RESEARCH SUMMARY

ADVANCES IN ENCEPHALITIS

2021

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Welcome to the Encephalitis Society's Research Summary 2021

Dr Ava Easton at the World Health Organization

The Research Summary - Advances in Encephalitis 2021 presents a collection of research papers published during that same year.

Studies were conducted across the continents to understand the current epidemiology of encephalitis (infectious and autoimmune). Whilst in some countries identification of a known cause has increased (65.7% in France), in some countries it remains low (35.2% in Brazil), and unfortunately in other parts of the world (for example Western Sub-Saharan Africa) causation cannot be ascertained as studies to understand it remain scarce.

Although in some countries the pandemic may be ending, many studies looked at the neurological complications of COVID-19. The rates of encephalitis-associated COVID-19 cases varied across different studies. However, it has been shown that the risk of encephalitis was greater in populations with COVID-19 than in non-COVID-19 populations.

Red flags among infectious encephalitis were made regarding the spread of tick-borne encephalitis (TBE) across Europe, the severity of varicella zoster and influenza encephalitis, the rise in cases of measles and resultantly SSPE, all of which are vaccine-preventable encephalitides. This poses the question what the medical, research and scientific communities can do now to improve vaccine uptake to limit future epidemics.

Diagnosis and management of autoimmune encephalitis has improved with studies now providing guidelines for diagnosis and treatment; however, certain categories of the population are still at risk of delays or misdiagnosis due to complicated and unusual clinical presentations. Therefore, studies looking into autoimmune encephalitis resembling dementia, patients with focal epilepsy of unknown aetiology, multiple antibodies or seronegative autoimmune encephalitis, and encephalitis as a severe immune-related adverse event secondary to treatment with immune checkpoint inhibitors, are important.

An increased number of studies have looked at predictors of, and the outcomes of, encephalitis. It is important that often hidden outcomes for patients such as fatigue and sleep difficulties, as well as the more visible such as seizures, are being given attention as these can impact greatly on the quality of life of people affected by encephalitis. Furthermore, looking at how patients themselves experience and make sense of their recovery is important. Areas like this are often not referred to in literature however they play an important role in the provision of support and information needed by these patients and their families.

Despite the various difficulties associated with the pandemic, the Encephalitis Society has continued its vision of ensuring encephalitis matters by supporting patients worldwide, raising global awareness of the condition and providing opportunities for learning, development, research and networking among professionals. We are collaborating with global stakeholders, including the World Health Organization, looking at the global impact of encephalitis. We have held our first masterclass on Japanese encephalitis following the Japanese encephalitis outbreak in Australia and following its success we have scheduled further masterclasses to include TBE and measles.

We have launched our fourth year of research seed funding, which is aimed again at projects in low-to-middle income countries where research is much needed. The deadline is 9th September (www.encephalitis.info/seedfund). Plans for our annual conference - Encephalitis 2022 are underway. Encephalitis 2021 saw a record number of participants (314 delegates from 50 countries) so we urge you to book your place now (www.encephalitis.info/encephalitis-2022). The best way to keep up to date with all our news and activities and help us with our mission to save lives and build better futures is to become a member of the Encephalitis Society. Sign up for a free membership here today: www.encephalitis.info/professional-membership.

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

Dr Ava Easton
CEO, Encephalitis Society

Contents

Epidemiology of encephalitis

"Although HSV and VZV are still the first-line pathogens to target when managing encephalitis patients, emerging etiologies – especially arboviruses but also long-known diseases such as measles – have to be considered in the differential diagnosis."
(Mailles et al., 2022)

Infectious encephalitis in Europe, Western Sub-Saharan Africa, South and Central America and Asia

Mailles et al. (2022) conducted a prospective study (ENCEIF) to assess the epidemiology of encephalitis in France. The study included 494 patients aged between 18 and 94 years from 62 hospitals. Only 12% of patients were immunocompromised. The authors noted two important clinical features: 19% of patients (with herpes simplex virus- HSV, varicella zoster virus-VZV and unknown cause) did not present with fever and only 58% of patients with VZV encephalitis presented with rash. Overall, 42% of patients required admission to intensive care unit. The mortality rate was 8% of which 32.4% of deaths occurred in patients with HSE. Using the Glasgow Outcome Scale score, 61.1% of patients had a good recovery. A cause was identified in 65.7% of patients: viruses (81.8%), bacteria (14.8%), funghi (1.2%). Vaccine-preventable diseases were identified in 23% of patients, with three cases being caused by measles virus.

Comparing with a study from 2007, the proportion of cases with a known aetiology increased by 13%; 32 pathogens were identified in 2016–2019 (only 17 in 2007). Tuberculosis cases decreased, but tick-borne encephalitis (TBE) cases increased, with TBE virus being the third identified agent after HSV and VZV. The authors concluded that that epidemiology of encephalitis has changed. There is a need to monitor and adapt management guidelines.

A scoping review (Rezaei and Mateen, 2021) that looked at cohort studies and case studies on meningitis and encephalitis in Western Sub-Saharan Africa identified 38 pathogens and a very high death rate (39%). However, the authors highlighted the lack of published literature to cover this region, which makes it difficult to understand the range of central nervous system pathogens in the population. Even those reported were mostly single cases or cases treated abroad. The authors urged for better screening and diagnosis among this population.

Leon et al. (2021) reported a known cause in 35.2% of patients with suspected nervous system infections in Brazil: 0.2% HSV1; 0.5% HSV2; 1.9% VZV; 1% Epstein-Barr virus (EBV); 0.2% cytomegalovirus; 7.6% HHV6; 7.1% non-polio enterovirus; 16.0% dengue virus, 0.7% yellow fever virus and 5% Zika virus.

In Poland, a study by Zbrzeźniak and Paradowska-Stankiewicz (2021) identified an increase in viral infections from 1,212 to 1,533 cases and a decrease in all bacterial causes from 886 to 873 cases (except for *S. pneumoniae*). Among laboratory confirmed cases of meningitis and/or encephalitis of known aetiology, cases caused by *Neisseria meningitidis* (102 cases), *Streptococcus pneumoniae* (212 cases) and tick-borne encephalitis (197 cases) were predominant.

The authors noted the difficulties in determining the cause for meningitis/encephalitis cases.

Ungureanu et al. (2021) reviewed the encephalitis, meningoencephalitis and meningitis cases treated in University Hospital Bern, Switzerland over three years. Off the total of 258 cases, HSV was the most common cause of encephalitis (18%); TBEV was the most common cause of nonbacterial meningoencephalitis (46%), and *Streptococcus pneumoniae* was the most common cause of bacterial meningoencephalitis/meningitis (49%). One third of patients had no cause identified.

In Odisha, India, a prospective hospital-based study (Das et al., 2021) that included 92 consecutive patients with clinically diagnosed acute encephalitis syndrome (AES) detected antibodies to leptospirosis in 30 patients, to Japanese encephalitis virus (JEV) in 27 patients, to EBV in 22, scrub typhus in 11, HSV1 in four, HSV2 in three and dengue in three patients. In another study by Tandale et al. (2021) of 280 cases who fulfilled the AES case definition, of 140 patients with viral causes, 31 patients had a cause established: JEV (22), chikungunya (5), Dengue (2) and Chandipura (2).

Sevilla-Acosta et al. (2021) investigated the epidemiology of childhood encephalitis in Costa Rica. During the study, the incidence of acute encephalitis in Costa Rica was 3.6 cases per 100,000 children. The cause was established in half of the patients (52.5%): probable or confirmed in 14 cases (six cases viral, the most common enterovirus; six cases bacterial, the most common *Streptococcus pneumoniae;* and two cases autoimmune) and possible in seven patients. No cases of HSV were reported. Nearly half of children 47.5% required admission to paediatric intensive care unit. Six patients died (15% mortality): three with viral encephalitis, two with bacterial encephalitis and one with unknown cause encephalitis. Sequelae were reported in 45.0% of patients: 25% mild and 20% moderate to severe.

Das B.K., Mohanty S., Sahoo P.K., et al. (2021) Association of leptospirosis and scrub typhus in acute encephalitis syndrome in a tertiary care hospital in Odisha, India. Trans R Soc Trop Med Hyg; 115(9): 1088-1090.

Leon L.L., Lima R.G., Boffi L.C., et al. (2021) Arbovirus, herpesvirus, and enterovirus associated with neurological syndromes in adult patients of a university hospital, 2017-2018. Rev Soc Bras Med Trop; 54: e0127.

Mailles A., Argemi X., Biron C., et al. (2022) Changing profile of encephalitis: Results of a 4-year study in France. Infect Dis Now: 52(1): 1-6.

Rezaei S.J., Mateen F.J. (2021) Encephalitis and meningitis in Western Africa: a scoping review of pathogens. Trop Med Int Health; 26(4): 388-396.

Sevilla-Acosta F., Gutiérrez-Mata A., Yock-Corrales A., et al. (2021) Epidemiology, etiology and clinical aspects of childhood acute encephalitis in a tertiary pediatric hospital in Costa Rica. Pediatr Infect Dis J; 40(3): 186-190.

Tandale B.V., Bondre V.P., Sapkal G.N., et al. (2021) Childhood encephalitis hospitalizations associated with virus agents in medium-endemic states in India. J Clin Virol; 144: 104970.

Zbrzeźniak J., Paradowska-Stankiewicz I. (2021) Meningitis and encephalitis in Poland in 2018. Przegl Epidemiol; 75(1): 63-75.

Ungureanu A., van der Meer J., Bicvic A., et al. (2021) Meningitis, meningoencephalitis and encephalitis in Bern: an observational study of 258 patients. BMC Neurol; 21(1): 474.

Epidemiology of autoimmune encephalitis (AE)

Ren et al. (2021) explored the epidemiology of AE in China and argued that it has changed significantly: fewer patients with positive AE antibodies, fewer patients with anti-NMDAR encephalitis and increased number of patients with infrequently observed autoantibodies and positivity for more than one antibody.

Wong et al. (2021) reported a high incidence of anti-NMDAR encephalitis in Malaysia, where the population consists predominantly of Austronesians and with a Chinese minority. The annual incidence was 2.29/million (Austronesians: 2.56/million, Chinese: 1.31/million). Among the paediatric population, the incidence was Austronesians: 3.63/million and Chinese: 2.59/million. The authors explain this high incidence compared with the predominantly Caucasian populations in Europe by racial and genetic factors. Nissen et al. (2021) reported an incidence of anti-NMDAR in Denmark of currently 0.17/100,000 persons per year, which has increased since 2009. Other characteristics include a higher median age, less frequent tumour association and lower female:male ratio.

In Tunisia, Douma et al. (2021) reviewed 19 patients with AE (median age of 7.68 years). Eleven patients were diagnosed with anti-NMDA receptor encephalitis, four cases with anti-Ma2 encephalitis, three cases with anti-GAD encephalitis, and one case with anti-SOX1 encephalitis.

In the first observational study from Iran on AE, Etemadifar et al. (2021) reported 39 patients. The mean age was 34.9 ± 12.8 years and 21 were female. The most detected antibody was anti-NMDAR (66.7%), followed by anti-$GABA_BR$ (20.5%), anti-Zic4 (10.3%) and anti-GAD65 (2.6%) antibodies. Four patients had AE following herpes simplex encephalitis.

Wickramasinghe et al. (2021) reported clinical characteristics of patients presenting with AE in Sri Lanka. In total, 65 patients fulfilled diagnostic criteria for probable anti-NMDAR encephalitis and six for limbic encephalitis (LE). NMDAR-antibodies were detectable in 44.6% of patients with probable anti-NMDAR encephalitis. None of the patients with LE had antibodies detectable.

Douma B., Ben Younes T., Benrhouma H., et al. (2021) Autoimmune encephalitis in Tunisia: Report of a pediatric cohort. J Immunol Res: 10: 6666117.

Etemadifar M., Aghababaei A., Nouri H., et al. (2021) Autoimmune encephalitis: the first observational study from Iran. Neurol Sci; 43(2): 1239-1248.

Nissen M.S., Ørvik M.S., Nilsson A.C., et al. (2021) NMDA-receptor encephalitis in Denmark from 2009 to 2019: a national cohort study. J Neurol; 269(3): 1618-1630.

Ren H., Fan S., Zhao Y., Guan H. (2021) The changing spectrum of antibody-mediated encephalitis in China. J Neuroimmunol; 361: 577753.

Wickramasinghe N., Dasanayake D., Malavige N., et al. (2021) Autoimmune encephalitis in a South Asian population. BMC Neurol; 21(1): 203.

Wong C.K., Hor J.Y., Loo Y.P., et al. (2021) High incidence of NMDAR encephalitis among Austronesians: A population-based study in Sabah, Malaysia. J Neuroimmunol; 356: 577584.

Herpes viruses: important causes of encephalitis

In a study by Garcia et al. (2021) on 502 patients suspected with encephalitis at the National Institute of Neurology and Neurosurgery (NINN) of Mexico, 59 had herpetic encephalitis confirmed by RT-PCR: 36% were positive for HSV1, 25% for Epstein-Barr virus, 17% for varicella zoster virus (VZV), 14% for cytomegalovirus, 5% for HHV6, and 3% for HSV2.

Lee et al. (2021) reviewed cases of HSV-1, HSV-2, and VZV central nervous system (CNS) infections identified at Pusan National University Hospital (South Korea) between 2010 and 2018. Among 471 patients with aseptic meningitis and encephalitis, the causative virus was identified in 145 patients. Eighty patients were diagnosed with herpes viruses as causative agents, 59 of them had meningitis, and 21 had encephalitis. Overall, there were 11 patients with HSV-1, 27 with HSV-2, and 42 with VZV CNS infections. The distribution of cases by age showed different patterns depending on the type of herpes virus infection. Compared with the HSV-1 group, the median age in the HSV-2 group was younger (HSV-1: 58 years; HSV-2: 38 years) and patients with VZV infections showed a bimodal age distribution. Encephalitis was more common in the HSV-1 group, which was associated with a poor prognosis at discharge.

Akkaya (2021) retrospectively investigated the prevalence of HSV-1 and HSV-2 in patients hospitalised with suspected meningitis/encephalitis in Konya province (Turkey) using the multiplex real-time polymerase chain reaction method. From 525 samples who had positive cerebrospinal fluid samples, ten were HSV positive: seven HSV-1 (two paediatric and five adults) and three HSV-2 (all paediatric).

Akkaya O. (2021) Prevalence of herpes simplex virus infections in the central nervous system. Clin Lab; 67(7).

Garcia E., Fajardo Q.F., Figueroa R. et al. (2021) Herpesvirus encephalitis diagnosed by polymerase chain reaction at the National Institute of Neurology of Mexico. J. Neurovirol; 27: 397-402.

Lee G.H., Kim J., Kim H.W., & Cho J.W. (2021). Herpes simplex viruses (1 and 2) and varicella-zoster virus infections in an adult population with aseptic meningitis or encephalitis: A nine-year retrospective clinical study. Medicine; 100(46): e27856.

West Nile virus (WNV) in the USA and Spain

García San Miguel Rodríguez-Alarcón et al. (2021) reported an increase of WNV cases in Spain. During the 2020 season, a total of 77 human cases of WNV infection (median age, 65 years; 60% males) were detected in the south-west of Spain; 72 (94%) of these cases developed WN neuroinvasive disease (WNND), presenting as meningoencephalitis, seven of which were fatal. In the previous two decades, only six human cases of WNND were detected in Spain. Reduced activities for vector control this season, together with other factors, might have contributed to the massive increase. The authors conclude that, going forward, maintenance of vector control activities and an update of the vector-borne diseases response plan in Spain is needed.

