes: We report a 1/4 (25%) mortality rate. The average hospital stay among survivors was 10 days. Two-fourth (50%) required intubation and mechanical ventilation. Two patients were discharged to rehabilitation facilities, one patient recovered fully with resolution of magnetic resonance imaging abnormalities at follow-up, and one patient experienced a fatal outcome after the family opted to withdraw care due to a poor prognosis.

Lessons: This case series underscores the importance of maintaining a high clinical suspicion of EEE in patients with acute neurological symptoms, especially in endemic areas. Early diagnosis and treatment are crucial, but the variability in presentation and imaging findings complicates this process. Early use of high-dose steroids can improve outcomes.

Garcia-Dominguez, Maria A et al. "The clinical and radiographic features of eastern equine encephalitis: A single-center retrospective case series." Medicine vol. 103,52 (2024): e41170. doi:10.1097/MD.0000000000041170

Case reports: bacterial encephalitis, Dengue and rare presentations of varicella zoster virus

Madiyal et al. describe a case of bacterial meningoencephalitis caused by *Streptococcus porcinus.* To the authors' knowledge, this is the first case described in the literature. The patient was treated with ceftriaxone and supportive treatment.

Skrobas et al report a rare presentation of rhombencephalitis by listeriosis in a 61-year-old male who initially suffered from subacute gastric disturbances and fever. Neurological consultation showed abnormal functions of cranial nerves and meningeal signs were observed. MRI revealed a poorly demarcated focus of approximately 45 × 16 × 15mm, indicating possible inflammatory processes, necessitating a lumbar puncture. Assessment of the CSF indicated infection with the bacterium- Listeria Monocytogenes, with the final diagnosis of Listeriosis encephalitis. Despite antibiotic therapy of Ceftazidine and Ampicillin, the patient's condition deteriorated, followed by death.

Fu et al report the case of an 83-year-old woman with symptoms of progressive limb weakness, difficulty swallowing food, and disturbed consciousness that occurred 4 weeks following herpes zoster infection. Autoimmune anti-sulfatide antibodies were positive and fluid-attenuated inversion recovery (FLAIR) sequences revealed clear high signal intensity in pons and bilateral thalamus. The patient was diagnosed with Bickerstaff brainstem encephalitis emphasizing the importance of a careful medical history and assessment of clinical symptoms, performing MRI, testing autoimmune antibodies for rapid diagnosis, and ruling out differential diagnoses.

Ahmed et al report the case of Ramsay Hunt syndrome (RHS) in an 8-year-old previously healthy boy who presented to a tertiary care hospital in Muscat, Oman in 2021 with fever, progressive left ear pain, vesicular rash around his ear pinna and left-sided facial nerve palsy. His course was complicated by VZV encephalitis where he was managed with intravenous (IV) acyclovir and IV corticosteroids. He improved significantly and was asymptomatic with a normal neurology examination at the 6-months follow-up.

Marinelli et al report a 32-year-old female with advanced human immunodeficiency virus infection presented to an Australian hospital with subacute, worsening symptoms of encephalitis. Metagenomic sequencing and Dengue NS3 antigen staining of brain tissue confirmed active dengue virus (DENV) encephalitis. The most recent possible DENV exposure was months prior in West Africa, indicating chronicity.

Madiyal, Mridula et al. "A rare case report of meningoencephalitis caused by Streptococcus porcinus." Indian journal of medical microbiology vol. 50 (2024): 100660. doi:10.1016/j.ijmmb.2024.100660

Skrobas, Urszula et al. "The rapidly progressing and fatal outcome of rhombencephalitis by listeriosis in a 61-year-old male." Annals of agricultural and environmental medicine: AAEM vol. 31,2 (2024): 311-314. doi:10.26444/aaem/178178

Fu, Xiaoxue et al. "Case report: Shingles-associated probable Bickerstaff brainstem encephalitis with IgM anti-sulfatide positivity." Frontiers in immunology vol. 15 1358886. 9 Apr. 2024, doi:10.3389/fimmu.2024.1358886

Ahmed, Eman Y et al. "Ramsay Hunt Syndrome Associated with Varicella-Zoster Virus Encephalitis in a Child." Sultan Qaboos University medical journal vol. 24,1 (2024): 127-130.

Marinelli, Tina et al. "Chronic and Neurotropic: A Paradigm-Challenging Case of Dengue Virus Encephalitis in a Patient With Advanced HIV Infection." Clinical infectious diseases : an official publication of the Infectious Diseases Society of America vol. 79,2 (2024): 498-501. doi:10.1093/cid/ciae061

Thrombocytopenia syndrome (SFTS) encephalitis

ABSTRACT: Background: The initial clinical symptoms of severe fever with thrombocytopenia syndrome (SFTS) mainly include high fever, thrombocytopenia and gastrointestinal symptoms, and severe patients may suffer from severe complications such as multiple organ failure, which can lead to death. Studies have shown that central nervous system symptoms are associated with severe adverse outcomes of SFTS, but there are few reports on confirmed cases of SFTS encephalitis. This is a special case in which her initial SFTS symptoms were atypical, while the disease deteriorated rapidly after the appearance of encephalitis. The purpose of this study was to report the clinical and epidemiological features of this case, isolate and trace the SFTS virus (SFTSV) strain, identify the genotype of the strain, and speculate on the infection route to provide an important reference for the diagnosis and control of SFTSV.

Methods: Cerebrospinal fluid and serum samples were collected, multipathogen detection was performed via next-generation sequencing (NGS), and SFTSV virus isolation was performed via inoculation of the samples with Vero cells. The serum of key populations closed to patients, parasitic ticks on the surface of domestic animal bodies and environmentally free ticks were collected for SFTSV monitoring. The whole genomes of the virus strains and positive nucleic acid samples were sequenced and compared with the GenBank reference sequence to construct a phylogenetic analysis tree.

Results: This patient was diagnosed with SFTSV encephalitis, and the viral strain was successfully isolated. The SFTSV strain is closely related to the Hubei strain HB2017-02, and the SFTSV M and L fragments belong to the B genotype, whereas the M fragments belong to the F genotype. In addition, the similarities of coding sequences of case strain to those of tick-carried SFTSV strain in the residence were more than 99.9%.

Conclusions: The patient was confirmed to have SFTSV-infected encephalitis and died rapidly. The SFTSV strain was of Chinese local origin, and tick bites were the most likely route of infection.

Liu, Rongjiao et al. "Pathogen isolation and traceability analysis of a fatal case of severe fever with thrombocytopenia syndrome virus (SFTSV) infectious encephalitis in China." Virology journal vol. 21,1 300. 22 Nov. 2024, doi:10.1186/s12985-024-02564-y

Anti-NMDAR encephalitis

Ataxia: frequency and long-term outcome

ABSTRACT: Introduction: Very rarely, adult NMDAR antibody-associated encephalitis (NMDAR-E) leads to persistent cerebellar atrophy and ataxia. Transient cerebellar ataxia is common in pediatric NMDAR-E. Immune-mediated cerebellar ataxia may be associated with myelin oligodendrocyte glycoprotein (MOG), aquaporin-4 (AQP-4), kelch-like family member 11 (KLHL11), and glutamate kainate receptor subunit 2 (GluK2) antibodies, all of which may co-occur in NMDAR-E. Here, we aimed to investigate the frequency, long-term outcome, and immunological concomitants of ataxia in NMDAR-E.

Methods: In this observational study, patients with definite NMDAR-E with a follow-up of >12 months were recruited from the GENERATE registry. Cases with documented ataxia were analyzed in detail.

Results: In 12 of 62 patients (19%), ataxia was documented. Bilateral cerebellar ataxia without additional focal CNS findings was found in four (one child and three adults); one of these was previously reported as a case with persistent cerebellar atrophy and ataxia. Two patients with bilateral cerebellar ataxia had additional focal neurological symptoms, optic neuritis and facial palsy. Two patients developed hemiataxia: one with diplopia suggesting brainstem dysfunction and the other probably resulting from cerebellar diaschisis due to contralateral status epilepticus. In all but the one developing cerebellar atrophy, cerebellar ataxia was transient and not associated with a worse long-term outcome. In all five patients with cerebellar ataxia tested, MOG, AQP-4, GluK2, and KLHL11 antibodies were negative. In two additional patients negative for both MOG and AQP-4 antibodies, ataxia was sensory and explained by cervical myelitis as part of multiple sclerosis (MS) manifesting temporal relation to NMDAR-E. One of the patients with bilateral ataxia with focal neurological deficits was also diagnosed with MS upon follow-up. Finally, in two patients, ataxia was explained by cerebral hypoxic damage following circulatory failure during an ICU stay with severe NMDAR-E.