McDonald et al. (2021) reported the national surveillance for WNV disease data between 2009–2018 in the USA. In total, there were 21,869 confirmed or probable cases of WNV disease, with 59% of those being WNND. The WNND occurred more predominant among older ages (≥70 years) and the majority of patients were hospitalised. Half of WNND cases were encephalitis (53%), with a median age of 66 years and predominant male. Hospitalisation and death rates were higher in patients with encephalitis.

García San Miguel Rodríguez-Alarcón L., Fernández-Martínez B., Sierra Moros M.J., et al. (2021) Unprecedented increase of West Nile virus neuroinvasive disease, Spain, summer 2020. Euro Surveill; 26(19): 2002010.

McDonald E., Mathis S., Martin S.W., et al. (2021) Surveillance for West Nile virus disease - United States, 2009-2018. Am J Transplant: 1959-1974.

Short reports: tick-borne encephalitis (TBE) virus, Powasan virus (POWV), Saint Louis encephalitis virus (SLEV), Toscana virus and La Crosse virus (LACV)

Mansbridge et al. (2021) reported the second probable case of acquired TBE in England and demonstrated deer TBE-serocomplex seropositivity in the surrounding area, providing further evidence of the presence of TBE in England.

Izurieta-Pacheco et al. (2021) reported the first imported case of TBE in Spain in an unvaccinated two-year-old boy returning from a two-month trip to a rural area in north-east Austria. The authors highlighted the importance of epidemiological surveillance of emerging endemic infectious diseases and the need of vaccination as highly effective tools for the prevention of diseases like TBE.

Stoefs et al. (2021) reported three confirmed autochthonous TBE cases in Belgium diagnosed during summer 2020, urging clinicians to consider this in the differential diagnosis for patients with a etiologically unexplained neurologic manifestations, even for persons without recent travel history.

Feder et al. (2021) reported a neuroinvasive POWV infection in two children from Connecticut; one patient infected by deer tick virus (DTV), representing the seventh reported case and the first documented case of DTV infection in a child.

Moraes et al. (2021) reported two patients, in two Brazilian states (São Paulo and Mato Grosso), with SLEV genotype V.

Popescu et al. (2021) reported a series of severe neuroinvasive infections caused by Toscana virus, lineage A in eight hospitalised patients in Romania, during the summer seasons of 2017 and 2018.

Vahey et al. (2021) reported an average annual national incidence for LACV neuroinvasive disease of 0.02 per 100,000 persons. Three-quarters of these patients were diagnosed with encephalitis. As the virus was reported in 318 counties in 27 states, the authors concluded that healthcare providers should consider LACV disease in patients, especially children, with febrile illness, meningitis or encephalitis in areas where the virus circulates and advise their patients on preventive measures to avoid mosquito bites.

Feder H.M., Telford S., Goethert H.K., Wormser G.P. (2021) Powassan virus encephalitis following brief attachment of Connecticut deer ticks. Clin Infect Dis; 73(7): e2350-e2354.

Izurieta-Pacheco A.C., Nou-Fontanet L., Nascimento A., et al. (2021) Tick-borne encephalitis. Description of the first imported case in Spain in a paediatric patient. An Pediatr (Engl Ed); 96(1): 68-69.

Mansbridge C.T., Osborne J., Holding M., et al. (2021) Autochthonous tick-borne encephalitis in the United Kingdom: A second probable human case and local eco-epidemiological findings. Ticks Tick Borne Dis; 13(1): 101853.

Moraes M.M., Kubiszeski J.R., Vieira C.J.D.S.P. et al. (2021) Detection of Saint Louis encephalitis virus in two Brazilian states. J Med Virol; 94(2): 776-781.

Popescu C.P., Cotar A.I., Dinu S., et al. (2021) Emergence of Toscana Virus, Romania, 2017-2018. Emerg Infect Dis; 27(5): 1482-1485.

Stoefs A., Heyndrickx L., De Winter J., et al. (2021) Autochthonous cases of Tick-Borne encephalitis, Belgium, Emerg Infect Dis; 27(8): 2179-2182.

Vahey G.M., Lindsey N.P., Staples J.E., Hills S.L. (2021) La Crosse Virus Disease in the United States, 2003-2019. Am J Trop Med Hyg; 105(3): 807-812.

Pathogenesis of encephalitis

"We performed a GWAS of anti-NMDA receptor encephalitis and identified 2 independent genome-wide significant association signals. Both genomic regions contain putative functional candidate genes." (Tietz et al., 2021)

Impact of T cells on neurodegeneration in anti-GAD65 limbic encephalitis

ABSTRACT

Direct pathogenic effects of autoantibodies to the 65 kDa isoform of glutamic acid decarboxylase (GAD65) in autoimmune limbic encephalitis (LE) have been questioned due to its intracellular localization. We therefore hypothesized a pathogenic role for T cells.

Methods: We assessed magnet resonance imaging, neuropsychological and peripheral blood, and CSF flow cytometry data of 10 patients with long-standing GAD65-LE compared to controls in a cross-sectional manner. These data were related to each other within the GAD65-LE group and linked to neuropathological findings in selective hippocampectomy specimen from another two patients. In addition, full-resolution human leukocyte antigen (HLA) genotyping of all patients was performed.

Results: Compared to controls, no alteration in hippocampal volume but impaired memory function and elevated fractions of activated HLADR+ CD4+ and CD8+ T cells in peripheral blood and cerebrospinal fluid were found. Intrathecal fractions of CD8+ T cells negatively correlated with hippocampal volume and memory function, whereas the opposite was true for CD4+ T cells. Consistently, antigen-experienced CD8+ T cells expressed increased levels of the cytotoxic effector molecule perforin in peripheral blood, and perforin expressing CD8+ T cells were found attached mainly to small interneurons but also to large principal neurons together with wide-spread hippocampal neurodegeneration. 6/10 LE patients harbored the HLA-A*02:01 allele known to present the immunodominant GAD65114–123 peptide in humans.

Interpretation: Our data suggest a pathogenic effect of CD8+ T cells and a regulatory effect of CD4+ T cells in patients with long-standing GAD65-LE.

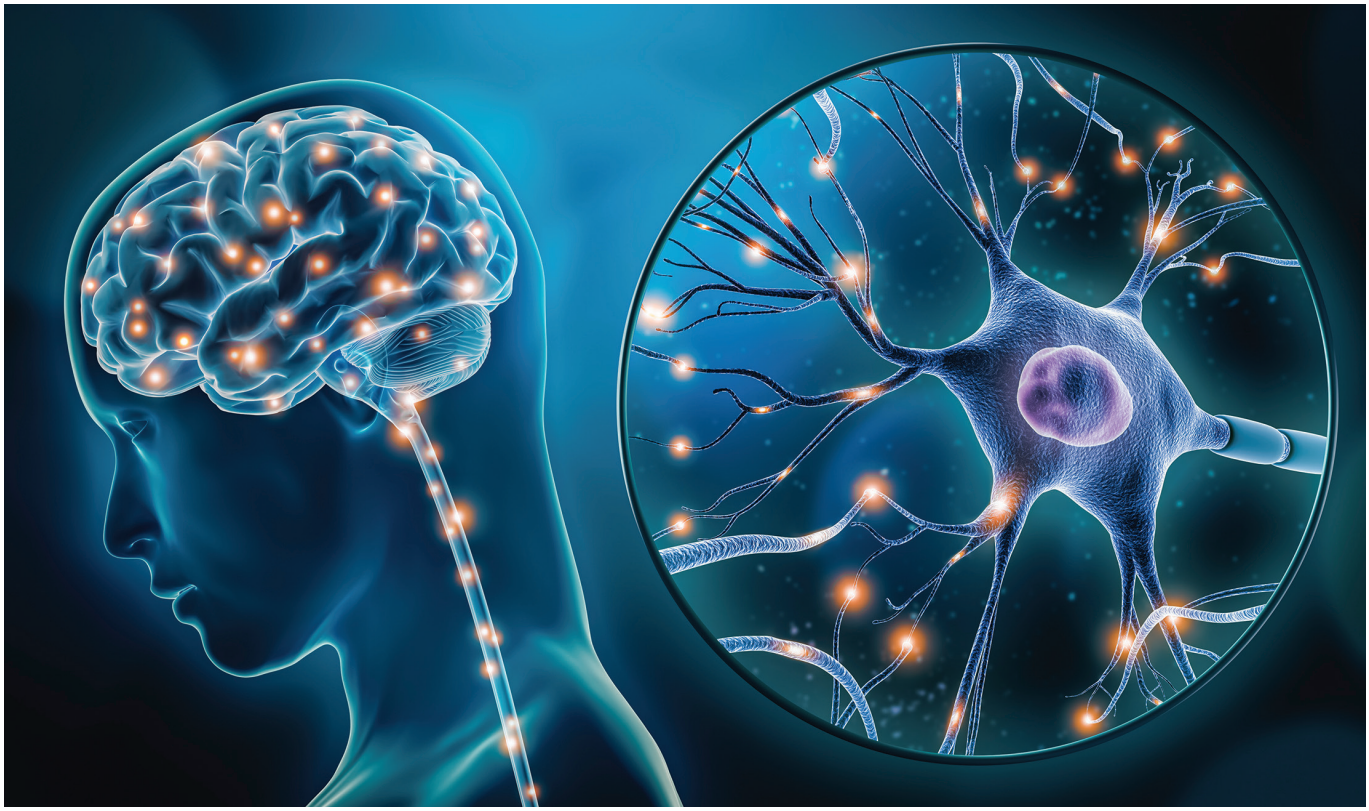
Dik A., Widman G., Schulte-Mecklenbeck A., et al. (2021) Impact of T cells on neurodegeneration in anti-GAD65 limbic encephalitis. Ann Clin Transl Neurol; 8(12): 2289-2301. doi:10.1002/acn3.51486

Genome-wide association study identifies two new loci associated with anti-NMDAR encephalitis

ABSTRACT

Background and Objectives

To investigate the genetic determinants of the most common type of antibody-mediated autoimmune encephalitis, anti-NMDA receptor (anti-NMDAR) encephalitis.



Methods: We performed a genome-wide association study in 178 patients with anti-NMDAR encephalitis and 590 healthy controls, followed by a colocalization analysis to identify putatively causal genes.

Results: We identified 2 independent risk loci harboring genome-wide significant variants ($p < 5 \times 10-8$, OR ≥ 2.2), 1 on chromosome 15, harboring only the LRRK1 gene, and 1 on chromosome 11 centered on the ACP2 and NR1H3 genes in a larger region of high linkage disequilibrium. Colocalization signals with expression quantitative trait loci for different brain regions and immune cell types suggested ACP2, NR1H3, MADD, DDB2, and C11orf49 as putatively causal genes. The best candidate genes in each region are LRRK1, encoding leucine-rich repeat kinase 1, a protein involved in B-cell development, and NR1H3 liver X receptor alpha, a transcription factor whose activation inhibits inflammatory processes.

Discussion: This study provides evidence for relevant genetic determinants of antibody-mediated autoimmune encephalitides outside the human leukocyte antigen (HLA) region. The results suggest that future studies with larger sample sizes will successfully identify additional genetic determinants and contribute to the elucidation of the pathomechanism.

Tietz A.K., Angstwurm K., Baumgartner T., et al. (2021) Genome-wide association study identifies 2 new loci associated with anti-NMDAR encephalitis. Neurol Neuroimmunol Neuroinflamm; 8(6): e1085. doi: 10.1212/NXI.0000000000001085. PMID: 34584012; PMCID: PMC8479862

Decreased inflammatory cytokine production of antigen-specific CD4(+) T cells in NMDA receptor encephalitis

ABSTRACT

Dao et al. (2021) characterized the ex vivo frequency and phenotype of circulating CD4+ T helper (TH) cells reactive to NR1 protein using antigen-reactive T cell enrichment (ARTE) in 24 patients with NMDAR encephalitis, 13 patients with LGI1 encephalitis and 51 matched controls. Unexpectedly, patients with NMDAR encephalitis had lower frequencies of CD154-expressing NR1-reactive TH cells than healthy controls and produced significantly less inflammatory cytokines. No difference was seen in T cells reactive to the synaptic target LGI1 (Leucine-rich glioma-inactivated 1), ubiquitous Candida antigens or neoantigens, suggesting that the findings are disease-specific and not related to therapeutic immunosuppression. Also, patients with LGI1 encephalitis showed unaltered numbers of LGI1 antigen-reactive T cells. The data reveal disease-specific functional alterations of circulating NMDAR-reactive TH cells in patients with NMDAR encephalitis and challenge the idea that increased pro-inflammatory NMDAR-reactive T cells contribute to disease pathogenesis.

Dao L.M., Machule M.L., Bacher P. et al. (2021) Decreased inflammatory cytokine production of antigen-specific CD4(+) T cells in NMDA receptor encephalitis. J Neurol; 268(6): 2123-2131. doi: 10.1007/s00415-020-10371-y.

Intrathecal antibody production against Epstein-Barr, herpes simplex, and other neurotropic viruses in autoimmune encephalitis

ABSTRACT

Background and Objectives

Neurotropic viruses are suspected to play a role in the pathogenesis of autoimmune diseases of the CNS such as the association between the Epstein-Barr virus (EBV) and multiple sclerosis (MS). A group of autoimmune encephalitis (AE) is linked to antibodies against neuronal cell surface proteins. Because CNS infection with the herpes simplex virus can trigger anti–NMDA receptor (NMDAR) encephalitis, a similar mechanism for EBV and other neurotropic viruses could be postulated. To investigate for previous viral infections of the CNS, intrathecally produced virus-specific antibody synthesis was determined in patients with AE.

Methods: Antibody-specific indices (AIs) against EBV and measles, rubella, varicella zoster, herpes simplex virus, and cytomegalovirus were determined in 27 patients having AE (anti-NMDAR encephalitis, n = 21, and LGI1 encephalitis, n = 6) and in 2 control groups comprising of 30 patients with MS and 21 patients with noninflammatory CNS diseases (NIND), which were sex and age matched.

Results: An intrathecal synthesis of antibodies against EBV was found in 5/27 (19%) patients with AE and 2/30 (7%) of the patients with MS. All these patients had also at least 1 additional elevated virus-specific AI. In contrast, in none of the patients with NIND, an elevated virus-specific AI was detected.

Discussion: Intrathecally produced antibodies against EBV can be found in patients with AE and MS but only together with antibodies against different neurotropic viruses. Evidence of these antibodies is the result of a polyspecific immune response similar yet distinct from MS response rather than an elapsed infection of the CNS.

Schwenkenbecher P., Skripuletz T., Lange P., (2021) Intrathecal antibody production against Epstein-Barr, herpes simplex, and other neurotropic viruses in autoimmune encephalitis. Neurology(R) neuroimmunology & neuroinflammation; 8(6): e1062. https://doi.org/10.1212/NXI.0000000000001062

Infectious encephalitis

"Increased vaccination rates, even in healthy children, early diagnosis and timely antiviral treatment are needed to reduce severe complications and death in severe influenza cases." (Teutsch et al., 2021)

Severe outcomes in influenza associated encephalitis/encephalopathy

Kutluk and Kadem (2021) reported 13 children with influenza-associated encephalitis. All patients presented with a prodromal phase with flu-like symptoms followed by the development of various neurological symptoms (alteration of consciousness, seizures, status epilepticus, autonomic dysfunction). On magnetic resonance imaging (MRI), the patients presented cortical and subcortical white matter signal alterations, localised or generalised edema and bilateral symmetrical multifocal lesions on the thalamus and cerebellar medulla. Treatment included antivirals (oseltamivir and acyclovir) and immunotherapies. Eleven patients required admission to paediatric intensive care unit (PICU). The after-effects included seizures, cognitive, physical or behavioural difficulties. The authors concluded that patients with seizures during influenza season should be suspected of influenza-associated encephalitis. Early treatment is associated with better outcomes.

A multicentre retrospective study in France (Cleuziou et al., 2021) investigated the mortality rate of severe influenza-associated encephalopathy/encephalitis among 41 children admitted to PICU. The main reasons for being admitted to PICU were altered consciousness (59%) and status epilepticus (34%). The outcomes were severe: death (17%) and neurological sequelae (49%), with 27% of them having severe disabilities defined by modified Rankin Score ≥4.

Severe outcomes for children with influenza-associated encephalitis are also reported by Teutsch et al. (2021) following a ten-year surveillance study on severe complication of influenza in Australian children (n = 613). Only 8.5% of children were vaccinated. Almost half of children were admitted to PICU and 30 died. Encephalitis was one of the mortality risks for children with influenza admitted to PICU.

Cleuziou P., Renaldo F., Renolleau S., et al. (2021) Mortality and neurologic sequelae in influenza-associated encephalopathy: retrospective multicenter PICU Cohort in France. Pediatr Crit Care Med; 22(11): e582-e587.

Kutluk M.G., Kadem E.N. (2021) Severe neurological manifestations of influenza during 2018-2019 influenza season: Case series of 13 pediatric patients. Arch Argent Pediatr; 119(2): e142-e148.

Teutsch S.M., Zurynski Y.A., Nunez C. et al. (2021) Ten years of national seasonal surveillance for severe complications of influenza in Australian children. Pediatr Infect Dis J; 40(3): 191-198.

Varicella zoster virus (VZV) encephalitis

Herlin et al. (2022) investigated the epidemiology and clinical characteristics of VZV encephalitis in a cohort study of adults at Danish departments of infectious diseases. Over four years, 92 adults were diagnosed with VZV encephalitis, bringing an incidence to 5.3/1,000,000 per year. The median age was 75 years. Immunocompromising status was observed in 39% of patients. Presenting features included confusion (76%), headache (56%), nausea (45%), gait disturbance (42%) and personality changes (41%). The median time to emergence of symptoms was four days and the median time from admission to lumbar puncture was 18.5 hours. Most patients (93%) had a positive cerebrospinal fluid (CSF) polymerase chain reaction (PCR). Magnetic resonance imaging showed abnormalities on the brainstem, deep brain structures including the basal ganglia, and the cerebellum. Electroencephalography (EEG) encephalitis characteristics were present in 50% of tested patients.

Intravenous acyclovir treatment was administered to all patients within a median of 13.4 hours since admission. During the hospital stay, 14% of patients were admitted to intensive care unit and 4% died. After discharge, 20% of patients died (9% at one month and 11% at three months) and 69% were left with sequelae. Age, vasculitis and Glasgow Coma Scale (GCS) <15 were considered independent risk factors. The authors argued that VZV encephalitis is more common than thought and more severe, especially in the elderly (over 75) and immunocompromised.

In another study in Denmark (Omland et al., 2021), which was a nationwide population-based cohort study of all Danish residents who had VZV DNA detected in the CSF by PCR between 1 January 1997 and 1 March 2016, mortality was also high, especially for those diagnosed with encephalitis (43% of all patients with VZV DNA in CSF had encephalitis) and in the first year of follow-up. Immunocompromised status was reported in 25% of patients and 90% of the whole cohort were above 15 years. Those who survived had an increased risk of dementia, epilepsy and depression.

No deaths were recorded in a study in France (Le Bot et al., 2021) that included 36 patients with VZV meningitis or encephalitis during 2000–2015 in one referral centre, but 33% of patients were left with neurological consequences. However, the median age was lower than the study in Denmark (51 years) and immunocompromised status was present only in 16.6%.

Herlin L.K., Hansen K.S., Bodilsen J., et al. (2021) Varicella zoster virus encephalitis in Denmark from 2015 to 2019—A Nationwide Prospective Cohort Study. Clinical Infectious Diseases; 727(1): 1192-1199.

Omland L.H., Vestergaard H.T., Dessau R.B., et al. (2021) Characteristics and long-term prognosis of Danish patients with varicella zoster virus detected in cerebrospinal fluid compared with the background population. J Infect Dis; 224(5): 850-859.

Le Bot A., Ballerie A., Pronier C., et al. (2021) Characteristics and outcome of varicella-zoster virus central nervous system infections in adults. Eur J Clin Microbiol Infect Dis; 40(11): 2437-2442.

Herpes simplex encephalitis (HSE): atypical presentations

Elshony et al. (2021) reported two cases of subacute HSE and reviewed four cases already described in the literature. They highlighted that HSE can present with a subacute form which can be diagnosed based on cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) findings without necessarily displaying specific cognitive impairment and focal neurological symptoms. The authors suggest that this form of HSE has a better prognosis than acute HSE.

Alvarez-Perez et al. (2021) reported a patient with HSV1 encephalitis, who initially presented a diffuse intracranial haemorrhage with predominant intraventricular bleeding. The patient was 66-years-old and had a history of alcohol consumption and ethylic hepatopathy. Although improving with acyclovir, he died due to multiple complications.

Hersh et al. (2021) reported four patients diagnosed with HSE following chemotherapy and whole-brain radiation therapy (WBRT). The authors argued that, although HSE predominantly affects immunocompetent host, HSE may be more common in immune-suppressed patients than it is currently recognised.

Ladak and Jurkiewicz (2021) reported a three-week-old girl with HSV2 encephalitis with non-specific exclusive bilateral corticospinal and frontal opercular involvement, which remained undiagnosed and untreated until three months of age. The authors emphasised the non-specific features of this type of encephalitis in neonates. Price and Wood (2021) drew attention to the reported cases of dual death of both a pregnant woman and her newborn from a herpesvirus infection. Their review study included 15 reports, of which five described pregnant women with HSE and ten described women with disseminated HSV infection. The most common cause was HSV2. The authors argue that although rare, these deaths can still happen.

Kargiotis et al. (2021) reported a case of HSV1 encephalitis in a 60-year-old patient who presented with unilateral brain MRI lesions with extensive cytotoxic oedema, resembling an acute ischemic stroke. The authors argued that HSE must be considered in the differential diagnosis of acute ischemic stroke with atypical presentation.

Alvarez-Perez F.J., Paiva F., Lino C.A. (2021) Intraventricular hemorrhage as clinical presentation of herpes simplex virus encephalitis. A case report and review of the literature. Int J Neurosci; 131(12): 1254-1259.

Elshony H., Idris A., Al-Ghamdi A., et al. (2021) Subacute herpes simplex type 1 encephalitis: case report with literature review. Neurologist; 26(5): 178-184.

Hersh N., Steiner I., Siegal T., Benninger F. (2021) Herpes simplex encephalitis in patients receiving chemotherapy and whole-brain radiation therapy. J Neurovirol; 27(5): 774-781.

Kargiotis O., Oikonomi K., Geka A., et al. (2021) HSV-encephalitis resembling acute cerebral infarction in a patient with atrial fibrillation: beware of stroke mimics. Neurologist; 27(1): 30-33.

Ladak I., Jurkiewicz M.T. (2021) Uncommon acute neuroimaging findings in severe neonatal herpes simplex virus 2 and consequences of delayed diagnosis. Emerg Radiol; 28(6): 1225-1228.

Price N.B., Wood K.E. (2021) Distinguishing features common to dual fatal herpes simplex virus infections that occur in both a pregnant woman and her newborn infant. Viruses; 13(12): 2542.

Enterovirus-A71 rhombencephalitis outbreak in Catalonia: characteristics, management and outcome

ABSTRACT

Background: Between April and June 2016, an outbreak of rhombencephalitis (RE) caused by enterovirus (EV) A71 was detected in Catalonia, Spain-the first documented in Western Europe. The clinical characteristics and outcome of patients with this condition differed from those reported in outbreaks occurring in Southeast Asia.

Results: Sixty-four patients met the clinical and virologic criteria for rhombencephalitis caused by EV-A71. All patients had symptoms suggesting viral disease, mainly fever, lethargy, ataxia and tremor, with 30% of hand-foot-mouth disease. Intravenous immunoglobulin therapy was given to 44/64 (69%) patients and methylprednisolone to 27/64 (42%). Six patients (9%) required pediatric intensive care unit admission. Three patients had acute flaccid paralysis of 1 limb, and another had autonomic nervous system (ANS) dysfunction with cardiorespiratory arrest. Outcome in all patients (except the patient with hypoxic-ischemic encephalopathy) was good, with complete resolution of the symptoms.

Conclusions: During the 2016 outbreak, rhombencephalitis without ANS symptoms was the predominant form of presentation and most patients showed no hand-foot-mouth disease. These findings contrast with those of other patient series reporting associated ANS dysfunction (10%-15%) and hand-foot-mouth disease (60%-80%). Complete recovery occurred in almost all cases. In light of the favorable outcome in untreated mild cases, therapies for this condition should be reserved for patients with moderate-severe infection. The main relevance of this study is to provide useful information for setting priorities, management approaches and adequate use of resources in future EV-A71 associated rhombencephalitis outbreaks.

Wörner N., Rodrigo-García R., Antón A., et al. (2021) Enterovirus-A71 rhombencephalitis outbreak in Catalonia: characteristics, management and outcome. Pediatr Infect Dis J; 40(7): 628-633. doi: 10.1097/INF.0000000000003114.

Difficulties in diagnostics: Dengue (DENV), Chikungunya (CHIKV), tick-borne encephalitis (TBE) and West Nile virus (WNV) encephalitis

Bentes et al. (2021) conducted a prospective study at a referral hospital for infectious diseases in Brazil between March 2014 and July 2019 to assess neurological complications in children with neuroinvasive DENV. There were 56 DENV-positive children included in the study, ages between one month and nine years and 26.8% of children presented with encephalitis. As the symptoms were not specific, only three children had a clinical diagnosis of DENV. At discharge, 39% of patients had neurologic complications: 19.6% were left with seizures, 10.7% developed motor complications (e.g., muscle weakness, paresis, ataxia and walking disability), 5.4% had headaches and 14.3% had sleep disorders. The authors highlight the difficulties of a clinical diagnosis of an infection that causes neurological complications after discharge in a significant number of children, but also the importance of an etiological diagnosis so patients can be followed-up for early interventions.

Ortiz-Quezada et al. (2021) presented an overview of CHIKV encephalitis in Honduras. Overall, there were seven cases (mean age 56) with CHIKV encephalitis. The mean duration from onset to diagnosis was five days. Patients presented with fever/arthralgia, headache/alteration of consciousness and status epilepticus. Electroencephalography was abnormal including slow background activity and generalised epileptiform discharge and the brain magnetic resonance imaging (MRI) showed bilateral white matter hyperintensities and focal encephalitis. Two patients died. The authors drew attention to the severity of this condition.

Voulgari et al. (2021) reported a 58-year-old patient who had TBE associated with uveitis. Considering the rise on TBE incidence recently, the authors drew attention of this association. Ayca et al. (2021) reported a 5-year-old girl diagnosed with a neuroinvasive WNV infection who had an unusual presentation with fever, vomiting, neck stiffness, walking difficulty and sudden deviation of eyes.

Bentes A.A., Maia De Castro Romanelli R., Crispim A.P.C., et al. (2021) Neurological manifestations due to dengue virus infection in children: clinical follow-up. Pathog Glob Health; 115(7-8): 476-482.

Ortiz-Quezada J., Rodriguez E.E., Hesse H., et al. (2021) Chikungunya encephalitis, a case series from an endemic country. J Neurol Sci; 420: 117279.

Voulgari N., Blanc C.M., Guido V., et al. (2021) Tick-borne encephalitis related uveitis: a case report. BMC Ophthalmol; 21(1): 315.

Ayça S., Akkoç G., Özdemir H., Selçuk-Duru H.N. (2021) An unusual neurologic presentation of pediatric neuroinvasive West Nile virus infection: ophthalmoplegia. Turk J Pediatr; 63(5): 909-912.

Eastern equine encephalitis

ABSTRACT

During three weeks in 2019, four human cases of Eastern equine encephalitis (EEE) were diagnosed at a single hospital in Connecticut, USA. The cases coincided with notable shifts in vector–host infection patterns in the northeastern United States and signified a striking change in EEE incidence. All four cases were geographically clustered, rapidly progressive and neurologically devastating. Diagnostic tests conducted by a national commercial reference laboratory revealed initial granulocytic cerebrospinal fluid pleocytosis and false-negative antibody results. EEE virus infection was diagnosed only after patient samples were retested by the arbovirus laboratory of the Centers for Disease Control and Prevention in Fort Collins, Colorado, USA. The crucial diagnostic challenges, clinical findings and epidemiologic patterns revealed in this outbreak can inform future public health and clinical practice.

Brown SC, Cormier J, Tuan J, et al. (2021) Four human cases of Eastern equine encephalitis in Connecticut, USA, during a larger regional outbreak, 2019. Emerg Infect Dis; 27(8): 2042-2051.

Autoimmune encephalitis

"AIE can mimic dementia. Antibody testing should be considered more often and sooner in the disease course, especially if red flags are present." (Bastiaansen et al., 2021)

Autoimmune encephalitis resembling dementia syndromes

ABSTRACT

Objective: As autoimmune encephalitis (AIE) can resemble neurodegenerative dementia syndromes, and patients do not always present as encephalitis, this study evaluates how frequently AIE mimics dementia and provides red flags for AIE in middle-aged and older patients.

Methods: In this nationwide observational cohort study, patients with anti-leucine-rich glioma-inactivated 1 (LGI1), anti-NMDA receptor (NMDAR), anti-gamma-aminobutyric acid B receptor (GABABR), or anti-contactin-associated protein-like 2 (CASPR2) encephalitis were included. They had to meet 3 additional criteria: age ≥45 years, fulfillment of dementia criteria, and no prominent seizures early in the disease course (≤4 weeks).

Results: Two-hundred ninety patients had AIE, of whom 175 were 45 years or older. Sixty-seven patients (38%) fulfilled criteria for dementia without prominent seizures early in the disease course. Of them, 42 had anti-LGI1 (48%), 13 anti-NMDAR (52%), 8 anti-GABABR (22%), and 4 anti-CASPR2 (15%) encephalitis. Rapidly progressive cognitive deterioration was seen in 48 patients (76%), whereas a neurodegenerative dementia syndrome was suspected in half (n = 33). In 17 patients (27%; 16/17 anti-LGI1), subtle seizures had been overlooked. Sixteen patients (25%) had neither inflammatory changes on brain MRI nor CSF pleocytosis. At least 1 CSF biomarker, often requested when dementia was suspected, was abnormal in 27 of 44 tested patients (61%), whereas 8 had positive 14-3-3 results (19%). Most patients (84%) improved after immunotherapy.

Conclusions: Red flags for AIE in patients with suspected dementia are: (1) rapidly progressive cognitive decline, (2) subtle seizures, and (3) abnormalities in ancillary testing atypical for neurodegeneration. Physicians should be aware that inflammatory changes are not always present in AIE, and that biomarkers often requested when dementia was suspected (including 14-3-3) can show abnormal results. Diagnosis is essential as most patients profit from immunotherapy.