Discussion: Ataxia of different types is quite common in NMDAR-E. Cerebellar ataxia in NMDAR-E is mostly transient. NMDAR-E followed by persistent ataxia and cerebellar atrophy is very rare. Cerebellar ataxia in NMDAR-E may not be explained by concomitant KLHL11, MOG, AQP-4, or GluK2 autoimmunity. Of note, ataxia in NMDAR-E may result from treatment complications and, most interestingly, from MS manifesting in temporal association with NMDAR-E.

Jesse, Sarah et al. "Frequency, characteristics, and immunological accompaniments of ataxia in anti-NMDAR antibody-associated encephalitis." Frontiers in immunology vol. 15 1500904. 13 Dec. 2024, doi:10.3389/fimmu.2024.1500904

Atypical manifestations and late relapses

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune disease that is rarely associated with AQP4-IgG and MOG-IgG demyelinating diseases and even more rarely with multiple sclerosis. Douglass et al. present a case of a woman in her 40s with confirmed NMDAR encephalitis and coexistent fulminant relapse of multiple sclerosis treated with alemtuzumab 6 years prior, who had a good outcome following treatment with ocrelizumab. The researchers proceed to systematically review similar reported cases, finding a lower than anticipated prevalence of underlying malignancy compared with isolated NMDAR encephalitis in this rare overlap syndrome.

Ribeiro et al aim to describe the abnormal behaviors during REM sleep in anti-NMDARe. Patients were monitored by video-polysomnography on a first night followed by multiple sleep latency tests and 18 hours of bed rest. Two patients with anti-NMDARe developed during the acute and postacute phase parasomnias including REM sleep behavior disorder and continuous finalistic quiet gesturing during a mixed N2/R sleep. The parasomnia disorder was improved by gabapentin and clonazepam. Video-polysomnography avoids misdiagnosing these parasomnia behaviors for seizure or movement disorders and allows adequate treatment.

Amiri et al reported on a 16-year-old Iranian female experiencing a relapse of anti-N-methyl-D-aspartate receptor encephalitis 8 years after her initial diagnosis. She was admitted to the hospital with dysphasia (a speech disorder) and dyslexia (reading and writing impairment). A thorough clinical evaluation revealed the presence of anti-glutamate receptor type N-methyl-D-aspartate receptor antibodies in her serum and cerebrospinal fluid, confirming the diagnosis. Following treatment with immunotherapy and plasmapheresis, she made a complete recovery. This case of relapsing anti-N-methyl-D-aspartate receptor encephalitis, occurring more than 5 years after the initial episode, is exceptionally rare. This late relapse underscores the importance of long-term follow-up for patients with this condition.

Douglass, Saxon, and Deborah Field. "NMDAR autoimmune encephalitis and fulminant relapse of multiple sclerosis: a rare overlap syndrome." BMJ case reports vol. 17,7 e260075. 31 Jul. 2024, doi:10.1136/bcr-2024-260075

Ribeiro, Luis et al. "REM and NREM Sleep Parasomnia in Anti-NMDA Receptor Encephalitis." Neurology® neuroimmunology & neuroinflammation vol. 11,5 (2024): e200203. Doi:10.1212/NXI.0000000000200203

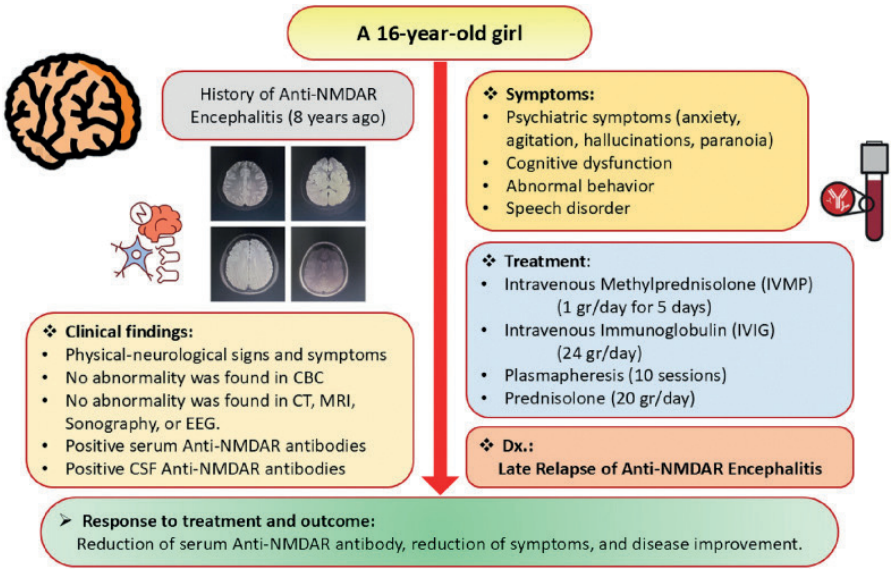
Amiri, Hamidreza et al. "Late relapse of anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis: a case report." Journal of medical case reports vol. 18,1 575. 29 Nov. 2024, doi:10.1186/s13256-024-04886-5

Late tumour association

ABSTRACT: Case: A 25-year-old previously-healthy female experienced a series of acute symptoms within two days, including confusion, disorientation, short-term memory loss, auditory hallucinations, abnormal behavior, refractory status epilepticus, etc. Her brain MRI and abdominal imaging showed no definite abnormality while her electroencephalogram exhibited the presence of low to moderate amplitude sharp, spike, and multi-spike waves. Serum and cerebrospinal fluid tests yielded positive results for anti-NMDAR antibodies. However, an ultrasound scan failed to identify an ovarian teratoma. Consequently, the diagnosis of anti-NMDAR encephalitis without teratoma was made after 4 days onset. After the plasma exchange and immunoglobulin therapy, her neurological symptoms improved and obtained a clinical cure. In the next eight months of follow-up, the patient accidentally touched a lump in the lower abdomen without any symptoms, and abdominal ultrasound and CT scan revealed a left ovarian tumor. Then she underwent left ovarian teratoma resection surgery and histopathology showed a mature cystic teratoma with neural components. The patient continued to receive five years of follow-up, and her condition remained stable without any recurrence, except that there had been a low titer of anti-NMDAR antibody in her serum.

Conclusion: Our case demonstrated the importance of long-term follow-up for female patients with anti-NMDAR encephalitis, since anti-NMDAR encephalitis-associated ovarian teratomas may develop in a delayed manner, even without any symptoms.

Xue, Hailong et al. "Anti-NMDAR encephalitis with delayed ovarian teratoma in a young woman: a case report with 5 years of follow-up." BMC neurology vol. 24,1 377. 8 Oct. 2024, doi:10.1186/s12883-024-03891-x



A summary of the case [Source: Amiri et al.]

Anti-LGI1 encephalitis

ABSTRACT: Background: Leucine-rich glioma inactivated 1 (LGI1) antibody-related autoimmune encephalitis is easily misdiagnosed clinically because of its complex and diverse clinical manifestations. We present two cases of LGI1 antibody-related encephalitis with negative imaging findings and perform a literature review on this disease entity.

Case description: The first case was that of a 60-year-old man who presented with involuntary movement of the paroxysmal right limb. The second case was that of a 66-year-old man who presented with hearing hallucinations, involuntary shaking of the right limb, and progressive cognitive impairment. Both patients in this study showed negative magnetic resonance imaging (MRI) results. Routine cerebrospinal fluid (CSF) and biochemical examinations showed no significant abnormalities, and positive LGI1 antibodies were detected in both the CSF and serum.

Conclusion: Based on our experience and the literature review, we recommend that LGI1 antibody-related encephalitis should be considered when faciobrachial dystonic seizures, acute and subacute-onset seizures, low serum sodium (possibly with low CSF chloride), and cognitive-psychiatric disorders are encountered, even in the absence of specific radiographic and altered CSF findings.