Bastiaansen A.E.M., van Steenhoven R.W., de Bruijn M.A.A.M., et al. (2021) Autoimmune encephalitis resembling dementia syndromes. Neurol Neuroimmunol Neuroinflamm; 8(5): e1039. doi: 10.1212/NXI.0000000000001039.

Thymoma and autoimmune encephalitis: clinical manifestations and antibodies

ABSTRACT

Objective: To report the clinical, neuroimaging, and antibody associations in patients with autoimmune encephalitis (AE) and thymoma.

Methods: A retrospective cohort study of 43 patients was conducted. Antibody determination and immunoprecipitation to characterize novel antigens were performed using reported techniques.

Results: Patients' median age was 52 years (range: 23-88 years). Forty (93%) had neuronal surface antibodies: gamma-aminobutyric acid receptor A ($GABA_AR$) (15), amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) (13), contactin-associated protein-like 2 (CASPR2) (4), leucine-rich, glioma inactivated 1 (LGI1) (3), glycine receptor (GlyR) (3), and unknown antigens (2).

Concurrent antibodies against intracellular antigens occurred in 13 (30%; 9 anti-collapsin response mediator protein 5 [CRMP5]) and were more frequent in anti-AMPAR encephalitis (54% vs 20%; p = 0.037). The most common clinical presentation was encephalitis with multiple T2/fluid-attenuated inversion recovery hyperintense lesions in 23 (53%) patients (15 $GABA_AR$, 5 AMPAR, and 1 unknown neuropil antibody), followed by encephalitis with peripheral nerve hyperexcitability in 7 (16%; 4 CASPR2, 2 LGI1, and 1 unknown antibody), limbic encephalitis in 6 (14%; 4 AMPAR, 1 LGI1, and 1 antibody negative), progressive encephalomyelitis with rigidity and myoclonus in 4 (9%; 3 GlyR and 1 AMPAR antibodies), and encephalitis with normal MRI in 3 (7%; AMPAR antibodies).

Anti-$GABA_AR$ encephalitis was more prevalent in Japanese patients compared with Caucasians and other ethnicities (61% vs 16%; p = 0.003). In anti-AMPAR encephalitis, 3/4 patients with poor and 0/6 with good outcome had concurrent CRMP5 antibodies (p = 0.033). Immunoprecipitation studies identified metabotropic glutamate receptor 3 antibodies that were additionally found in 5 patients (3 with and 2 without encephalitis).

Conclusions: AE in patients with thymoma include several clinical-radiologic syndromes that vary according to the associated antibodies. Anti-$GABA_AR$ encephalitis was the most frequent AE and occurred more frequently in Japanese patients.

Guasp M., Landa J., Martinez-Hernandez E., et al. (2021) Thymoma and autoimmune encephalitis: clinical manifestations and antibodies. Neurol Neuroimmunol Neuroinflamm; 8(5): e1053. doi: 10.1212/NXI.0000000000001053.

Anti-AMPAR encephalitis: clinical characteristic, prognosis and unusual presentation

Zhang et al. (2021) investigated clinical characteristics and prognosis of anti-AMPAR encephalitis. Nine patients (seven females and two males) with a median age of 59 years were enrolled. Three clinical syndromes, including limbic encephalitis (n = 7; 78%), pure amnesia (n = 1; 11%) and fulminant encephalitis (n = 1; 11%) were identified. Novel symptoms for this entity included

dysphagia and deafness. All patients had AMPAR antibodies in the blood, and six patients had AMPAR antibodies in the cerebrospinal fluid (CSF). Brain magnetic resonance imaging (MRI) was abnormal in 75% of the patients with no specific patterns recognized. Six patients (67%) had tumours, including lung cancers and thymomas. After immunotherapy and oncotherapy, partial improvement of neurological symptoms was observed among all six patients with available records during their hospitalisation. After a mean follow-up of 72 weeks, three patients had marked decrease of modified Rankin Scale (mRS) score, one patient had unchanged mRS score, four patients died and the other one was lost to follow-up. The authors conclude that anti-AMPAR encephalitis mainly presents as limbic encephalitis and is paraneoplastic in 67% of cases. Thus, intensive screening for tumours is recommended for all patients with anti-AMPAR encephalitis. Although patients showed a good short-term therapeutic response, the overall prognosis was not satisfactory.

Ricken et al. (2021) reported un unusual presentation of anti-AMPAR encephalitis in three patients who presented with acute-to-subacute global amnesia without affection of cognitive performance, attention, concentration or verbal function. No other changes in behaviour or personality or seizures were observed. Two patients had an abnormal MRI with increased fluid-attenuated inversion recovery/T2 signal in the hippocampus. One patient who had an underlying adenocarcinoma of the lung did not improve and subsequently died.

Ashok et al. (2021) described an unusual presentation of anti-AMPAR encephalitis. The patient, a 42-year-old female, had unique clinical features affecting both the central nervous system (CNS) (psychosis, ataxia, cognition) and the peripheral nervous system (PNS) (ptosis, restricted eye movements, bulbar disturbances).

Ashok V.R., Nagabushana D., Yashwanth G., et al. (2021) A rare case of wobbly, psychotic patient with frozen eyes - anti-AMPA receptor encephalitis. Neurol India; 69(1): 149-152.

Ricken G., Zrzavy T., Macher S., et al. (2021) Autoimmune global amnesia as manifestation of AMPAR encephalitis and neuropathologic findings. Neurol Neuroimmunol Neuroinflamm; 8(4): e1019.

Zhang Z., Fan S., Ren H., et al. (2021) Clinical characteristics and prognosis of anti-alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic acid receptor encephalitis. BMC Neurol; 21(1): 490. doi: 10.1186/s12883-021-02520-1.

Characterizing the features and course of psychiatric symptoms in children and adolescents with autoimmune encephalitis

ABSTRACT

Autoimmune encephalitis (AE) can present like a psychiatric disorder. We aimed to illustrate the psychiatric manifestations, course and management of AE in a paediatric cohort. Neuropsychiatric symptoms, investigations and treatment were retrospectively retrieved in 16 patients (mean age 11.31, SD 2.98) with an AE diagnosis at the liaison psychiatry services in two UK tertiary paediatric centres. Psychiatric presentation was characterised by an acute polysymptomatic (predominantly agitation, anger outbursts/aggressiveness, hallucinations, and emotional lability) onset. Antipsychotics produced side effects and significant worsening of symptoms in four cases, and benzodiazepines were commonly used. This psychiatric phenotype should make clinicians suspect the diagnosis of AE and carefully consider use of treatments.

Rosello R., Girela-Serrano B., Gómez S., et al. (2022) Characterizing the features and course of psychiatric symptoms in children and adolescents with autoimmune encephalitis. European Archives of Psychiatry and Clinical Neuroscience; 272: 477-482.

Anti-AK5 encephalitis

Muñiz-Castrillo et al. (2021) reviewed ten new and 16 previously reported cases of anti-AK5 encephalitis. The condition was more common in males (76.9%) between 48 to 94 years old. All patients presented with severe episodic amnesia, 68% with depression, 44% with weight loss, asthenia and anorexia. Seizures were reported later in the disease course in 16% of patients.

Cerebrospinal fluid (CSF) was abnormal in all patients including pleocytosis (72%), oligoclonal bands (72%) and increased Tau (78.6%). On magnetic resonance imaging (MRI), temporal lobe hyperintensities were present at disease onset in 88.5% of patients and evolved towards severe atrophy in subsequent MRIs in 89.5% of patients. Only five patients responded to immunotherapy.

IgG1 was the predominant subclass, being the most frequently detected and the one with the highest titres in nine CSF-serum paired samples. When comparing the CSF proteomic profile with the control and other non-paraneoplastic limbi encephalitis cases, the authors revealed 31 and seven significantly upregulated proteins in anti-AK5 limbic encephalitis which, the authors suggested, implies a distinct T cell-mediated pathogenesis, with major cytotoxicity-induced apoptosis leading to a prompt and aggressive neuronal loss, likely explaining the poor prognosis and response to immunotherapy.

Muñiz-Castrillo S., Hedou J.J., Ambati A., et al. (2021) Distinctive clinical presentation and pathogenic specificities of anti-AK5 encephalitis. Brain; 144(9): 2709-2721.

Acute haemorrhagic leukoencephalitis (AHLE)

Pujari et al. (2021) presented a case series of eight patients with acute haemorrhagic leukoencephalitis (AHLE). The patients presented with altered sensorium, acute focal deficits with or without seizures. Seven patients showed evidence of haemorrhagic lobar or thalamic lesions. Repeated magnetic resonance imaging (MRI)s showed increase in oedema in the lesions and appearance/expansion of haemorrhage in the thalamic/hemispherical lesions. Cerebrospinal fluid (CSF) findings were unremarkable. All patients were commenced on steroids without improvement. Furthermore, four received plasmapheresis (PLEX), one received intravenous immunoglobulin (IVIG) and one received both second-line immunotherapies, without significant improvement. In three patients, diagnosis was confirmed via biopsy – inflammatory demyelination and areas of haemorrhage. Outcomes were severe: six deaths and two patients left with substantial disability.

The authors concluded that acute encephalopathy, multifocal deficits accompanied by haemorrhagic central nervous system demyelinating lesions with oedema and mass effect are the key features of AHLE – a rare but severe form of ADEM.

Pujari S.S., Kulkarni R.V., Ojha P., et al. (2021) Acute haemorrhagic leukoencephalitis (AHLE) - our experience and a short review. J Neuroimmunol; 361: 577751.

Clinical and prognostic value of immunogenetic characteristics in anti-LGI1 encephalitis

ABSTRACT

Objective: Antibodies against leucine-rich glioma-inactivated 1 (LGI1-Abs) characterize a limbic encephalitis (LE) strongly associated with HLA-DRB1*07:01, although some patients lack LGI1- Abs in CSF or do not carry this allele. Whether they represent a different subtype of disease or have different prognoses is unclear.

Methods: Retrospective analysis of clinical features, IgG isotypes, and outcome according to LGI1-Ab CSF positivity and DRB1*07:01 in a cohort of anti-LGI1 LE patients.

Results: Patients with LGI1-Abs detected in both CSF and serum (105/134, 78%) were compared with those who were CSF negative (29/134, 22%). Both groups had similar clinical features and serum levels, but CSF-positive patients had shorter diagnostic delay, more frequently hyponatremia, inflammatory CSF, and abnormal MRI ($p < 0.05$). Human leukocyte antigen (HLA) genotyping was performed in 72/134 (54%) patients and 63/72 (88%) carried DRB1*07:01. Noncarriers (9/72, 12%) were younger, more commonly women, and had less frequently psychiatric and frontal symptoms ($p < 0.05$). No difference in IgG isotypes according to CSF positivity or HLA was found ($p > 0.05$). HLA and IgG isotypes were not associated with poor outcome (mRS >2 at last follow-up) in univariate analyses; CSF positivity was only identified as a poor outcome predictor in the multivariate analysis including the complete follow-up, whereas age and female sex also remained when just the first year was considered.

Conclusions: LE without CSF LGI1-Abs is clinically indistinguishable and likely reflects just a lesser LGI1-Ab production. HLA association is sex and age biased and presents clinical particularities, suggesting subtle differences in the immune response. Long-term outcome depends mostly on demographic characteristics and the intensity of the intrathecal synthesis.

Muñiz-Castrillo, S., Haesebaert, J., Thomas, L., et al. (2021) Clinical and prognostic value of immunogenetic characteristics in anti-LGI1 encephalitis. Neurology(R) neuroimmunology ; 8(3): e974. doi: 10.1212/NXI.0000000000000974.

Case studies

Chevalier et al. (2021) reported a very rare case of anti-Ma2 encephalitis secondary to Sjogren's syndrome (SS) in an 81-year-old woman.

Xie et al. (2021) reported a 60-year-old patient with coexistence of positive serum LGI1 and GABABR antibodies.

Yao et al. (2021) reported a case of thymoma associated autoimmune encephalitis who also presented Titin antibodies, suggesting that the latter may have a role in management and prognosis of this type of autoimmune encephalitis.

Lee et al. (2021) reported a novel antibody in two patients with autoimmune encephalitis-antibody against CaV α2δ (voltage-gated calcium channel alpha-2/delta subunit). The authors argued that further analysis of this antibody in autoimmune encephalitis might promote early diagnosis and treatment.

Liu et al. (2021) reported two patients mimicking progressive brainstem infarction with severe neurological manifestations. However, both cases had detectable CASPR2 antibodies in sera, and an exclusive IgG1 subclass was documented in the further analysis.

Lockhart and Boers (2021) reported two patients who presented with classical paraneoplastic syndromes with multiple central nervous system (CNS) autoantibodies in each case. They both had small cell lung carcinoma detected.

Morano et al. (2021) reported a case of seronegative autoimmune encephalitis causing musicogenic epilepsy, in a 25-year-old man, educated in music over a long period of time.

Valle et al. (2021) reported a six-year-old patient who presented with an association of autoimmune encephalitis (anti-γ-aminobutyric acid type A (GABAA) receptor antibodies) with B19 infection. Following immunosuppressive therapy, the patient improved substantially with complete resolution of symptoms and age-appropriate neuropsychomotor development.

Liu P., Bai M., Ma C., et al. (2021) Case report: prominent brainstem involvement in two patients with anti-CASPR2 antibody-associated autoimmune encephalitis. Front Immunol; 12: 772763.

Lockhart A., Boers P. (2021) Paraneoplastic neurologic syndromes with multiple neural autoantibodies: A report of two cases. J Neuroimmunol; 358: 577665.

Lee S.T., Lee B.J., Bae J.Y. et al. (2021) Ca(V) α2δ Autoimmune encephalitis: a novel antibody and its characteristics. Ann Neurol; 89(4): 740-752.

Morano A., Orlando B., Fanella M., et al. (2021) Musicogenic epilepsy in paraneoplastic limbic encephalitis: a video-EEG case report. Epileptic Disord.; 23(5): 754-759.

Yao Y., Li X., Lin J., et al. (2021) Thymoma-associated autoimmune encephalitis with positive Titin antibodies: A case report. J Neuroimmunol; 358: 577670.

Valle D.A.D., Santos M.L.S.F., Spinosa M.J., et al. (2021) GABAA receptor encephalitis associated with human parvovirus B19 virus infection: Case report. Medicine (Baltimore); 100(23): e26324.

Chevalier K., Noel N., Benoudiba F., et al. (2021) Anti-Ma2 antibody encephalitis associated with Sjogren's syndrome. Rev Med Interne; 42(8): 575-578.

Xie Y., Wen J., Zhao Z., et al. (2021) Autoimmune encephalitis with coexistent LGI1 and GABA(B)R1 antibodies: case report. BMC Neurol; 21(1): 461. doi: 10.1186/s12883-021-02460-w.

Anti-NMDAR encephalitis

"This review on immunotherapy in NMDARE establishes a clear role for early immunotherapy and timely escalation to second-line treatment, particularly with rituximab." (Nosadini et al., 2021)

International consensus recommendations for the treatment of paediatric NMDAR antibody encephalitis

ABSTRACT

Objective: To create an international consensus treatment recommendation for paediatric NMDA receptor antibody encephalitis (NMDARE).