Lian, Xia et al. "Autoimmune encephalitis related to LGI1 antibodies with negative MRI study: Description of two cases." Medicina clinica vol. 162,1 (2024): 35-38. Doi:10.1016/j.medcli.2023.06.024

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, Gloria et al. "A Case of Anti-Ma2 Encephalitis Presenting with Pendular Torsional Nystagmus." Cerebellum (London, England) vol. 23,3 (2024): 1249-1253. Doi:10.1007/s12311-023-01601-w

MOG-associated cerebral cortical encephalitis

ABSTRACT: Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease is a neuroinflammatory disorder (MOGAD) with heterogeneous phenotype including paroxysms of optic neuritis, transverse myelitis, acute disseminated encephalomyelitis, brainstem demyelination, and encephalitis. Fluid-attenuated inversion recovery hyperintense cortical lesions in MOG-associated encephalitis with seizures, or FLAMES, is a manifestation of cerebral cortical encephalitis seen less frequently than other typical MOG antibody-associated disease presentations. Cases of FLAMES are rarer in children, and frequently initially misdiagnosed with infectious meningoencephalitis. Other meningocortical manifestations of MOG antibody-associated disease have been described and likely exist along a continuum. In this retrospective single-center case series, we describe the demographic, clinical, radiographic, laboratory, and electroencephalographic features of 5 children with clinicoradiographic features consistent with the spectrum of MOG-IgG-positive meningocortical syndromes.

Carozza, Richard B et al. "Cerebral Cortical Encephalitis and Other Meningocortical Manifestations of Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease in Children: Case Series and Review of the Literature." Journal of child neurology vol. 39,13-14 (2024): 487-493. Doi:10.1177/08830738241282354

Anti-$GABA_B$ receptor encephalitis

ABSTRACT: Li et al aim to summarize the clinical characteristics, imaging features, treatments, outcomes and explore the potential prognosis risk factors of patients with anti-$GABA_B$R encephalitis.

Methods: Patients tested positive for anti-$GABA_B$R were retrospective studied from a single medical center in China over a period of 3 years. They were followed up for a maximum period of 18 months. Clinical data were summarized and prognostic factors including demographic characteristics, laboratory tests, and neurological functions were compared between survived and deceased patients at 18 months follow-up.

Results: Twenty-six patients, 10 females (38.5%) and 16 males (61.5%), diagnosed with anti-$GABA_B$R encephalitis were studied. The median age was 58 years. Of the 23 cases with complete clinical data, their main manifestations were epileptic seizures (65%), mental and behavioral abnormalities (52%), and cognitive impairment (48%). 7 (30.4%) cases had tumors: 5 small cell lung cancer (SCLC), 1 rectum adenocarcinoma (moderately differentiated) and 1 esophageal squamous cell carcinoma. MRI showed 5 (22%) cases had T2 FLAIR increased signals in cortex but with different regions affected. One of the two patients scanned for PET-CT showed hypermetabolism in the left temporal lobe region. The disease course ranged from 5 days to 3 years. 2 patients (one had esophageal carcinoma) without immunotherapy and 3 patients (one had SCLC) that did not response to immunotherapy died soon after diagnosis. 18 patients improved after immunotherapy while 3 (all had SCLC) died after relapses. The prevalence of epileptic seizures and malignancies was significantly lower in the survival group than in the deceased group at 18-months follow-up, the same as the admission mRS score. Serum fibrinogen, cerebrospinal fluid immunoglobulin G quotient, and 24-hour intrathecal synthesis rate were significantly lower in the survival groups as well.

Conclusions: Cortex T2 FLAIR abnormalities were only observed in a small proportion of anti-$GABA_B$R encephalitis patients with heterogeneous MRI phenotypes. High Mrs score at admission, epileptic seizures and the presence of a tumor indicated a poor prognosis, while the underlying mechanism of the later two factors should be investigated further.

Santos et al. present a rare case of anti- $GABA_B$ case in Soth America in a 21-year-old male patient with an unremarkable previous medical history who was hospitalized because of a new onset of seizures and status epilepticus. The unexplained seizures, persisting altered mental status despite the reduction of sedatives, CSF pleocytosis, and oligoclonal bands, along with reasonable exclusion of alternative disorders, suggested

AE. The diagnosis was confirmed with positive anti-$GABA_B1$-$_B2$ receptor antibody titers in serum and CSF. The patient received treatment with methylprednisolone, plasmapheresis, and immunoglobulin therapy, with excellent response. The patient has been followed up for seven months, taking immunomodulation with mycophenolate. He is seizure-free with valproic acid and levetiracetam treatment and is receiving cognitive rehabilitation after mild cognitive decline was noted in the psychometric analysis.

Li, Dongrui et al. "Anti-$GABA_B$ receptor encephalitis: clinical and laboratory characteristics, imaging, treatments and prognosis." Frontiers in immunology vol. 15 1442733. 9 Oct. 2024, doi:10.3389/fimmu.2024.1442733

Santos, Ana B et al. "Anti-$GABA_B$ Receptor Autoimmune Encephalitis: A Report of a Rare Case in Central America." Cureus vol. 16,8 e68111. 29 Aug. 2024, doi:10.7759/cureus.68111

Autoimmune encephalitis following COVID-19 disease

ABSTRACT: Rationale: This article reports a case of coronavirus disease (COVID-19)-associated autoimmune encephalitis (AE) and reviews the relevant literature to investigate the clinical manifestations, auxiliary inspection, diagnosis and treatment, and prognosis of AE associated with COVID-19.

Patient concerns: A 68-year-old female with fatigue developed altered consciousness after 2 days of fever, thereafter testing positive for COVID-19. The protein levels in the lumbar puncture cerebrospinal fluid were elevated, and cranial magnetic resonance imaging (MRI) scan indicated T2-weighted hyperintensity in the temporal lobe.

Diagnoses: The patient was diagnosed with COVID-19-associated AE.

Interventions: After admission, the patient received pulse steroid therapy with methylprednisolone. Additionally, gastric protection, blood glucose control, nutritional support, and other treatments were administered.

Outcomes: The symptoms were significantly relieved by steroid pulse therapy. At the 3-month follow-up, the patient had recovered completely without any obvious discomfort.

Lessons: The possibility of AE should be considered if neurological symptoms occur a few days after infection with COVID-19, with early diagnosis and immediate steroid pulse therapy resulting in better outcomes.

Chen, Yang-Chuan et al. "COVID-19-associated autoimmune encephalitis: A case report and literature review." Medicine vol. 103,38 (2024): e39533. Doi:10.1097/MD.0000000000039533

Other encephalitis types

Immune checkpoint inhibitor (ICI)-induced encephalitis

ABSTRACT: Background: Immune checkpoint inhibitors (ICI) have revolutionized cancer treatment but can trigger immune-related encephalitis. We report one of the largest case series of patients with immune-related encephalitis and review of the literature.

Methods: Retrospective series of patients with immune-related encephalitis and literature review.

Results: Fourteen patients with cancer treated with ICI (50% combination therapy) developed immune-related encephalitis. Diagnostic testing revealed cerebral spinal fluid (CSF) lymphocytic pleocytosis (85%) and elevated protein (69%), abnormal brain magnetic resonance imaging (MRI) (33%) or brain FDG-PET (25%), electroencephalogram (EEG) abnormalities (30%), and autoantibodies (31%). Encephalitis treatment included: corticosteroids (86%), intravenous immunoglobulin (IVIg) (36%), plasmapheresis (7%), and rituximab (29%). There were no deaths and 12 patients had significant recovery, although long-term complications were observed. All patients discontinued ICI. Longitudinal follow-up demonstrated anti-cancer response to ICI at 3 months (85%) and 6 months post-ICI initiation (77%). A literature review identified 132 patients with immune-related encephalitis. Most were treated with PD-1 inhibitors (18% combination). Common abnormalities included elevated CSF protein (84%) or pleocytosis (77%), abnormal brain MRI (65%), or autoantibodies (47%). Nearly all were treated with corticosteroids, many required additional therapy with IVIg (26%) or rituximab (12%). Most patients had clinical improvement (81%) but a minority (10%) had a clinical relapse after completing corticosteroid taper. ICIs were resumed in 7 patients (5%), with relapse in 3.

Conclusions and relevance: Immune-related encephalitis is treatable and improves with corticosteroids in most cases but may require additional immunosuppression. Re-emergence of encephalitis is rare and does not typically result in adverse outcomes, and this should be considered in neurological immune-related adverse event management guidelines.

Buckley, Monica W et al. "Immune-related encephalitis after immune checkpoint inhibitor therapy." The oncologist vol. 30,1 (2025): oyae186. Doi:10.1093/oncolo/oyae186

Rasmussen's encephalitis with hemispherectomy and pregnancy

ABSTRACT: Background: Rasmussen's encephalitis (RE) is a rare neurologic disorder characterized by progressive seizures and unilateral cerebral atrophy with onset during childhood and unknown etiology. When medical therapy appears refractory, surgical disconnection of the affected hemisphere is indicated. Quality of life after functional hemispherectomy is largely good, affected females may therefore pursue pregnancy. However, data on pregnancy and delivery in RE post hemispherectomy is extremely rare.

Case presentation: We present the case of a patient with left functional hemispherectomy for RE at the age of seven, who experienced two successful pregnancies. In both pregnancies, her post-surgical symptoms including right-sided spasticity, cephalgia, dizziness, and impairment of vision and speech deteriorated but improved to pre-pregnancy level after delivery. Neurologic sequelae post-hemispherectomy overlapped with clinical signs of preeclampsia and required close diagnostic surveillance during both pregnancies.

Conclusion: There are no data on the interaction between RE, hemispherectomy and pregnancy, making maternal and fetal risk assessment difficult. Due to the complexity of the condition and symptoms, management of RE in pregnancy remains highly challenging and requires an interdisciplinary approach. This is the first case description of two successful pregnancies in a woman with RE and status post-hemispherectomy. Further evidence is urgently required to improve counselling and management of affected women.

Jost, Elena et al. "Pregnancy and delivery after functional hemispherectomy for Rasmussen's encephalitis: a case report." BMC neurology vol. 24,1 410. 23 Oct. 2024, doi:10.1186/s12883-024-03906-7

Seizures and encephalitis

ABSTRACT: Background and objectives: Patients with ongoing seizures are usually not allowed to drive. The prognosis for seizure freedom is favorable in patients with autoimmune encephalitis (AIE) with antibodies against NMDA receptor (NMDAR), leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein-like 2 (CASPR2), and the gamma-aminobutyric-acid B receptor ($GABA_BR$). We hypothesized that after a seizure-free period of 3 months, patients with AIE have a seizure recurrence risk of <20% during the subsequent 12 months. This would render them eligible for noncommercial driving according to driving regulations in several countries.

Methods: This retrospective multicenter cohort study analyzed follow-up data from patients aged 15 years or older with seizures resulting from NMDAR-, LGI1-, CASPR2-, or $GABA_BR$-AIE, who had been seizure-free for ≥3 months. We used Kaplan-Meier (KM) estimates for the seizure recurrence risk at 12 months for each antibody group and tested for the effects of potential covariates with regression models.

Results: We included 383 patients with NMDAR-, 440 with LGI1-, 114 with CASPR2-, and 44 with $GABA_BR$-AIE from 14 international centers. After being seizure-free for 3 months after an initial seizure period, we calculated the probability of remaining seizure-free for another 12 months (KM estimate) as 0.89 (95% confidence interval [CI] 0.85-0.92) for NMDAR, 0.84 (CI 0.80-0.88) for LGI1, 0.82 (CI 0.75-0.90) for CASPR2, and 0.76 (CI 0.62-0.93) for $GABA_BR$.

Discussion: Taking a <20% recurrence risk within 12 months as sufficient, patients with NMDAR-AIE and LGI1-AIE could be considered eligible for noncommercial driving after having been seizure-free for 3 months.

Rada, Anna et al. "Risk of Seizure Recurrence Due to Autoimmune Encephalitis With NMDAR, LGI1, CASPR2, and $GABA_BR$ Antibodies: Implications for Return to Driving." Neurology® neuroimmunology & neuroinflammation vol. 11,4 (2024): e200225. Doi:10.1212/NXI.0000000000200225

Diagnosis and treatment of encephalitis

Distinguishing between autoimmune and viral encephalitis

Distinguishing between viral encephalitis (VE) and autoimmune limbic encephalitis (ALE) is a clinical challenge due to symptom overlap. Here, Kong et al. aimed to develop and validate a diagnostic prediction model to differentiate VE and ALE. Methods included prospective observational multicentre cohort study, which continuously enrolled patients diagnosed with either ALE or VE from October 2011 to April 2023. Demographic data, clinical features, and laboratory test results were collected and subjected to logistic regression analyses. A total of 2423 individuals were recruited, and 1001 (496 VE, 505 ALE) patients were included. Based on the derivation cohort (389 VE, 388 ALE), the model was developed with eight variables including age at onset, acuity, fever, headache,34ausea/vomiting, psychiatric or memory complaints, status epilepticus, and CSF white blood cell count. The model showed good discrimination and calibration in both derivation (AUC 0.890; 0.868-0.913) and external validation (107 VE, 117 ALE, AUC 0.872; 0.827-0.917) cohorts. The scored prediction tool had a total point that ranged from – 4 to 10 also showing good discrimination and calibration in both derivation (AUC 0.885, 0.863-0.908) and external validation (AUC 0.868, 0.823-0.913) cohorts. The prediction model provides a reliable and user-friendly tool for differentiating between these two encephalitis types, which would benefit early diagnosis and appropriate treatment, as well as alleviate economic burdens for both the individual and wider society.

Kong, Xueying et al. "Differentiation between viral and autoimmune limbic encephalitis: a prospective cohort study with development and validation of a diagnostic model." Journal of neurology vol. 271,8 (2024): 5301-5311. Doi:10.1007/s00415-024-12468-0

Intrathecal rituximab for anti-NMDAR encephalitis

ABSTRACT: Background: Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is one of the most prevalent etiologies of autoimmune encephalitis. Approximately 25% of anti-NMDAR encephalitis cases prove refractory to both first- and second-line treatments, posing a therapeutic dilemma due to the scarcity of evidence-based data for informed decision-making. Intravenous rituximab is commonly administered as a second-line agent; however, the efficacy of its intrathecal administration has rarely been reported.

Case summary: We report two cases of severe anti-NMDAR encephalitis refractory to conventional therapies. These patients presented with acute-onset psychosis progressing to a fulminant picture of encephalitis manifesting with seizures, dyskinesia, and dysautonomia refractory to early initiation of first- and second-line therapeutic agents. Both patients received 25 mg of rituximab administered intrathecally, repeated weekly for a total of four doses, with no reported adverse effects. Improvement began 2-3 days after the first intrathecal administration, leading to a dramatic recovery in clinical status and functional performance. At the last follow-up of 6 months, both patients remain in remission without the need for maintenance immunosuppression.

Conclusion: Our cases provide evidence supporting the intrathecal administration of rituximab as a therapeutic option for patients with refractory anti-NMDAR encephalitis. Considering the limited penetration of intravenous rituximab into the central nervous system, a plausible argument can be made favoring intrathecal administration as the preferred route or the simultaneous administration of intravenous and intrathecal rituximab. This proposition warrants thorough investigation in subsequent clinical trials.

Reda, Mahasen et al. "Case report: Rapid recovery after intrathecal rituximab administration in refractory anti-NMDA receptor encephalitis: report of two cases." Frontiers in immunology vol. 15 1369587. 6 Mar. 2024, doi:10.3389/fimmu.2024.1369587

Misdiagnosis and mimics of autoimmune encephalitis

Li et al describes a 40-year-old male adult patient who was initially diagnosed with persistent somatoform pain disorder (PSPD) in 2022. The patient reported a reduction in pain while resting on his back. There were no fever or relevant medical history. Despite 8 months of symptomatic treatment, the symptoms did not improve. Moreover, the patient developed confusion, gibberish speech, non-cooperation during questioning, and increased frequency and amplitude of upper limb convulsions. Lumbar puncture revealed elevated protein levels and protein-cell dissociation. The autoimmune encephalitis antibody NMDAR (+) was detected, leading to a diagnosis of autoimmune encephalitis (NMDAR).

Zhang et al. details the case of a 46-year-old male who initially presented with depressive symptoms, personality changes, and visual hallucinations. Over time, his condition progressed to include memory impairment, disorganised

behaviour, and seizures. Initially misdiagnosed with schizophrenia, the correct diagnosis of LGI1 antibody-associated encephalitis was eventually established through positive serum and cerebrospinal fluid (CSF) tests for LGI1 antibodies. Neuroimaging findings revealed characteristic bilateral temporal lobe lesions.