Results: Corticosteroids are recommended in all children with NMDARE (pulsed IV preferred), with additional IV immunoglobulin or plasma exchange in severe patients. Prolonged first-line immunotherapy can be offered for up to 3–12 months (oral corticosteroids or monthly IV corticosteroids/immunoglobulin), dependent on disease severity. Second-line treatments are recommended for cases refractory to first-line therapies (rituximab preferred over cyclophosphamide) and should be considered about 2 weeks after first-line initiation. Further immunotherapies for refractory disease 1-3 months after second-line initiation include another second-line treatment (such as cyclophosphamide) and escalation to tocilizumab. Maintenance immune suppression beyond 6 months (such as rituximab redosing or mycophenolate mofetil) is generally not required, except for patients with a more severe course or prolonged impairments and hospitalization. For patients with relapsing disease, second line and prolonged maintenance therapy should be considered. The treatment of NMDARE following herpes simplex encephalitis should be similar to idiopathic NMDARE. Broad guidance is provided for the total treatment duration (first line, second line, and maintenance), which is dictated by the severity and clinical course (i.e., median 3, 9 and 18 months in the best, average, and worst responders, respectively). Recommendations on the timing of oncologic searches are provided.

Conclusion: These international consensus recommendations for the management of paediatric NMDARE aim to standardize the treatment and provide practical guidance for clinicians, rather than absolute rules. A similar recommendation could be applicable to adult patients.

Nosadini M., Thomas T., Eyre M., et al. (2021) International consensus recommendations for the treatment of pediatric NMDAR antibody encephalitis. Neurol Neuroimmunol Neuroinflamm; 8(5): e1052. doi: 10.1212/NXI.0000000000001052.

Use and safety of immunotherapeutic management of N-Methyl-d-Aspartate receptor antibody encephalitis: a meta-analysis

ABSTRACT

Objective: To map the use and safety of immunotherapies in individuals with NMDARE, identify early predictors of poor functional outcome and relapse, evaluate changes in immunotherapy use and disease outcome over the 14 years since first reports of NMDARE, and assess the Anti-NMDAR Encephalitis One-Year Functional Status (NEOS) score.

Results: Data from 1550 patients from 652 articles were evaluated. Of these, 1105 of 1508 (73.3%) were female and 707 of 1526 (46.3%) were 18 years or younger at disease onset. Factors at

first event that were significantly associated with good functional outcome included adolescent age and first-line treatment with therapeutic apheresis, corticosteroids plus intravenous immunoglobulin (IVIG), or corticosteroids plus IVIG plus therapeutic apheresis. Factors significantly associated with poor functional outcome were age younger than two years or age of 65 years or older at onset, intensive care unit admission, extreme delta brush pattern on electroencephalography, lack of immunotherapy within the first 30 days of onset, and maintenance IVIG use for six months or more. Factors significantly associated with non relapsing disease were rituximab use or maintenance IVIG use for six months or more. Adolescent age at onset was significantly associated with relapsing disease. Rituximab use increased from 13.5% (52 of 384; 2007 to 2013) to 28.3% (311 of 1100; 2013 to 2019) (P < .001), concurrent with a falling relapse rate over the same period (22% [12 of 55] in 2008 and earlier; 10.9% [35 of 322] in 2017 and later; P = .006). Modified NEOS score (including 4 of 5 original NEOS items) was associated with probability of poor functional status at one year (20.1% [40 of 199] for a score of 0 to 1 points; 43.8% [77 of 176] for a score of 3 to 4 points; P = .05).

Conclusions and relevance: Factors influencing functional outcomes and relapse are different and need to be considered independently in development of evidence-based optimal management guidelines of patients with NMDARE.

Nosadini M., Eyre M., Molteni E. et al. (2021) Use and safety of immunotherapeutic management of N-Methyl-d-Aspartate receptor antibody encephalitis: a meta-analysis. JAMA Neurol; 78(11): 1333-1344. doi: 10.1001/jamaneurol.2021.3188.

Anti-NMDAR antibody encephalitis in infants and older adults

Ren et al. (2021) reviewed clinical features and outcomes of anti-NMDAR encephalitis in 41 infants and toddlers. Very interestingly, 54% of patients had viral encephalitis initially. Patients presented with similar symptoms: movement disorders (100%), developmental regression (90%), abnormal behaviours (90%). All patients were administered first-line therapy, with only 17% of them receiving second-line therapy. Two patients died, but there were no relapses observed. Outcomes varied, being more severe for those with post-viral autoimmune encephalitis.

The nationwide observational Dutch cohort study of 126 patients diagnosed with anti-NMDAR encephalitis between 2007 and 2019 included 19% patents with older illness onset (≥45 years of age). This population group was characterised by fewer seizures, fewer symptoms during disease course, more often undetectable serum antibodies, and all tumours were carcinomas. In the late-onset group, outcome was worse. (Bastiaansen et al., 2021)

Giné-Servén et al. (2021) also investigated anti-NMDA receptor encephalitis (NMDARE) in older patients (>65 years). The systematic literature review revealed 23 case reports. The median age was 70.1 years and females were preponderant (60.9%). Clinical manifestations included acute behavioural and cognitive changes (95.7%), atypical psychosis (47.8%), hallucinations (30.4%), and motility disturbances (34.8%) including catatonia (17.4%). Nine patients presented with seizures (39.1%).

Sun et al. (2021) investigated the prognosis of late-onset anti-NMDARE in China in a retrospective study of 31 patients in four hospitals in China and compared with 81 patients with an early onset. The older adults had a poorer outcome and a higher rate of relapses.

Bastiaansen A.E.M., de Bruijn M.A.A.M., Schuller S.L., et al. (2021) Anti-NMDAR encephalitis in the Netherlands, focusing on late-onset patients and antibody test accuracy. Neurology(R) neuroimmunology & neuroinflammation; 9(2): e1127.

Giné-Servén E., Serra-Mestres J., Martinez-Ramirez M., et al. (2021) Anti-NMDA receptor encephalitis in older adults: A systematic review of case reports. Gen Hosp Psychiatry; 74: 71-77.

Ren C., Zhang W., Ren X., et al. (2021) Clinical features and outcomes of anti-N-Methyl-d-Aspartate receptor encephalitis in infants and toddlers. Pediatr Neurol; 119: 27-33.

Sun Y., Ren G., Ren J., et al. (2021) The prognosis of late-onset anti-N-methyl-D-aspartate receptor encephalitis in China. Acta Neurol Scand; 145(4): 449-455.

Overlapping anti-NMDA receptor encephalitis and MOG antibody-associated diseases

Nan et al. (2021) reviewed cases with dual-positive anti-NMDA cerebrospinal fluid receptors and MOG serum antibodies during the disease course reported in the literature. There were 25 patients reported with ages between three and 54. Clinical manifestations included seizures and cognitive decline accompanied by atypical central nervous system demyelination. Treatment included first-line immunotherapy with methylprednisolone and immunoglobulin and second-line mycophenolate mofetil, rituximab, interferon-β, azathioprine, cyclophosphamide, and temozolomide. The outcomes were good, and the median number of relapses was 2.8.

Weihua et al. (2021) reported clinical characteristics and relapses rates of NMDAR encephalitis with anti-MOG-Ab positivity serostatus in a cohort of 12 paediatric patients. The rate of relapses was high with eight patients experiencing relapses. However, these were reduced after patients received disease-modifying drugs.

Nan D., Zhang Y., Han J., Jin T. (2021) Clinical features and management of coexisting anti-N-methyl-D-aspartate receptor encephalitis and myelin oligodendrocyte glycoprotein antibody-associated encephalomyelitis: a case report and review of the literature. Neurol Sci; 42(3): 847-855.

Weihua Z., Shuai G., Changhong R., et al. (2021) Pediatric anti-N-methyl-D-aspartate receptor encephalitis with MOG-Ab co-existence: Relapse propensity and treatability. Mult Scler Relat Disord; 58: 103447.

Anti-NMDAR antibody encephalitis: relapses and post herpes simplex encephalitis (HSE)

ABTRACT

Zeng et al. (2021) analysed the clinical profile and long-term prognosis of relapsing anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in ten patients.

Results: The main symptoms at first onset and relapse included psychiatric symptoms, cognitive impairment, speech dysfunction, seizures, consciousness disturbance, movement disorders, central hypoventilation and autonomic dysfunction. There were significantly fewer seizures and consciousness disturbances at relapse. At the first onset, the antibody positivity rate was significantly higher in the cerebrospinal fluid (CSF) than in the serum, and abnormal electroencephalograms results were noted in all patients. The relapse rate was 12.2%. After first-onset discharge, the duration of medication intake was 3.10 ± 2.69 months; the relapse time was 18.3 ± 16.5 months. The Modified Rankin Scale (MRS) score at relapse was significantly lower than that at the first onset. The MRS scores at relapse and first onset after immunotherapy were significantly lower than those before immunotherapy. At follow-up, the average duration of antiepileptic drug (AED) intake was <1 year; the relapse rate was low.

Conclusions: Patients have fewer symptoms and better quality of life at relapse than at the first onset. Active immunotherapy can significantly improve the quality of life during first onset and relapse. Encephalitis antibody testing in the CSF is preferred at first onset and relapse. Increasing antibody titers suggest clinical relapse. Prematurely stopping immunotherapy may lead to relapse, but prolonged AED intake is unnecessary.

Marcus and Ness (2021) compared anti-NMDAR encephalitis with post herpes simplex encephalitis (HSE) anti-NMDAR in children. In total, there were 17 children, of which six had a history of HSE. This second group were younger with five children being infants. All children with only anti-NMDAR had behavioural problems, but only 50% of post HSE anti-NMDAR manifested them. Seizures were present in all children post HSE, but in only 73% of anti-NMDAR only group. Movement disorders were similar percentage in both groups. Post HSE anti-NMDAR patients received a median of one immunotherapy compared with a median of 4.5 immunotherapies in the NMDAR-only group.

Marcus L., Ness J.M. (2021) Pediatric N-Methyl-d-Aspartate (NMDA) receptor encephalitis, with and without Herpes Encephalitis. J Child Neurol; 36(9): 743-751.

Zeng W., Cao L., Zheng J., Yu L. (2021) Clinical characteristics and long-term prognosis of relapsing anti-N-methyl-D-aspartate receptor encephalitis: a retrospective, multicenter, self-controlled study. Neurol Sci:199-207. doi: 10.1007/s10072-020-04482-7.

Case Reports

- Sartori et al. (2021) reported two patients with anti-NMDAR encephalitis following herpes simplex encephalitis (HSE), both with genetic testing for TLR3 negative. The authors are questioning the link and mechanisms of post-HSE anti-NMDARE and TLR3 mutations.
- Hu et al. (2021) reported a 23-year-old diagnosed with HSE encephalitis who developed anti-NMDAR antobody (IgG) on day 11 after disease onset. The authors suggest detecting autoimmune encephalitis (AE) antibodies simultaneously with each cerebrospinal fluid (CSF) analysis.
- Chadwick et al. (2021) presented the first known successful use of an appliance-based therapy for managing orofacial dyskinesias in the anti-NMDARE patient population through an adaptation of traditional maxillomandibular fixation techniques. This approach eliminated further orofacial trauma and enabled physicians to use safer means to manage and assess patients with this condition during their long intensive care unit stay.
- Nishimura et al. (2021) reported a ten-month-old boy with IRAK4 deficiency presenting with anti-NMDAR encephalitis and human herpes virus 6 (HHV6) reactivation suggesting a possible link between inborn errors of immunity and early onset anti-NMDAR encephalitis.
- Tappata et al. (2021) reported a patient with a long-term persistence of NMDAR antibodies even 15 years after encephalitis and whose case raises the question of the link between NMDAR antibodies and demyelinating disorders in the form of multiple sclerosis.
- Panda et al. (2021) reported an adolescent girl, who developed anti-N-methyl-d-aspartate receptor encephalitis after the resolution of systemic symptoms of leptospirosis advocating for early recognition to enable the reverse of the neurological symptoms.
- Liu and Chen (2021) reported a 19-year-old pregnant woman with recurrent anti-NMDAR encephalitis and double-antibody positive. First episode during her eighth week of pregnancy and second episode two years later at her tenth week of her pregnancy, double positive: anti-NMDAR-IgG and anti-AMPAP-IgG. In both instances the pregnancy was terminated with improved symptoms.

Chadwick J. W., Brooks P. J., Singh J. M., & Lam D. K. (2021). Prevention of oral and maxillofacial trauma secondary to orofacial dyskinesias associated with anti-N-methyl-D-aspartate receptor encephalitis: a case series. BMC oral health; 21(1). 511.

Hu S., Lan T., Bai R., et al. (2021) HSV encephalitis triggered anti-NMDAR encephalitis: a case report. Neurol Sci; 42(3): 857-861.

Liu H., Chen X. (2021) Recurrent anti-NMDAR encephalitis during pregnancy combined with two antibodies positive. Arch Womens Ment Health; 24(6): 1045-1050.

Nishimura S., Kobayashi Y., Ohnishi H., et al. (2021) IRAK4 deficiency presenting with anti-NMDAR encephalitis and HHV6 reactivation. J Clin Immunol; 41(1): 125-135.

Panda P.K., Sharawat I.K., Bolia R. (2021) Leptospira triggered Anti-N-Methyl-d-Aspartate receptor encephalitis. J Trop Pediatr; 67(1).

Sartori S., Salviati L., Nosadini M. (2021) Toll-like receptor 3 pathway deficiency, herpes simplex encephalitis, and anti-NMDAR encephalitis: more questions than answers. Pediatr Res; 89(5): 1043.

Tappatà M., Riguzzi P., Volpi L., et al. (2021) Long-term persistence of NMDAR antibodies after encephalitis with de novo occurrence of demyelinating disorder. Neurol Sci; 42(1): 301-303.

Covid-19 and encephalitis

"Meningoencephalitis is an unusual form of COVID presentation, but is more than 4-fold more frequent than in non-COVID patients attending the Emergency Departments."
(Fragiel et al., 2021)

Neuropathophysiology of acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Pilotto et al. (2021) investigated the cerebrospinal fluid (CSF) abnormalities in SARS-CoV-2-related encephalitis to answer the question whether SARS-CoV-2 may cause neurological manifestations through a direct neuropathic effect or by promoting a hyperinflammatory reaction in the host's immune system in the form of cytokine release syndrome. Overall, the study included 13 patients with polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection and encephalitis (COV-Enc), 21 patients with encephalitis only (ENC), and 18 healthy controls. In COV-Enc cases, CSF was negative for SARS-CoV-2 real-time PCR but exhibited increased IL-8 levels independently from presence of pleocytosis/hyperproteinorracchia. COV-Enc patients showed increased IL-6, TNF- α, and β2-microglobulin and glial markers (GFAP, sTREM2, YKL-40) levels like ENC but normal CXCL13 levels. Neuronal markers NfL and T-tau were abnormal only in severe cases. The authors concluded that their study proved that SARS-CoV-2 encephalitis are associated with early IL-8 increases and glial alterations, whereas neuronal damage markers were elevated in severe cases. Moreover, the pattern of neuroinflammatory markers assessed is highly suggestive for a cytokine-release syndrome as driver of SARS-CoV-2-related encephalitis.

Thakur et al. (2021) presented the clinical, neuropathological and molecular findings of 41 consecutive patients with SARS-CoV-2 infections who died and underwent autopsy. Neuropathological examination revealed hypoxic/ischaemic changes in all brains, both global and focal; large and small infarcts, many of which appeared haemorrhagic; and microglial activation with microglial nodules accompanied by neuronophagia, most prominently in the brainstem; sparse T lymphocyte accumulation in either perivascular regions or in the brain parenchyma. The PCR analysis of multiple fresh frozen and fixed tissues from 28 brains revealed low to very low, but detectable, viral RNA levels in most brains, although they were far lower than those in the nasal epithelia. As their study only detected very low levels of virus in the brains, the authors suggested that microglial activation, microglial nodules and neuronophagia, observed in most brains, do not result from direct viral infection of brain parenchyma, but more likely from systemic inflammation, perhaps with synergistic contribution from hypoxia/ischaemia

Pilotto A., Masciocchi S., Volonghi I., et al. (2021) Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) encephalitis is a cytokine release syndrome: evidences from cerebrospinal fluid analyses. Clin Infect Dis; 73(9): e3019-e3026.