Li, Baizhu, and Xiuli Shang. "A case of NMDAR Encephalitis with muscular pain as the main presentation." BMC neurology vol. 24,1 142. 27 Apr. 2024, doi:10.1186/s12883-024-03652-w

Zhang, Jin-He et al. "Anti-LGI1 Antibody-Associated Encephalitis Misdiagnosed as Schizophrenia: A Case Report." Schizophrenia bulletin vol. 50,6 (2024): 1273-1276. Doi:10.1093/schbul/sbae155

Anti-LGI1 and anti-CASPR2 encephalitis – MRI characteristics

ABSTRACT: Importance: Rapid and accurate diagnosis of autoimmune encephalitis encourages prompt initiation of immunotherapy toward improved patient outcomes. However, clinical features alone may not sufficiently narrow the differential diagnosis, and awaiting autoantibody results can delay immunotherapy. **Objective:** To identify simple magnetic resonance imaging (MRI) characteristics that accurately distinguish 2 common forms of autoimmune encephalitis, LGI1- and CASPR2-antibody encephalitis (LGI1/CASPR2-Ab-E), from 2 major differential diagnoses, viral encephalitis (VE) and Creutzfeldt-Jakob disease (CJD). **Design, setting, and participants:** This cross-sectional study involved a retrospective, blinded analysis of the first available brain MRIs (taken 2000-2022) from 192 patients at Oxford University Hospitals in the UK and Mayo Clinic in the US. These patients had LGI1/CASPR2-Ab-E, VE, or CJD as evaluated by 2 neuroradiologists (discovery cohort; n = 87); findings were validated in an independent cohort by 3 neurologists (n = 105). Groups were statistically compared with contingency tables. Data were analyzed in 2023. Main outcomes and measures: MRI findings including T2 or fluid-attenuated inversion recovery (FLAIR) hyperintensities, swelling or volume loss, presence of gadolinium contrast enhancement, and diffusion-weighted imaging changes. Correlations with clinical features. **Results:** Among 192 participants with MRIs reviewed, 71 were female (37%) and 121 were male (63%); the median age was 66 years (range, 19-92 years). By comparison with VE and CJD, in LGI1/CASPR2-Ab-E, T2 and/or FLAIR hyperintensities were less likely to extend outside the temporal lobe (3/42 patients [7%] vs 17/18 patients [94%] with VE; P < .001, and 3/4 patients [75%] with CJD; P = .005), less frequently exhibited swelling (12/55 [22%] with LGI1/CASPR2-Ab-E vs 13/22 [59%] with VE; P = .003), and showed no diffusion restriction (0 patients vs 16/22 [73%] with VE and 8/10 [80%] with CJD; both P < .001) and rare contrast enhancement (1/20 [5%] vs 7/17 [41%] with VE; P = .01). These findings were validated in an independent cohort and generated an area under the curve of 0.97, sensitivity of 90%, and specificity of 95% among cases with T2/FLAIR hyperintensity in the hippocampus and/or amygdala. **Conclusions and relevance:** In this study, T2 and/or FLAIR hyperintensities confined to the temporal lobes, without diffusion restriction or contrast enhancement, robustly distinguished LGI1/CASPR2-Ab-E from key differential diagnoses. These observations should assist clinical decision-making toward expediting immunotherapy. Their generalizability to other forms of autoimmune encephalitis and VE should be examined in future studies.

Kelly, Mark J et al. "Magnetic Resonance Imaging Characteristics of LGI1-Antibody and CASPR2-Antibody Encephalitis." JAMA neurology vol. 81,5 (2024): 525-533. doi:10.1001/jamaneurol.2024.0126

Kappa index as a marker for autoimmune encephalitis

ABSTRACT: Background: The presence of inflammatory changes in the cerebrospinal fluid (CSF), including immunoglobulin intrathecal synthesis (IS), can support the diagnosis of autoimmune encephalitis (AE) and allow prompt treatment. The main aim of our study was to calculate the Kappa index as a marker of IS, in patients with AE. **Methods:** Charts of patients undergoing a diagnostic work-up for suspected AE between 2009 and 2023 were reviewed and the Graus criteria applied. CSF and serum kappa free light chains were determined using the Freelite assay (The Binding Site Group) and the turbidimetric Optilite analyzer. **Results:** We identified 34 patients with "definite" AE (9 anti-NMDAR AE and 25 limbic AE) and nine patients with "possible" AE. Five patients (15%) with definite AE had pleocytosis and twelve (34%) showed CSF-restricted oligoclonal bands (OCB) at isoelectric focusing. The Kappa index was >6 in 29.4% and > 3 in 50% of the definite AE patients. It was elevated (>3) in 36.4% of patients with definite AE who resulted negative to OCB testing and was the only altered parameter suggestive of an ongoing inflammatory process in the CNS in three definite AE patients with otherwise normal CSF findings (i.e. normal cell count and protein levels, no OCBs). In the possible AE group, one patient had a Kappa index >3 in the absence of OCB. **Conclusions:** The Kappa index could be useful, as a more sensitive marker of IS and as a supportive marker of neuroinflammation, in the diagnostic work-up of suspected AE.

De Napoli, Giulia et al. "Kappa index in the diagnostic work-up of autoimmune encephalitis." Journal of the neurological sciences vol. 463 (2024): 123146. doi:10.1016/j.jns.2024.123146

Metabolomic signatures to differentiate autoimmune encephalitis

ABSTRACT: Objective: Differentiating forms of autoimmune encephalitis (AE) from other causes of seizures helps expedite immunotherapies in AE patients and informs studies regarding their contrasting pathophysiology. We aimed to investigate whether and how Nuclear Magnetic Resonance (NMR)-based metabolomics could differentiate AE from drug-resistant epilepsy (DRE), and stratify AE subtypes. **Methods:** This study recruited 238 patients: 162 with DRE and 76 AE, including 27 with contactin-associated protein-like 2 (CASPR2), 29 with leucine-rich glioma inactivated 1 (LGI1) and 20 with N-methyl-d-aspartate receptor (NMDAR) antibodies. Plasma samples across the groups were analyzed using NMR spectroscopy and compared with multivariate statistical techniques, such as orthogonal partial least squares discriminant analysis (OPLS-DA). **Results:** The OPLS-DA model successfully distinguished AE from DRE patients with a high predictive accuracy of 87.0 ± 3.1% (87.9 ± 3.4% sensitivity and 86.3 ± 3.6% specificity). Further, pairwise OPLS-DA models were able to stratify the three AE subtypes. Plasma metabolomic signatures of AE included decreased high-density lipoprotein (HDL, -(CH2) n-, -CH3), phosphatidylcholine and albumin (lysyl moiety). AE subtype-specific metabolomic signatures were also observed, with increased lactate in CASPR2, increased lactate, glucose, and decreased unsaturated fatty acids (UFA, -CH2CH=) in LGI1, and increased glycoprotein A (GlycA) in NMDAR antibody patients. **Interpretation:** This study presents the first non-antibody-based biomarker for differentiating DRE, AE and AE subtypes. These metabolomics signatures underscore the potential relevance of lipid metabolism and glucose regulation in these neurological disorders, offering a promising adjunct to facilitate the diagnosis and therapeutics.

Xiong, Wenzheng et al. "Distinct plasma metabolomic signatures differentiate autoimmune encephalitis from drug-resistant epilepsy." Annals of clinical and translational neurology vol. 11,7 (2024): 1897-1908. doi:10.1002/acn3.52112

Characterising the cerebrospinal fluid (CSF) in autoimmune encephalitis

ABSTRACT: Intrathecal synthesis of central nervous system (CNS)-reactive autoantibodies is observed across patients with autoimmune encephalitis (AE), who show multiple residual neurobehavioral deficits and relapses despite immunotherapies. We leveraged two common forms of AE, mediated by leucine-rich glioma inactivated-1 (LGI1) and contactin-associated protein-like 2 (CASPR2) antibodies, as human models to comprehensively reconstruct and profile cerebrospinal fluid (CSF) B cell receptor (BCR) characteristics. We hypothesized that the resultant observations would both inform the observed therapeutic gap and determine the contribution of intrathecal maturation to pathogenic B cell lineages. From the CSF of three patients, 381 cognate-paired IgG BCRs were isolated by cell sorting and scRNA-seq, and 166 expressed as monoclonal antibodies (mAbs). Sixty-two percent of mAbs from singleton BCRs reacted with either LGI1 or CASPR2 and, strikingly, this rose to 100% of cells in clonal groups with ≥4 members. These autoantigen-reactivities were more concentrated within antibody-secreting cells (ASCs) versus B cells ($P < 0.0001$), and both these cell types were more differentiated than LGI1- and CASPR2-unreactive counterparts. Despite greater differentiation, autoantigen-reactive cells had acquired few mutations intrathecally and showed minimal variation in autoantigen affinities within clonal expansions. Also, limited CSF T cell receptor clonality was observed. In contrast, a comparison of germline-encoded BCRs versus the founder intrathecal clone revealed marked gains in both affinity and mutational distances ($P = 0.004$ and $P < 0.0001$, respectively). Taken together, in patients with LGI1 and CASPR2 antibody encephalitis, our results identify CSF as a compartment with a remarkably high frequency of clonally expanded autoantigen-reactive ASCs whose BCR maturity appears dominantly acquired outside the CNS.

Theorell, Jakob et al. "Ultrahigh frequencies of peripherally matured LGI1- and CASPR2-reactive B cells characterize the cerebrospinal fluid in autoimmune encephalitis." Proceedings of the National Academy of Sciences of the United States of America vol. 121,7 (2024): e2311049121. doi:10.1073/pnas.2311049121

Outcomes of encephalitis

Outcomes of encephalitis in poor resources countries

ABSTRACT: Introduction: Acute encephalitis syndrome (AES) poses a significant health challenge to children across India. Late arrival at tertiary care hospitals is a primary contributor to disease severity and poor outcomes. This study by Alam et al identifies the determinants of delayed health seeking and disease severity in AES cases.

Methods: We interviewed the parents/guardians/caregivers of 242 patients with AES admitted at a tertiary care centre. Multivariable analyses identified factors for delayed health seeking, defined as >3days spent at home after symptom onset; and disease severity on admission, defined as need for oxygen support. 131 patients were evaluated for long-term outcomes after 3 years using the Liverpool Outcome Score.

Results: 90 (37.2%) patients had delayed health seeking and 202 (83.5%) had severe disease on admission. Lack of awareness about AES was a significant risk factor (OR 2.4, 95% CI 1.2 to 5.0, p=0.01) for delayed health seeking. Disease severity was associated with seeking treatment from uncertified medical practitioners (UMPs) (OR 7.3, 95% CI 2.7 to 19.8, p<0.01) and ≥2days of time spent between the first healthcare provider and tertiary care admission (OR 3.0, 95% CI 1.3 to 7.3, p=0.01). At follow-up, disability was observed in 18.3% (n=24) of the patients.

Conclusion: Delayed health seeking, treatment from UMPs and multiple healthcare consultations contributed to disease severity in patients with AES on admission at tertiary care health facilities.

ABSTRACT: Morillos et al describe a series of patients diagnosed with AE in a resource-limited public hospital in southern Brazil to analyze therapeutics and outcomes.

Methods: We retrospectively reviewed the electronic medical records of patients diagnosed with AE at the Hospital de Clínicas de Porto Alegre from 2014 to 2022. Data collected included clinical presentation, neuroimaging, cerebrospinal fluid testings, electroencephalogram, autoantibodies, treatments, outcomes, follow-up time, degree of neurological impairment, and mortality.

Results: Data from 17 patients were retrieved. Eleven cases were classified as definite AE and 6 as possible AE. Autoantibodies were identified in 9 patients. Timing for diagnosis was impacted by the high costs associated with autoantibody testing. Most patients became functionally dependent (82.4%) and most survivors remained with autoimmune-associated epilepsy (75%). Five patients died during hospitalization, and one after a 26-month of follow-up.

Conclusion: In this resource-limited hospital, patients with AE had a worse clinical outcome than that previously described in the literature. Development of epilepsy during follow-up

and mortality were greater, whilst functional outcome was inferior. Autoantibody testing was initially denied in most patients, which impacted the definitive diagnosis and the use of second-line therapies.

Alam, Umaer et al. "Factors associated with delayed health-seeking behaviour and disease severity on admission among patients diagnosed with acute encephalitis syndrome: an observational study from North India." BMJ public health vol. 2,2 e001071. 24 Nov. 2024, doi:10.1136/bmjph-2024-001071

Morillos, Matheus Bernardon et al. "Autoimmune encephalitis in a resource-limited public health setting: a case series analysis." "Encefalite autoimune em um hospital universitário público: análise de uma série de casos." Arquivos de neuro-psiquiatria vol. 82,2 (2024): 1-10. Doi:10.1055/s-0044-1779054

Predictors of disease severity and quality of life in anti-LGI1 encephalitis

ABSTRACT: Aboseif et al 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: Thirty 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.

Patient-reported quality-of-life (QoL) and carer impacts are not reported after leucine-rich glioma-inactivated 1-antibody encephalitis (LGI1-Ab-E). In a study by Binks et al, from 60 patients, 85% (51 out of 60) showed one abnormal score across QoL assessments and 11 multimodal validated questionnaires. Compared to the premorbid state, QoL significantly deteriorated ($p < 0.001$) and, at a median of 41 months, fatigue was its most important predictor ($p = 0.025$). In total, 51% (26 out of 51) of carers reported significant burden. An abbreviated five-item battery explained most variance in QoL. Wide-ranging impacts post-LGI1-Ab-E include decreased QoL and high caregiver strain. We identify a rapid method to capture QoL in routine clinic or clinical trial settings.

Aboseif, Albert et al. "Clinical Determinants of Longitudinal Disability in LGI-1-IgG Autoimmune Encephalitis." Neurology® neuroimmunology & neuroinflammation vol. 11,1 e200178. 10 Nov. 2023, doi:10.1212/NXI.0000000000200178

Binks, Sophie N M et al. "Fatigue predicts quality of life after leucine-rich glioma-inactivated 1-antibody encephalitis." Annals of clinical and translational neurology vol. 11,4 (2024): 1053-1058. Doi:10.1002/®3.52006

Anti-NMDAR encephalitis outcomes in children and adults

ABSTRACT: Mazowiecki et al aimed to evaluate NEOS score and biomarker (neurofilament light chains [NfL], total-Tau protein, glial fibrillary acidic protein, and serum cytokines) correlation with modified Rankin Scale (Mrs), cognitive impairment, and clinical recovery in pediatric NMDARE over 2 years.

Methods: In this French multicenter observational study, 104 pediatric patients with NMDARE were followed for a minimum of 2 years. Clinical data and serum/plasma samples were collected. Biomarker levels, measured using electroluminescence mesoscale discovery (MSD) S-PLEX, were compared between patients and controls and assessed for correlations with disease activity, Mrs, cognitive/language impairment, and recovery status at 2 years.

Results: At a median follow-up of 39.5 months, 68 percent of patients had unfavorable recovery and 54% had significant cognitive impairment. Both outcomes were strongly associated with younger age at diagnosis (OR 6.10 [1.91-27.3] $p < 0.01$ and 5.69 [1.46-27.7] $p = 0.02$, respectively). A higher NEOS score was significantly correlated with increased cognitive impairment (OR 2.53 [1.52-4.21], $p < 0.001$), higher Mrs scores (OR 2.12 [1.34-3.57], $p < 0.01$), and unfavorable recovery at 2 years (OR 2.00 [1.30-3.06], $p = 0.015$). Elevated NfL levels were significantly associated with unfavorable recovery (OR 3.62 [1.29-10.9] $p = 0.012$) and severe cognitive impairment (OR 3.77 [1.38-10.9] $p = 0.012$) at 2 years. The combined area under the curve (AUC) for NfL and NEOS was significantly higher than the AUCs of NEOS and NfL alone ($p = 0.01$).

Discussion: The NEOS score strongly predicts long-term outcomes in NMDARE, with its predictive value extending beyond the first-year Mr prediction. NfL levels at disease onset seem to improve accuracy in predicting poor outcomes, providing valuable information for treatment decisions and future clinical trials.

ABSTRACT: Heine et al aimed to evaluate postacute neuropsychiatric symptoms, subjective cognitive complaints, and disease coping mechanisms and identify predictors of health-related quality of life (HRQoL) after N-methyl-D-aspartate receptor (NMDAR) encephalitis. This cross-sectional observational study investigated patients with NMDAR encephalitis in the postacute phase. Psychometric scales included assessment of neuropsychiatric symptoms (i.e., fatigue, sleep, anxiety, and depressive symptoms), HRQoL, everyday independence, metamemory (i.e., self-rated ability, satisfaction, and use of strategies), and coping strategies (i.e., self-efficacy, disease-related coping, and stress management). A total of 50 patients (mean age 26.0 ± 10.1 years, 86% female) participated at a median of 4.15 (range 0.3-30.3) years after symptom onset. Patients reported significantly increased levels of anxiety (Beck Anxiety Inventory: 10.5 ± 7.7 [mean ± SD], 95% CI [8.32-12.71], p < 0.001) and depressive (Beck Depression Inventory-II: 11.4 ± 7.7 [9.22-13.62], p = 0.001) symptoms compared with the normative population. Both sleep problems (Pittsburgh Sleep Quality Index: 5.8 ± 3.0 [4.98-6.66], p < 0.001) and motor and cognitive fatigue (Fatigue Scale for Motor and Cognitive Function: 50.5 ± 23.1 [42.5-58.4], p < 0.001) were significantly more prevalent. Moreover, lower self-rated memory ability (Multifactorial Memory Questionnaire score: 54.6 ± 8.5 [52.1-57.1], p = 0.004) was associated with greater reliance on compensatory strategies and memory aids (r = -0.41, p = 0.004). Patients used significantly fewer cognitive coping strategies, such as relativization (11.7 ± 4.7 [10.3-13.1], p = 0.001), while depressive coping prevailed (49.1 ± 15.5 [44.5-53.8], p < 0.001). It is important to note that HRQoL was predicted by self-reported affective symptoms, self-efficacy, and coping behaviors in multivariable regression analyses, but not by acute disease severity or postacute physical disability. The team's findings show that persistent neuropsychiatric and subjective cognitive concerns explain a large part of the reduced quality of life in patients with NMDAR encephalitis. These findings have important implications for a patient-centered postacute care and the role of disease coping strategies in the neurorehabilitation of autoimmune encephalitis.