Thakur K.T., Miller E.H., Glendinning M.D., et al. (2021) COVID-19 neuropathology at Columbia University Irving Medical Center/New York Presbyterian Hospital. Brain; 144(9): 2696-2708.

Acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related encephalitis

Pilotto et al. (2021) reported clinical presentations, clinical course, response to treatment, and outcomes of 25 patients with encephalitis positive for SARS-CoV-2 infection included in the SARS-CoV-2 related encephalopaties (ENCOVID) multicentre study. The incidence of encephalitis in this study was 50/100,000 patients with Covid-19. In 11 patients, neurological symptoms were concomitant with COVID-19 symptomatology; in 12 cases neurological onset followed COVID-19 symptoms with a median of eight days and, in two cases, neurological symptoms preceded the onset of COVID-19 symptoms after three and five days. Neurological manifestations included headache, delirum/altered mental status, aphasia/dysarthria, seizures, status epilepticus, focal motor deficits. One patient developed a parkinsonian syndrome. Electroencephalography was abnormal in all patients. The cerebrospinal fluid findings included pleocytosis in 68% of cases; however, SARS-CoV-2 RNA by reverse-transcription polymerase chain reaction was negative.

Based on magnetic resonance imaging (MRI) findings, cases were classified as acute demyelinating encephalomyelitis (ADEM) in three patients, limbic encephalitis (LE) in two patients, encephalitis with normal imaging in 13 patients and encephalitis with MRI alterations in seven patients. Patients with ADEM and LE had a delayed onset compared with the other patients with encephalitis, and were associated with more severe COVID-19 respiratory involvement. Six patients experienced a spontaneous recovery, five patients improved with immunotherapy and four patients died. Worse outcomes were observed in patients with encephalitis with MRI alterations.

Vasilevska et al. (2021) identified eight SARS-CoV-2-associated cases of anti-NMDA receptor encephalitis in a systematic review study. All had cerebrospinal fluid antibodies against the NMDA receptor and a recent onset of working memory deficits, altered mental status, or psychiatric symptoms, such as confusion, agitation, auditory hallucination, catatonia and speech dysfunction. All patients received high-dose steroid and immunoglobulin therapeutics and conditions improved in each case. These findings suggest that clinical attention should be paid to warning signs of autoimmune encephalitis in severe COVID-19 cases. If characteristic features of autoimmune encephalitis are present, autoantibody diagnostics should be performed and confirmed cases should be treated with immunotherapy to minimise neurological impairments.

Valencia Sanchez et al. (2021) aimed to determine the frequency and diagnostic features of coronavirus disease 2019 (COVID-19)-related autoimmune encephalitis (AE) in a cohort study of 556 consecutive Mayo Clinic Rochester patients who underwent autoimmune encephalopathy neural immunoglobulin G (IgG) evaluation. Five patients met diagnostic criteria for AE, representing 0.05% of all patients with COVID-19 illnesses at their institution.

Neural IgG testing was negative in all patients. Three patients had a "possible" AE diagnosis only and had spontaneous resolution of symptoms. One patient with definite limbic encephalitis responded to immunotherapy but had residual mood and memory difficulties. One patient with probable autoimmune rhombencephalitis died despite immune therapy. The authors emphasised that application of diagnostic criteria assists in differentiation of AE from toxic-metabolic causes arising in the setting of systemic infection.

Ray et al. (2021) investigated the spectrum of neurological and psychiatric complications associated with paediatric SARS-CoV-2 infection in hospitalised children and adolescents. For ten months, 52/1334 children and adolescents with Covid-19 were identified, of which 27 were included in a Covid-19 neurology group and 25 in a paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. In the neurology group, seven patients had status epilepticus, five patients had encephalitis, five had Guillain-Barré syndrome, three had acute demyelinating syndromes, two chorea, two psychosis, two isolated encephalopathy and one had transient ischaemic attack. At discharge, 37% of patients from neurology group had a disability. The authors conclude that although COVID-19 requiring hospital treatment is very rare in children and young people overall, among hospitalised children and adolescents, neurological or psychiatric manifestations are common (3·8 cases per 100 hospitalised patients). The authors also noted that these neurological or psychiatric manifestations disproportionately affected children from minority ethnic groups.

Fragiel et al. (2021) investigated the incidence, clinical characteristics, risk factors and outcome of meningoencephalitis (ME) in patients with COVID-19 attending 61 Spanish emergency departments (ED) during the Covid-pandemic. They identified 29 patients with ME in 71,904 patients with COVID-19 attending Eds, making an incidence of 0.40‰, which was higher than in non-Covid patients (150/1,358,134; 0.11‰). Characteristic for patients with Covid-ME were dyspnea and chest X-ray abnormalities. Neck stiffness was more frequent in patients with non-Covid ME. Risk factors for developing ME in Covid-19 patients included vomiting, headache and altered mental status. Patients with COVID-ME had a higher in-hospital mortality than non-COVID-ME patients and a higher need for hospitalisation and intensive care admission. The authors concluded that, although ME is an unusual form of COVID presentation, it is more than 4-fold more frequent than in non-COVID patients attending the ED.

Cleret de Langavant et al. (2021) reviewed the records of patients presented with neurological disorders associated with SARS-CoV-2 infection in a single centre. Their study included 26 patients diagnosed with SARS-CoV-2 infection. Neurological manifestations included encephalitis in eight patients, encephalopathy in six, cerebrovascular events in six, other central nervous system (CNS) disorders in four and Guillain-Barré syndrome in two. Remarkably, the diagnosis of SARS-CoV-2 was delayed on average 1.6 days after the onset of neurological disorder, especially in case of encephalitis 3.9 days, encephalopathy 1.0 day, and cerebrovascular event 2.7 days. The authors noted that anti-SARS-CoV2 antibody detection in RT-PCR SARS CoV-2 negative suspected cases is useful to confirm a posteriori the diagnosis of atypical COVID-19 presentations.

Guilmot et al. (2021) reported 15 patients (4.3%) with neurological manifestation out of 349 patients with Covid-19. CSF PCR for SARS-CoV-2 was negative in all patients. Two patients presented CSF pleocytosis: one patient with anti-contactin-associated protein 2 (anti-Caspr2) antibody encephalitis and one patient with para-infectious polyradiculitis.

In a study in Egypt of neurological complications of Covid-19, from 439 patients confirmed/probable COVID-19, neurological manifestations occurred in 222. The central nervous system was affected in 75 patients, encephalitis reported in six patients and meningoencephalitis in one patient (Khedr et al., 2021).

Cleret de Langavant L., Petit A., et al. (2021) Clinical description of the broad range of neurological presentations of COVID-19: A retrospective case series. Rev Neurol (Paris); 177(3): 275-282.

Fragiel M., Miró Ò., Llorens P., et al. (2021) Incidence, clinical characteristics, risk factors and outcomes of meningoencephalitis in patients with COVID-19. Eur J Clin Microbiol Infect Dis; 40(8): 1645-1656.

Guilmot A. Maldonado Slootjes S., Sellimi A. et al. (2021) Immune-mediated neurological syndromes in SARS-CoV-2-infected patients. J Neurol; 268(3): 751-757.

Khedr E.M., Abo-Elfetoh N., Deaf E., et al. (2021) Surveillance study of acute neurological manifestations among 439 Egyptian patients with COVID-19 in Assiut and Aswan University Hospitals. Neuroepidemiology; 55(2): 109-118.

Pilotto A., Masciocchi S., Volonghi I., et al. (2021) Clinical presentation and outcomes of severe acute respiratory syndrome coronavirus 2-related encephalitis: The ENCOVID Multicenter Study. J Infect Dis; 223(1): 28-37.

Ray S.T.J., Mannan O., Sa M., et al. (2021) Neurological manifestations of SARS-CoV-2 infection in hospitalised children and adolescents in the UK: a prospective national cohort study. Lancet Child Adolesc Health; 5(9): 631-641.

Valencia Sanchez C., Theel E., Binnicker M., et al. (2021) Autoimmune Encephalitis After SARS-CoV-2 Infection: Case Frequency, Findings, and Outcomes. Neurology; 97(23): e2262-e2268.

Vasilevska V., Guest P.C., Bernstein H.G. et al. (2021) Molecular mimicry of NMDA receptors may contribute to neuropsychiatric symptoms in severe COVID-19 cases. J Neuroinflammation; 18(1): 245.

Other types of encephalitis

"Neurologists will likely encounter ICI-associated encephalitis more often in the future, but important unresolved questions include the pathophysiologic mechanisms, the epidemiology, and the best treatment approaches associated with ICI-associated encephalitis." (Nerserjan et al., 2021)

Encephalitis associated with immune checkpoint inhibitor (ICI) treatment

Velasco et al. (2021) investigated the features and prognosis of encephalitis associated with ICIs by doing a systematic review of case series published in the literature (77) and medical record of five patients from one centre. Of 82 patients included in the study, 63% were male, and the median age was 61 years. At presentation, 48% of patients had focal syndrome (limbic or extra limbic), 44% meningoencephalitis and 9% non-classifiable ICI-induced encephalitis. Over a quarter of patients had neuronal autoantibodies, most common being onconeuronal (71%). Prognosis was associated with presentation; focal syndrome had the worst outcomes. Patients with a focal presentation had better outcomes if they did not have autoantibodies identified. From all patients with autoantibodies, those with anti-glutamic acid decarboxylase or anticell surface responded to treatment and had a favourable prognosis. Magnetic resonance imaging (MRI) findings were also associated with prognosis, patients with abnormal findings had a poorer outcome. Furthermore, an undetected pre-existing paraneoplastic encephalitic syndrome, which was triggered by ICIs, has the worst outcome among all the different types of ICI-induced encephalitis syndromes.

Nersesjan et al. (2021) summarised the features of ICI-associated autoimmune encephalitis (AE) reported in the literature. Fifty-four patients were included in the study. The most common cancers were melanoma and non-small cell lung cancer, and the most frequently used ICI was nivolumab. AE symptoms occurred after a median of three treatment cycles, and presentation included both limbic and nonlimbic, although nonlimbic was predominant (two-thirds). Radiological MRI showed bitemporal fluid-attenuated inversion recovery lesions and the electroencephalography (EEG) showed continuous slow waves and diffuse slowing. Cerebrospinal fluid findings included monocytic pleocytosis, and the most common autoantibodies were intraneuronal, which were also associated with a poorer outcome.

Nersesjan V., McWilliam O., Krarup L.H., Kondziella D. (2021) Autoimmune encephalitis related to cancer treatment with immune checkpoint inhibitors: a systematic review. Neurology; 97(2).

Velasco R., Villagrán M., Jové M., et al. (2021) Encephalitis induced by immune checkpoint inhibitors: a systematic review. JAMA Neurol; 78(7): 864-873.

Acute fulminant cerebral edema (AFCE)

Krishnan et al. (2021) reported a new phenotype of encephalitis in children – encephalitis with acute fulminant cerebral edema – and proposed a case definition. This study included all children enrolled in the California Encephalitis Project (CEP) from 1998 to 2012 who presented with AFCE (1.5%). The case definition for this new entity included the CEP case definition for encephalitis and progression to diffuse cerebral edema on neuroimaging and/or autopsy, and no other recognised aetiology for cerebral edema (e.g., organic, metabolic, toxin). Comparing the children with AFCE with children without, they were of similar ages (median, 8.2/8.0) but were more predominantly Asian-Pacific Islanders. ACFE more commonly had a prodromal phase and a poor outcome (80% mortality/ 13% mortality). A cause was confirmed in 2/30 children: enterovirus and human herpes virus type 6.

Krishnan P., Glenn O.A., Samuel M.C., et al. (2021) Acute fulminant cerebral edema: a newly recognized phenotype in children with suspected encephalitis. J Pediatric Infect Dis So; 10(3): 289-294.

Subacute sclerosing panencephalitis (SSPE)

Lam et al. (2022) drew attention to a recent rise in the cases of SSPE in the UK. Six children presented with an early SSPE over 24 months. They had a median age of five, and the time from the infection to the symptoms was median three years. Presenting features included visual impairment, focal and generalised tonic-clonic seizures, headache, vomiting and movement disorders. On imaging, the initial magnetic resonance imaging (MRI) was normal in four cases, and two cases showing focal and widespread white matter changes. Electroencephalography (EEG) showed typical findings in five cases. Treatment included both antiviral and immunomodulatory treatment, which unfortunately had no benefit. The outcome was death in all cases. The authors argued that these cases show that there is a global surge in measles cases and doctors need to be mindful of children presenting with neurological regression.

Dey and Ghosh (2021) presented a case series of four patients with atypical presentation of SSPE, presented at very early age with history of congenital measles infection (n = 1) and gait abnormality as initial symptom (n = 1), acute disseminated encephalomyelitis (ADEM) with refractory seizures (n = 1) and unilateral myoclonus with hemiparesis (n = 1). Diagnostic was confirmed after elevated cerebrospinal fluid (CSF), typical periodic EEG complexes, and serum anti-measles antibodies. Kathuria et al. (2021) reported an unusual case of SSPE in a 15-year-old who presented extensive involvement of brainstem with no significant involvement of other cortical structures of the brain on MRI.

Hashimoto et al. (2021) discussed the treatment options for SSPE: the current treatment regimen with interferon-α and ribavirin administered intracerebroventricularly. Furthermore, the study investigated the effect of favipiravir against measles virus (Edmonston and Yamagata-1 strains) in vitro. The authors argued

that their results showed that the 50% effective concentration (EC50) of favipiravir against Edmonston and Yamagata-1 strains were 108.7 ± 2.0 µM (17.1 ± 0.3 µg/mL) and 38.6 ± 6.0 µM (6.1 ± 0.9 µg/mL), respectively, which were like those of ribavirin. The authors concluded that their study shows that favipiravir has antiviral properties against the measles virus. Sonoda et al. (2021) reported a favourable outcome after intraventricular infusions of interferon-α in a ten-year-old patient with SSPE who was followed-up for 14 years.

Hashimoto K., Maeda H., Miyazaki K., et al. (2021) Antiviral effect of favipiravir (T-705) against measles and subacute sclerosing panencephalitis viruses. Jpn J Infect Dis; 74(2): 154-156.

Dey P.K., Ghosh A. (2021) Atypical presentation of fulminating subacute sclerosing panencephalitis: a case series. Neuropediatrics; 52(1): 52-55.

Kathuria H., Prabhat N., Shree R., Singh R. (2021) Subacute sclerosing panencephalitis and brain stem involvement: a rare combination. BMJ Case Rep; 14(2).

Lam T. Ranjan R., Newark K., et al. (2021) A recent surge of fulminant and early onset subacute sclerosing panencephalitis (SSPE) in the United Kingdom: An emergence in a time of measles. Eur J Paediatr Neurol; 34: 43-49.

Sonoda Y., Sonoda M., Yonemoto K., et al. (2021) Favorable outcomes of interferon-α and ribavirin treatment for a male with subacute sclerosing panencephalitis. J Neuroimmunol; 358: 577656.

MOG antibody-positive cerebral cortical encephalitis

Tian et al. (2021) investigated the clinical presentation of MOG antibody-positive cerebral cortical encephalitis by summarising the findings in the literature and two cases presented at the local hospital. Overall, the study included 24 patients: 20 adults and four children. The most common presenting symptoms were seizures (83%), headache (75%) and fever (54%). Cerebrospinal fluid (CSF) findings included increased cell number in 92% of patients. On imaging, characteristic was the enhanced FLAIR signal in cortical in all patients and enhanced fluid-attenuated inversion recovery (FLAIR) signal in unilateral cortical in 83% of patients. Doig et al. (2021) also reported two patients with cortical encephalitic presentations and anti-MOG-antibody-positive. On imaging, both children had bilateral cortical swelling and T2/fluid-attenuated inversion recovery (FLAIR) hyperintensity with corresponding regions of reduced diffusion. The authors concluded that, although rare, these cases happen, and early detection of MOG antibodies in these patients will enable quicker treatment.

Doig D., McNamara C., Mewasingh L., et al. (2021) Autoimmune cortical encephalitis in two children with anti-myelin oligodendrocyte glycoprotein (MOG) antibody. J Neurol; 268(3): 1096-1101.

Tian F., Liu X., Yang C., Wang B. et al. (2021) MOG antibody-positive cerebral cortical encephalitis: Two case reports and literature review. Int J Dev Neurosci; 81(4): 342-351.

Seizures and encephalitis

"Seizures are a frequent symptom in the beginning of AE and development of autoimmune-associated epilepsy with unprovoked seizures is rare." (Ilyas-Feldmann et al., 2021)

Seizures in anti-LGI1 encephalitis

ABSTRACT

Lin et al. (2021) investigated the semiology of seizure disorders, including electroencephalographic characteristics, and seizure outcomes in participants with anti-leucine-rich gliomainactivated 1 (LGI-1) encephalitis.

Results: At the time of presentation, 48 (68.6%) participants had generalised seizures and 57 (81.4%) had focal seizures. The most common focal motor seizures were faciobrachial dystonic seizures (FDS). The main manifestations of focal nonmotor seizures were dyscognitive features, goosebumps and disorders of sensation. All participants received immunomodulatory therapy. Thirty-five (50%) participants were seizure free after one year of follow-up, and 48 (68.6%) participants were seizure free over a follow-up of two years. Participants with seizures continued longer than one year were older than participants whose seizure duration was shorter than one year (P = 0.021). However, after an extended follow-up period, the difference between the incidences of seizures based on age was not significant. The frequency of focal motor seizures was higher in participants who became seizure free within one year, compared to participants who had seizures for longer than one year (75% vs 54.3%, respectively; P = 0.015). Participants with seizures continued over two years tended to have focal nonmotor seizures, and tended to show an elevated incidence of abnormal EEG results. Participants receiving early corticosteroid and longer duration immunosuppressant treatments tended to have a lower risk of persistent seizures and better seizure outcomes, with no statistical significance.

Conclusions: Most participants obtained remission from seizures after immunomodulatory therapy. The seizure manifestation of anti-LGI1 encephalitis is diverse and variable. The type of focal seizures may affect the outcome of participants with seizures. Older age could lead to longer duration of the seizure disorder but did not affect the rate of seizures over the long term. Early and prolonged administration of immunomodulatory therapy may be useful for shortening the time to becoming seizure free.

Smith et al. (2021) determined the risk factors associated with clinical relapses and development of chronic epilepsy in 49 patients with anti-LGI1 encephalitis ≥24 months of follow-up from disease onset. Definite chronic epilepsy was observed in eight and possible chronic epilepsy in two patients. Risk factors were female sex and younger age at onset. Relapses occurred in 40.8% of patients with a median time to first relapse of 7.5 months. Factor associated with a reduced risk of relapsed was long-term steroid-sparing immunotherapy.

Lin N, Liu Q, Chen J, et al. (2021) Long-term seizure outcomes in patients with anti-Leucine-rich glioma-inactivated 1 encephalitis. Epilepsy Behav; 122: 108159. doi: 10.1016/j.yebeh.2021.108159.

Smith K.M., Dubey D., Liebo G.B., et al. (2021) Clinical course and features of seizures associated with LGI1-antibody encephalitis. Neurology; 97(11).

Seizures in autoimmune encephalitis (AE): incidence, characteristics

Yeshokumar et al. (2021) ascertained the proportion of patients with seizures and electroencephalography (EEG) abnormalities in autoimmune encephalitis (AE). Of 3,722 antibody-positive patients with AE, 2,601 (69.9%) had clinical seizures during the course of their illness. Of the 2,025 patients with antibody-positive AE and available EEG data, 1,718 (84.8%) had some EEG abnormality. In anti-NMDA receptor encephalitis, 71.8% (n = 1425/1985) had clinical seizures during their illness, and 89.7% (n = 1172/1306) had EEG abnormalities.

Cousyn et al. (2021) characterised seizure semiology and EEG features associated with different subtypes of autoimmune encephalitis (AE) in a cohort of patients with AE managed in a tertiary referral centre for epilepsy and a neuro-intensive care unit. Overall, 66 patients experienced seizures: early tonic-clonic seizures (TCS) in anti-NMDAR AE, early mesial temporal lobe seizures with emotional symptoms in anti-GAD AE, somatosensory seizures in RE, and a lower frequency of TCS in anti-LGI1 AE. EEG helped to differentiate anti-NMDAR encephalitis patients (generalised rhythmic) and anti-GAD AE (temporal interictal epileptiform activity and temporal seizures). The authors have identified a new EEG pattern consisting of temporal low-voltage and periodic spikes which could be a sign of inflammatory mesial temporal involvement.

De Bruijn et al. (2021) aim to identify antibodies in patients with focal epilepsy of unknown etiology, and to create a score to preselect patients requiring testing.

ABSTRACT

Methods: In this prospective, multicenter cohort study, adults with focal epilepsy of unknown etiology, without recognized AIE, were included, between December 2014 and December 2017, and followed for 1 year. Serum, and if available cerebrospinal fluid, were analyzed using different laboratory techniques. The ACES score was created using factors favoring an autoimmune etiology of seizures (AES), as determined by multivariate logistic regression. The model was externally validated and evaluated using the Concordance (C) statistic.

Results: We included 582 patients, with median epilepsy duration of 8 years (interquartile range = 2-18). Twenty patients (3.4%) had AES, of whom 3 had anti-leucine-rich glioma inactivated 1, 3 had anti-contactin-associated protein-like 2, 1 had anti-N-methyl-D-aspartate receptor, and 13 had anti-glutamic acid decarboxylase 65 (enzyme-linked immunosorbent assay concentrations >10,000IU/ml).

Risk factors for AES were temporal magnetic resonance imaging hyperintensities (odds ratio [OR] = 255.3, 95% confidence interval [CI] = 19.6-3332.2, p < 0.0001), autoimmune diseases (OR = 13.31, 95% CI = 3.1-56.6, p = 0.0005), behavioral changes (OR 12.3, 95% CI = 3.2-49.9, p = 0.0003), autonomic symptoms (OR = 13.3, 95% CI = 3.1-56.6, p = 0.0005), cognitive symptoms (OR = 30.6, 95% CI = 2.4-382.7, p = 0.009), and speech problems (OR = 9.6, 95% CI = 2.0-46.7, p = 0.005). The internally validated C statistic was 0.95, and 0.92 in the validation cohort (n = 128). Assigning each factor 1 point, an antibodies contributing to focal epilepsy signs and symptoms (ACES) score ≥ 2 had a sensitivity of 100% to detect AES, and a specificity of 84.9%.

Interpretation: Specific signs point toward AES in focal epilepsy of unknown etiology. The ACES score (cutoff ≥ 2) is useful to select patients requiring antibody testing.

de Bruijn M.A.A.M., Bastiaansen A.E.M., Mojzisova H., et al. (2021) Antibodies contributing to focal epilepsy signs and symptoms score Ann Neurol; 89(4): 698-710.

Yeshokumar A.K., Coughlin A., Fastman J., et al. (2021) Seizures in autoimmune encephalitis-A systematic review and quantitative synthesis. Epilepsia; 62(2): 397-407.

Cousyn L., Lambrecq V., Houot M., et al. (2021) Seizures in autoimmune encephalitis: specific features based on a systematic comparative study. Epileptic Disord; 23(6): 879-892.

Seizures: outcomes and recurrence

Cooray et al. (2021) investigated whether it is possible to predict the outcomes of post-encephalitic epilepsy based on findings during the acute phase of disease. The study included 89 children with ages between 28 days and 17 years followed up to 24 months. The prevalence of post-encephalitic epilepsy was 9% (n = 8) at 24 months. Of these, three patients responded to monotherapy with antiepileptic drugs and five required two or more. Three patients were medically refractory at 24 months. Development of post-encephalitis epilepsy was associated with acute seizures during admission, epileptic activity on electroencephalographic (EEG) recordings and new-onset structural lesions. These patients also had a longer duration of hospital admission and longer care in intensive care units. The authors developed an algorithm to predict cohorts of patients with increased risk of developing post-encephalitic epilepsy.

Ilyas-Feldmann et al. (2021) reported long-term seizure outcome, use of antiseizure medication (ASM) and seizure recurrence risk after its withdrawal in patients with autoimmune encephalitis (AE) due to neuronal surface and GAD antibodies. The study included 75 patients: 47 patients had NMDAR, 17 LGI1, seven GAD, three CASPR2 and one mGluR5 antibodies. Overall, 53 patients experienced seizures at onset. After a median follow-up of six years, 47 patients had one year terminal seizure remission; the median duration of terminal seizure freedom was five years. The rate of one year terminal seizure remission was significantly higher in patients with neuronal surface antibodies compared with patients with GAD antibodies. In seizure-free patients, anti-epileptic medication was withdrawn after 13 months (median) without any relapse seizures.

Dhawan et al. (2021) reported the results of a comparative, parallel-group assignment, open-label, randomised control study to compare the proportion of children with seizure recurrence/s during 6–18 months of follow-up among children with acute symptomatic seizures underlying acute encephalitis syndrome (AES) treated with either four weeks or 12 weeks of antiseizure medication (ASM). The study included 60 children with ages between three months and 12 years. The authors established that this study provides Class I evidence that a shorter duration (four weeks) of ASM is comparable with 12 weeks therapy for preventing seizure recurrences in children with AES. Furthermore, they argued that there was no association of seizure recurrences with seizure characteristics, abnormal electroencephalography and neuroradiology. However, children with disabilities at randomisation had a higher risk of seizure recurrence at 18 months of follow-up.

Cooray G., Ygberg S., Fowler Å., Wickström R. (2021) Post-encephalitic epilepsy in childhood: results from a prospective cohort study. Epileptic Disord. 23(1): 133-142.

Dhawan S.R., Sahu J.K., Singhi P., et al. (2021) Comparison of 4 weeks versus 12 weeks antiseizure medication for acute symptomatic seizures in children with Acute Encephalitis Syndrome: An open-label, randomized controlled trial. Seizure; 92: 182-188.

Ilyas-Feldmann M., Prüß H., Holtkamp M. (2021) Long-term seizure outcome and antiseizure medication use in autoimmune encephalitis. Seizure; 86: 138-143.

Diagnosis and management of encephalitis

Autoimmune encephalitis: diagnosis and management

Best practice recommendations summary for acute management of autoimmune encephalitis (AE) suggested by Abboud et al. (2021):

1. Evaluate the likelihood of AE relative to the patient's clinical picture.
2. Perform brain MRI and/or EEG to look for focal or multifocal brain abnormality.
3. Perform lumbar puncture to support inflammatory aetiology and rule out infective/neoplastic causes. Test oligoclonal bands, IgG index, IgG synthesis rate and neuronal autoantibodies in the cerebrospinal fluid (CSF).
4. Send blood tests to rule out other potential causes guided by neuroanatomical and clinical data. Test neuronal autoantibodies in the serum.
5. Consider brain FDG-PET when there is a high clinical suspicion of AE and other paraclinical studies are uninformative.
6. Perform cancer screening with CT chest, abdomen, and pelvis with contrast in relevant cases (or MRI when CT is contraindicated or not preferred). If negative, consider further testing with mammogram/breast MRI, pelvic ultrasound, and/or whole body FDG-PET guided by the clinical presentation and each patient's specific cancer risk factors.
7. Once infection is ruled out based on basic CSF results (e.g., number of cells) and if biopsy for primary CNS lymphoma or neurosarcoidosis is not a consideration, start acute immunotherapy with high dose corticosteroids (or IVIG or PLEX if steroids are not preferred or contraindicated).
8. If there is no clinical, radiological or electrophysiological improvement by the end of the initial treatment cycle, add IVIG or PLEX. Consider IVIG first in agitated patients and in those with bleeding disorders. Consider PLEX first in patients with severe hyponatraemia, high thromboembolic (or cancer) risk, and if there is associated brain or spinal demyelination.
9. Consider starting with a combination therapy of steroids/IVIG or steroids/PLEX from the beginning (as opposed to sequentially) in patients with severe initial presentation (e.g., severe NMDAR-antibody presentation, new onset refractory status epilepticus, severe dysautonomia, etc).
10. If there is no clinical or radiological improvement 2–4 weeks after completion of combined acute therapy, consider starting a second-line agent when the clinical suspicion is high and/or a clinically relevant antibody is present.
11. Consider rituximab in known or highly suspected antibody-mediated autoimmunity (e.g., NMDAR-antibody encephalitis) and consider cyclophosphamide in known or highly suspected cell-mediated autoimmunity (e.g., classical paraneoplastic syndrome).
12. If no clear objective or subjective evidence of improvement with conventional second-line therapies, consider novel approaches such as tocilizumab or bortezomib, although there is only minimal evidence to support their use.
13. Start bridging therapy with gradual oral prednisone taper or monthly intravenous Ig or intravenous methylprednisolone. Avoid steroid taper or implement a shorter taper in vague cases with poor response to initial immunosuppressive therapy or when immunosuppression may impose higher risks than benefits (e.g., patients with cancer or active infection).

Abboud H., Probasco J.C., Irani S., et al. (2021) Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management J Neurol Neurosurg Psychiatry; 92: 757-768.

Uy et al. (2021) highlight practical aspects of diagnosis and treatment of autoantibody-mediated encephalitis syndromes with neuronal cell-surface antigens.

ABSTRACT

Autoimmune encephalitis defines brain inflammation caused by a misdirected immune response against self-antigens expressed in the central nervous system. It comprises a heterogeneous group of disorders that are at least as common as infectious causes of encephalitis. The rapid and ongoing expansion of this field has been driven by the identification of several pathogenic autoantibodies that cause polysymptomatic neurological and neuropsychiatric diseases. These conditions often show highly distinctive cognitive, seizure and movement disorder phenotypes, making them clinically recognisable. Their early identification and treatment improve patient outcomes, and may aid rapid diagnosis of an underlying associated tumour. Here we summarise the well-known autoantibody-mediated encephalitis syndromes with neuronal cell-surface antigens.

We focus on practical aspects of their diagnosis and treatment, offer our clinical experiences of managing such cases and highlight more basic neuroimmunological advances that will inform their future diagnosis and treatments.

KEY-POINTS:

- Autoimmune causes of encephalitis are at least as common as infectious causes and should be considered early.
- Several characteristic core phenotypic manifestations may strongly suggest an underlying autoantibody-mediated encephalitis; this should raise the consideration of empiric immunotherapy once infectious causes are reasonably excluded.
- Early immunotherapy improves outcomes in patients with autoimmune encephalitis.
- Whenever possible, paired cerebrospinal fluid and serum should be tested, and clinicians should emphasise the clinical hypothesis when interpreting the results.