ABSTRACT: Chen et al aimed to assess the daily function of children with anti-N-methyl-d-aspartate receptor encephalitis (NMDARe) after a minimal follow-up of 5 years. Methods: Patients 18 years and younger by the time of disease onset, whose serum and CSF were studied in our center between 2013 and 2017, were included in the study. Patients' daily life function was assessed by their physicians using a 15-domain question format (Liverpool Outcome Score). Results: Of 76 patients, 8 (11%) died and 68 were followed for a mean of 7.1 years (SD 1.5 years, range: 5.0-10.1). Three outcome patterns were identified: full recovery (50; 73%); behavioral and school/working deficits (12; 18%); and multidomain deficits (6; 9%) involving self-care ability, behavioral-cognitive impairment, and seizures. Younger age of disease onset was significantly associated with multidomain deficits (OR 1.6, 95% CI 1.02-2.4, p = 0.04), particularly in children younger than 6 years, among whom 8 of 23 (35%) remained sociofamiliar dependent. Discussion: After a minimal follow-up of 5 years, most children with NMDARe had substantial or full functional recovery, but approximately one-fifth remained with behavioral and school/working deficits. The younger the patient at disease onset, the more probable it was to remain with multidomain deficits and dependent on sociofamiliar support.

Chen, Li-Wen et al. "Very Long-Term Functional Outcomes and Dependency in Children With Anti-NMDA Receptor Encephalitis." Neurology® neuroimmunology & neuroinflammation vol. 11,3 (2024): e200235. Doi:10.1212/NXI.0000000000200235

Heine, Josephine et al. "Patient-Reported Outcome Measures in NMDA Receptor Encephalitis." Neurology® neuroimmunology & neuroinflammation vol. 12,1 (2025): e200343. D

Mazowiecki, Maxime et al. "Long-Term Clinical and Biological Prognostic Factors of Anti-NMDA Receptor Encephalitis in Children." Neurology® neuroimmunology & neuroinflammation vol. 12,2 (2025): e200346. Doi:10.1212/NXI.0000000000200346 Doi:10.1212/NXI.0000000000200343

Anti-$GABA_B$ receptor encephalitis prognosis

ABSTRACT: Background and objectives: While patients with paraneoplastic autoimmune encephalitis (AE) with gamma-aminobutyric-acid B receptor antibodies ($GABA_B$R-AE) have poor functional outcomes and high mortality, the prognosis of nonparaneoplastic cases has not been well studied. **Methods:** Patients with $GABA_B$R-AE from the French and the Dutch Paraneoplastic Neurologic Syndromes Reference Centers databases were retrospectively included and their data collected; the neurologic outcomes of paraneoplastic and nonparaneoplastic cases were compared. Immunoglobulin G (IgG) isotyping and human leukocyte antigen (HLA) genotyping were performed in patients with available samples. **Results:** A total of 111 patients (44/111 [40%] women) were enrolled, including 84 of 111 (76%) paraneoplastic and 18 of 111 (16%) nonparaneoplastic cases (cancer status was undetermined for 9 patients). Patients presented with seizures (88/111 [79%]), cognitive impairment (54/111 [49%]), and/or behavioral disorders (34/111 [31%]), and 54 of 111 (50%) were admitted in intensive care unit (ICU). Nonparaneoplastic patients were significantly younger (median age 54 years [range 19-88] vs 67 years [range 50-85] for paraneoplastic cases, p < 0.001) and showed a different demographic distribution. Nonparaneoplastic patients more often had CSF pleocytosis (17/17 [100%] vs 58/78 [74%], p = 0.02), were almost never associated with KTCD16-abs (1/16 [6%] vs 61/70 [87%], p < 0.001), and were more frequently treated with second-line

immunotherapy (11/18 [61%] vs 18/82 [22%], p = 0.003). However, no difference of IgG subclass or HLA association was observed, although sample size was small (10 and 26 patients, respectively). After treatment, neurologic outcome was favorable (mRS ≤2) for 13 of 16 (81%) nonparaneoplastic and 37 of 84 (48%) paraneoplastic cases (p = 0.03), while 3 of 18 (17%) and 42 of 83 (51%) patients had died at last follow-up (p = 0.008), respectively. Neurologic outcome no longer differed after adjustment for confounding factors but seemed to be negatively associated with increased age and ICU admission. A better survival was associated with nonparaneoplastic cases, a younger age, and the use of immunosuppressive drugs. **Discussion:** Nonparaneoplastic $GABA_BR$-AE involved younger patients without associated KCTD16-abs and carried better neurologic and vital prognoses than paraneoplastic $GABA_BR$-AE, which might be due to a more intensive treatment strategy. A better understanding of immunologic mechanisms underlying both forms is needed.

Lamblin, Florian et al. "Comparative Study of Paraneoplastic and Nonparaneoplastic Autoimmune Encephalitis With $GABA_BR$ Antibodies." Neurology(R) neuroimmunology & neuroinflammation vol. 11,3 (2024): e200229. doi:10.1212/NXI.0000000000200229

Neuropsychological tests (NPT) in autoimmune encephalitis

ABSTRACT: Background and objectives: Identifying optimal methods for evaluation and monitoring of cognitive outcomes in AE is important for clinical care and research. This scoping review aimed to evaluate neuropsychological tests (NPT) that are most frequently impaired in AE cohorts to provide recommendations for a standardized NPT battery for AE outcome.

Methods: PubMed search for studies examining NPT in patients with AE was conducted on June 9, 2023. Studies were screened for inclusion/exclusion criteria as follows: at least 1 NPT, individual NPT test scores with comparison with healthy controls or normative data and neural-IgG status, total sample size ≥5, and English manuscript available.

Results: The search yielded 5,393 studies, of which 3,359 were screened, 107 were full text reviewed, and 32 met inclusion/exclusion criteria, anti-NMDA-R (k = 18), anti-LGI1 (k = 10), anti-$GABA_B$-R (k = 2), anti-GAD-65 (k = 4), and anti-CASPR2 (k = 3). The cognitive domains most frequently impaired were visual and verbal episodic memory, attention/working memory, processing speed, and aspects of executive functions.

Discussion: Given the dearth of literature examining NPT in AE in combination with small sample sizes and methodological differences, more research in this area is needed. However, we provide recommendations for a test battery to be used in future studies, with the aim of standardizing research in this area. Based on the available literature, we recommend the use of comprehensive NPT batteries, spanning all cognitive domains. The highest yield measures may include the tests of (1) visual and verbal learning/memory, (2) basic and sustained attention, (3) processing speed, and (4) executive functions.

Galioto, Rachel et al. "Neuropsychological Testing in Autoimmune Encephalitis: A Scoping Review." Neurology® neuroimmunology & neuroinflammation vol. 11,1 e200179. 10 Nov. 2023, doi:10.1212/NXI.0000000000200179

Criminal behaviours: postencephalitic association

ABSTRACT: Background and purpose: Despite it being an immunotherapy-responsive neurological syndrome, patients with autoimmune encephalitis (AE) frequently exhibit residual neurobehavioural features. Here, we report criminal behaviours as a serious and novel postencephalitic association.

Methods: This retrospective cohort study included 301 AE patients. Five of who committed crimes underwent direct assessments and records review alongside autoantibody studies.

Results: Five of 301 patients (1.7%) with AE exhibited criminal behaviours, which included viewing child pornography (n = 3), repeated shoplifting, and conspiracy to commit murder. All five were adult males, with LGI1 autoantibodies (n = 3), CASPR2 autoantibodies, or seronegative AE. None had evidence of premorbid antisocial personality traits or psychiatric disorders. Criminal behaviours began a median of 18 months (range = 15 months-12 years) after encephalitis onset. At the time of crimes, two patients were immunotherapy-naïve, three had been administered late immunotherapies (at 5 weeks-4 months), many neurobehavioural features persisted, and new obsessive behaviours had appeared. However, cognition, seizure, and disability measures had improved, alongside reduced autoantibody levels.

Conclusions: Criminal behaviours are a rare, novel, and stigmatizing residual neurobehavioural phenotype in AE, with significant social and legal implications. With caution towards overattribution, we suggest they occur as part of a postencephalitis limbic neurobehavioural syndrome.

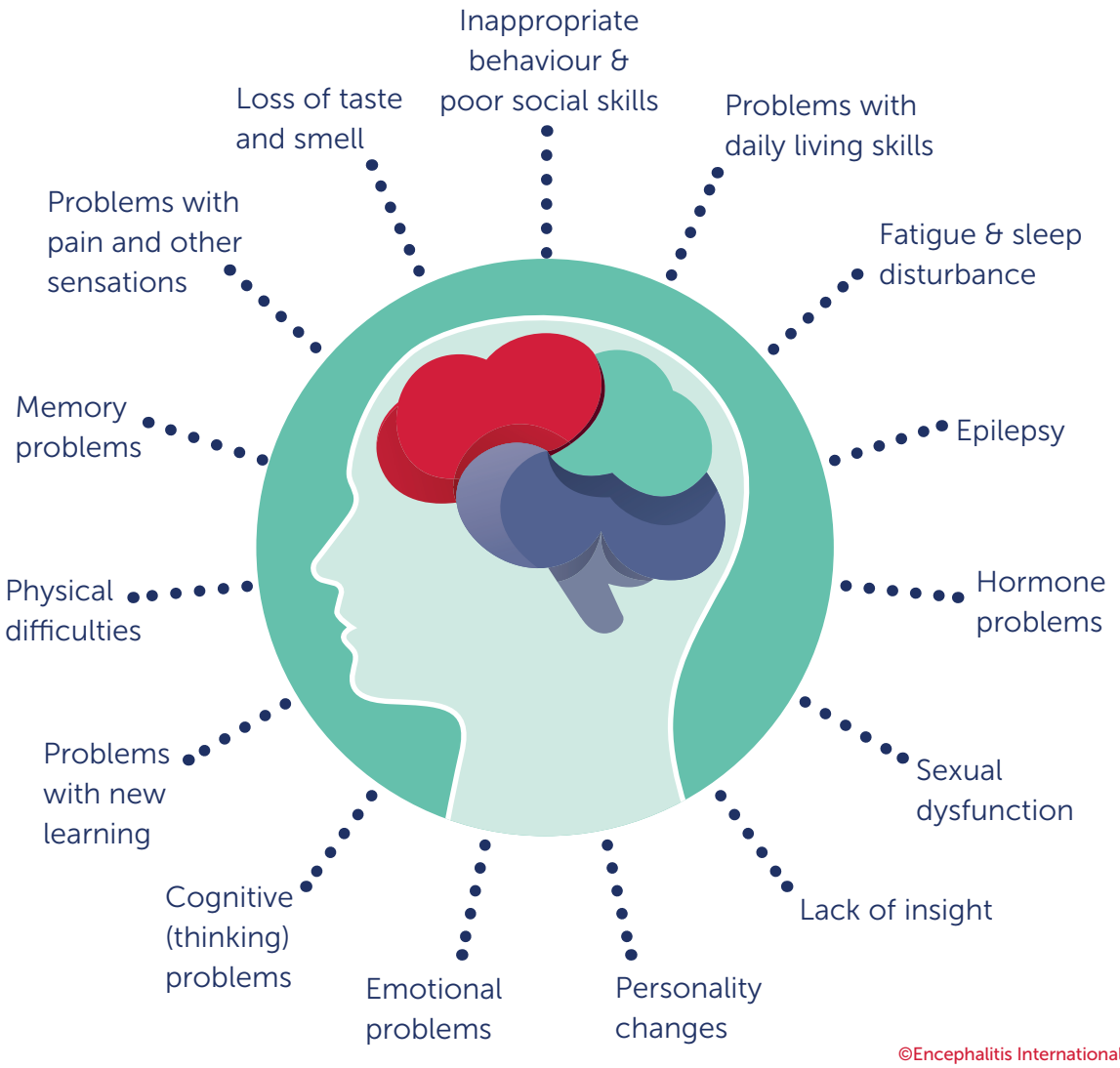
Michael, Sophia et al. "Criminality in patients with autoimmune encephalitis: A case series." European journal of neurology vol. 31,4 (2024): e16197. doi:10.1111/ene.16197

Cost of encephalitis

ABSTRACT: Encephalitis is a significant global health problem, especially in children. Knowledge of its economic burden is essential for policymakers in prioritizing the development and implementation of interventions but remains limited. An observational study was prospectively conducted at a major children's hospital in Ho Chi Minh City, Vietnam from 2020 to 2022. Data on direct medical costs, direct nonmedical costs, and productivity costs were collected alongside demographic information, clinical features, diagnosis, severity, and outcomes of study participants. This was used to undertake a cost of illness analysis from a societal perspective. Data were collected from a total of 164 pediatric patients. The median cost of illness was estimated at US $1,859 (interquartile range [IQR]: US $1,273-$3,128). The direct costs were the main cost driver, accounting for 83.9% of the total cost of illness (US $1,560; IQR: US $975-$2,460). The productivity costs accounted for a median of US $275 (IQR: US $154-$474). The cost of illness was higher in more severe patients, patients with sequelae, patients with morbidities, and ventilated patients. Most direct medical costs were attributed to hospitalization and resulted in out-of-pocket payments from the patient's family (30.2%; US $316). The results showed that the cost of illness of encephalitis in children is considerable and will be useful for policymakers in prioritizing resources for the development and implementation of intervention strategies to reduce the burden of pediatric encephalitis.

Huong, Nguyen Hoang Thien et al. "A Cost of Illness Analysis of Children with Encephalitis Presenting to a Major Hospital in Vietnam." The American journal of tropical medicine and hygiene vol. 112,2 422-430. 19 Nov. 2024, doi:10.4269/ajtmh.24-0409

OUTCOMES AFTER ENCEPHALITIS



How Encephalitis International facilitates and supports PPIE in research studies

Encephalitis International is prioritising the ways in which we can support and facilitate Patient and Public Involvement and Engagement (PPIE) in research. We can support researchers at all stages of their project; as co-applicants on funding applications, ongoing study or trial support and assisting with disseminating findings. Encephalitis International also offers other research-related support opportunities such as networking opportunities, corporate collaboration, and we also have the capacity to support translated resources in selected languages.

We are the leading international encephalitis non-profit, and our extensive 30-year expertise and experience with those affected and the professionals supporting them gives us the opportunity to make a meaningful and unique contribution to research projects. Our contributions and involvement as a patient organisation help to ensure that the voice of patients and their families are held at the centre of encephalitis research.

Our CEO and Patient and Public Involvement Manager facilitate and are members of several international patient panels and clinical trial working groups, which helps us to achieve our aim of improving the accessibility of research to the lay community. In doing this, we are continually working on increasing the participation of a diverse range of patients into research.

To ensure that global change happens we are committed to seeking mutually beneficial partnerships, driven by our vision and the voice and needs of those affected by encephalitis, which will help to drive both the mission of EI and that of the scientific, academic, medical, and research teams we work with.

Partnerships will be tailored to the needs of the researchers and the priorities of the project, helping to enhance the impact of the research funding, including liaising with policy makers or industry where appropriate to drive impact.

We work with scientific, research, medical, and academic institutions, other non-profit organisations, and research funders around the world to develop exciting partnerships.

Read more about the ways in which Encephalitis International can support your PPIE work here: www.encephalitis.info/collaborations-in-research

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. Each year, we are fortunate to have a global network of fundraisers undertaking a range of activities for us - everything from sponsored walks, runs and swims through to online gaming competitions, concerts and obstacle courses.

We also receive support from corporate partners, trusts, foundations and philanthropists across the world.

All these wonderful people ensure the continuation of our support service, sponsor our events and campaigns, and kindly donate to our appeals and initiatives, including our aims to raise at least £100,000 each year to fund life-saving encephalitis research.

Can you help?

- Could you take part in a challenge event to raise awareness and funds?
- Do you work for or know a company that might make us their Charity of the Year?
- Have you any contacts with trusts or foundations we can apply to for funding?
- Can you put us in touch with an individual or organisation who would like to sponsor our research work or support services?

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!

Thank you
Encephalitis International Fundraising Team

Get in touch!

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