- Brain sections and neuronal cultures are valuable methods to detect autoantibodies in patients who have a suspected autoimmune condition despite negative antigen-specific results.

Uy C.E., Binks S., Irani S.R. (2021) Autoimmune encephalitis: clinical spectrum and management. Pract Neurol; 0: 1-14. doi:10.1136/practneurol-2020-002567

Metagenomic next-generation sequencing (mNGS)

Kang et al. (2021) reviewed the results of NGS of cerebrospinal fluid (CSF) in a series of patients diagnosed with atypical herpes simplex encephalitis (HSE).

ABSRACT

Results: Four patients lacking classical clinical manifestations of HSE, including no fever, headache or other typical neurological deficit symptoms, 1–2 106 cells/L CSF leucocyte count, and no typical imaging features, were diagnosed with atypical HSE by NGS of CSF. The NGS reads corresponding to herpes simplex virus type 1 ranged from 2 to 13,174.

Conclusions: Mild HSE may not present with classic frontotemporal lobe syndrome and fever may not be an inevitable symptom in patients with immunosuppression. However, the possibility of HSE should be considered in patients with atypical intracranial infection, and these patients should be tested by NGS.

Kang Z., Jin X., Wei N., et al. (2021) Next-generation sequencing of cerebrospinal fluid for diagnosis of atypical herpes simplex encephalitis. J Int Med Res; 49(10): 3000605211049645.

Rituximab in autoimmune encephalitis

ABSTRACT

Background and objectives: To determine the real-world use of rituximab in autoimmune encephalitis (AE) and to correlate rituximab treatment with the long-term outcome.

Results: Of the 358 patients, 163 (46%) received rituximab (NMDAR-AE: 57%, CASPR2-AE: 44%, LGI1-AE: 43%, and GAD65 disease: 37%). Rituximab treatment was initiated significantly earlier in NMDAR- and LGI1-AE (median: 54 and 155 days from disease onset) compared with CASPR2-AE or GAD65 disease (median: 632 and 1,209 days). Modified Rankin Scale (mRS) scores improved significantly in patients with NMDAR-AE, both with and without rituximab treatment. Although being more severely affected at baseline, rituximab-treated patients with NMDAR-AE more frequently reached independent living (mRS score ≤2) (94% vs 88%).

In LGI1-AE, rituximab-treated and nontreated patients improved, whereas in CASPR2-AE, only rituximab-treated patients improved significantly. No improvement was observed in patients with GAD65 disease. A significant reduction of the relapse rate was observed in rituximab-treated patients (5% vs 13%). Detection of NMDAR antibodies was significantly associated with mRS score improvement. A favorable outcome was also observed with early treatment initiation.

Discussion: We provide real-world data on immunosuppressive treatments with a focus on rituximab treatment for patients with AE in Germany. We suggest that early and short-term rituximab therapy might be an effective and safe treatment option in most patients with NMDAR-, LGI1-, and CASPR2-AE.

Class of evidence: This study provides Class IV evidence that rituximab is an effective treatment for some types of AE.

Thaler F.S., Zimmermann L., Kammermeier S., et al. (2021) Rituximab treatment and long-term outcome of patients with autoimmune encephalitis: real-world evidence from the GENERATE Registry. Neurol Neuroimmunol Neuroinflamm; 8(6): e1088. doi: 10.1212/NXI.0000000000001088.

Treatment in refractory cases of autoimmune encephalitis (AE)

Jang et al. (2021) reported the use of tofacitinib to treat intractable cases of AE. Eight patients who showed insufficient responses to multimodal conventional immunotherapies were administered tofacitinib orally at a dose of 5 mg twice daily. Two patients showed improvement and the cessation of the new-onset refractory status epilepticus, two had partial responses and three no improvement. No serious side-effects were reported. The authors argue that tofacitinib can be a possible therapeutic option for central nervous system autoimmune diseases.

Chen et al. (2021) reported the use of immunoadsorption with Staphylococcal Protein A Column (SPA-IA) in three patients with AE wherein the first-line treatment was ineffective or contraindicated. After treated with SPA-IA, all antibody titres, except for the serum antibody titer in one patient, were markedly decreased in both the cerebral spinal fluid and serum. The modified Rankin Scale scores and their symptoms improved significantly after the last SPA-IA session or three months later.

Yang et al. (2021) reported successful treatment with immunoadsorption therapy in four patients with severe and refractory anti-N-methyl-D-aspartate receptor encephalitis. Immunoadsorption was performed during the fulminant stage of disease and was followed by a gradual and steady improvement. The only adverse effect observed was mild hypotension for one patient.

Wang et al. (2021) presented five treatment-resistant patients with anti-NMDAR who received Bortezomib, which resulted in a decrease in the antibody secreting cell (ASC) count and anti-NMDAR antibody titres. At follow-up (median, 31 months), all five patients had a favourable prognosis (mRS ≤2).

Eaton et al. (2021) reported the use of intrathecal methotrexate (IT-MTX) in five patients with refractory autoimmune encephalitis (three definite anti-NMDAR encephalitis and two probable anti-NMDAR encephalitis). All patients received at least one dose of IT-MTX after failing conventional therapies: methylprednisolone (five), IVIG (three), PLEX (four), and rituximab (four). All patients tolerated IT-MTX well and all improved substantially.

Chen J., Feng L., Zhou H., et al. (2021) Immunoadsorption with staphylococcal protein A column in autoimmune encephalitis. Transfusion; 61(11): 3272-3276.

Eaton J.E., Kleinholz-Owens P., Sriram S., Pawate S. (2021) Intrathecal methotrexate - another tool for the treatment of refractory autoimmune encephalitis - Single institution cohort and literature review. J Neurol Sci; 431: 120042.

Jang Y., Lee W.J., Lee H.S., et al. (2021) Tofacitinib treatment for refractory autoimmune encephalitis. Epilepsia; 62(4): e53-e59.

Wang T., Wang B., Zeng Z., et al. (2021) Efficacy and safety of bortezomib in rituximab-resistant anti-N-methyl-d-aspartate receptor (anti-NMDAR) encephalitis as well as the clinical characteristics: An observational study. Neuroimmunol; 577527.

Yang Y., Zhang B., Li M., Li J. (2021) Successful treatment with immunoadsorption therapy in four patients with severe and refractory anti-N-methyl-D-aspartate receptor encephalitis. J Clin Apher; 36(6): 886-892.

Cerebrospinal fluid (CSF) findings in autoimmune encephalitis (AE)

Durr et al. (2021) characterised CSF findings in acute, therapy-naïve NMDAR-E and LGI1-E in a multicentric, retrospective, cross-sectional setting.

ABSTRACT

Results: CSF was abnormal in 94% of NMDAR-E but only in 36% of LGI1-E patients. Robust quantitative intrathecal immunoglobulin synthesis (IIS, IgG > IgM >> IgA) was characteristic for NMDAR-E, but absent in LGI-E. In NMDAR-E, CSF leukocytes were higher when IIS was present or more pronounced. In addition, in NMDAR-E, CSF leukocytes were lower and IIS occurred less often and if so to a lesser degree at older age. Patients with NMDAR-E with severe functional impairment more often had positive OCBs. In CSF obtained later than 3 weeks of onset, leukocytes were lower. In parallel, the correlation of leukocytes with IIS disappeared as IIS was partially independent of disease duration. The MRZ reaction was positive in 5 (36%) patients with NMDAR-E. All these associations were completely absent in LGI1-E. Here, younger patients showed more blood-CSF barrier dysfunction. In LGI1-E, but not in NMDAR-E, the blood-CSF barrier was more dysfunctional when CSF leukocytes were higher.

Discussion: NMDAR-E and LGI-E differ in their typical extent of CSF inflammation. In addition, the patterns formed by the different inflammatory CSF parameters and their relationship with disease severity, age, and disease duration are subtype-characteristic. Moreover, signs for multiple sclerosis-like chronic inflammation are present in a subgroup of patients with NMDAR-E. These CSF patterns might be markers for the different immunopathogeneses of LGI1-E and NMDAR-E.

Broadley et al. (2021) retrospectively studied 57 cases of seropositive AE to examine the prognostic value of CSF abnormalities. The authors found that CSF WCC had prognostic significance, being associated with treatment failure (WCC >5 cells/mm^3) and ICU admission (WCC >20 cells/mm3). The authors also noted that different types of AE have different CSF characteristic abnormalities.

Zrzavy et al. (2021) described initial and serial CSF findings of 33 patients diagnosed with antibody-associated AIE (LGI1 (n=8), NMDA (n=7), CASPR2 (n=3), IgLON5 (n=3), AMPAR (n=1), GAD65/67 (n=4), Yo (n=3), Ma-1/2 (n=2), CV2 (n=2)). Routine CSF parameters of 12.1% of AIE patients were in normal ranges, while 60.6% showed elevated protein levels and 45.4% had intrathecal oligoclonal bands (OCBs). Repeated CSF analyses showed a trend towards normalisation of initial pathological CSF findings, while relapses were more likely to be associated with increased cell counts and total protein levels. OCB status conversion in anti-NMDARE patients coincided with clinical improvement. In summary, the study shows that in routine CSF analysis at diagnosis, a considerable number of patients with AIE did not exhibit alteration in the CSF and therefore, diagnosis may be delayed if antibody testing is not performed.

Zrzavy T, Höftberger R, Wimmer I, et al. (2021) Longitudinal CSF Findings in Autoimmune Encephalitis—A Monocentric Cohort Study. Front. Immunol; 12: 646940. doi: 10.3389/fimmu.2021.646940

Broadley J., Wesselingh R., Seneviratne U., et al. (2021) Prognostic value of acute cerebrospinal fluid abnormalities in antibody-positive autoimmune encephalitis. J Neuroimmunol; 353: 577508.

Dürr M, Nissen G, Sühs KW, et al. (2021) CSF findings in acute NMDAR and LGI1 antibody-associated autoimmune encephalitis. Neurol Neuroimmunol Neuroinflamm; 8(6): e1086. doi: 10.1212/NXI.0000000000001086.

Outcomes after encephalitis

"Fatigue is a prominent feature affecting the quality of life in AE, should be evaluated as part of ongoing medical care, and may be an important outcome in treatment trials."
(Diaz-Arias et al., 2021)

Fatigue after autoimmune encephalitis (AE)

ABSTRACT

Methods: In a first cohort recruited via several encephalitis support organisations, self-reported questionnaires were used to evaluate fatigue, depression and sleep quality in adults after autoimmune encephalitis. In a second cohort where more in-depth clinical characterisation could be performed, adults with encephalitis from 2 tertiary hospitals were evaluated using the same questionnaires. Patients' characteristics were retrospectively captured.

Results: In the first cohort (mean [SD] age; 43 [16] years, 220 [65%] female), 220 of 338 participants (65%) reported fatigue, 175 of 307 (57%) depression and 211 of 285 (74%) poor sleep quality. In the second cohort (48 [19] years; 43 [50%] women), 42 of 69 participants (61%) reported fatigue, whereas 23 of 68 (34%) reported depression and 44 of 66 (67%) poor sleep quality, despite more than 80% having "good" modified Rankin scale (mRS) scores (0-2). Individuals with anti-NMDA receptor encephalitis reported lower fatigue scores than those with other autoimmune encephalitis types. In a multivariate analysis examining factors at discharge that might predict fatigue scores, only anti-NMDA receptor encephalitis was a (negative) predictor of fatigue and remained so when potential confounders were included.

Discussion: The impact of fatigue after autoimmune encephalitis is prominent and not fully accounted for by depression or sleep quality, nor adequately captured by mRS scores for disability. Fatigue is pervasive across autoimmune encephalitis, although lower scores are reported in anti-NMDA receptor encephalitis. Fatigue should be screened routinely, considered as an outcome measure in clinical trials, and further studied from a mechanistic standpoint.

Diaz-Arias L.A., Yeshokumar A.K., Glassberg B., et al. (2021) Fatigue in survivors of autoimmune encephalitis. Neurol Neuroimmunol Neuroinflamm; 8(6): e1064.

Outcomes of anti-NMDAR encephalitis in children

Wu et al. (2021) enrolled ten children aged below 18 years old with antibody-proved anti-NMDA receptor encephalitis in a tertiary medical centre from 2010 to 2019 in a retrospective study. Long-term neurological consequences of anti-NMDA receptor encephalitis in children were followed.

ABSTRACT

Results: One boy and nine girls were enrolled with a median onset age of 3.6 years. The most common initial presentation was verbal reduction and psychiatric symptoms soon after some flu-like prodromal symptoms. Nearly all patients then developed decreased level of consciousness, mutism, seizures and orofacial-lingual dyskinesia. Autonomic instability occurred in five patients, particularly in pre-pubertal children. Only one adolescent patient had ovarian teratoma. All patients survived after immunotherapy and were followed for 5.8±3 3.3 years after discharge. Four had epilepsy within two years after encephalitis, four had a cognitive deficit, one had mild psychiatric symptoms of hallucination and none had residual involuntary movements. Moreover, two pre-pubertal children developed central precocious puberty about three years after encephalitis, and one required gonadotropin-releasing hormone agonist treatment.

Conclusion: Central precocious puberty could be a consequence of anti-NMDA receptor encephalitis in the pre-pubertal children. The paediatrician should pay attention to its occurrence at follow-up.

Wilkinson-Smith et al. (2021) evaluated areas of impairment in 23 children recovering from anti-NMDAR encephalitis who were, on average, 18.5 months from diagnosis. There were variations in how patients recovered. However, memory and fine motor dexterity were particularly affected. More than two-thirds of the children were considered impaired based on neuropsychological impairment index (NPI) scores on performance measures. Most of the caregivers reported more concerns than average on at least one measure of emotional-behavioural, adaptive or executive functioning. The authors conclude by highlighting that those paediatric patients recovering from anti-NMDAR encephalitis experience cognitive difficulties for which ongoing monitoring and support is recommended.

Wilkinson-Smith A., Blackwell L.S., Howarth R.A. (2021) Neuropsychological outcomes in children and adolescents following anti-NMDA receptor encephalitis. Child Neuropsychol; 28(2): 212-223.

Wu P.M., Teng C.K., Chou Y.Y., Tu Y.F. (2021) Precocious puberty as a consequence of anti-NMDA receptor encephalitis in children. Pediatr Neonatol; 62(4): 361-368. doi: 10.1016/j.pedneo.2021.03.004.

Outcomes of Japanese encephalitis (JE)

Wang et al. (2021) aimed to evaluate the long-term neurological sequelae and the disease burden of JE in Gansu, China.

ABSTRACT

Results: Forty-four point seven percent of the JE patients had objective neurological deficits, compared with 2.4% of controls. Subnormal intelligence was found in 21.2% of JE subjects, compared with 1.2% control who exhibited a mildly reduced IQ. Abnormal MQ scores were noted in 56.3% JE subjects, compared with only 12.7% controls. Prevalence of each sequelae caused by JE were significantly higher in adults than in younger subjects. Furthermore, median DALY lost due to JE was 9.2 per subject. Median economic cost of JE was approximately $2776.6 per subject and significantly higher in adults than in younger subjects.

Findings and conclusions: JE patients suffered from severe neurological sequelae and high disease burden, resulting in a significant downstream burden for both the patients (especially adults) and the healthcare system.

Dutta et al. (2021) reported the long-term morbidity and functional outcome of 56 children (0–12 years old) with JE. During their hospital stay, ten children died. At discharge, according to the Liverpool Outcome Score, 17 children were left with severe sequelae, five had moderate sequelae, six developed minor sequelae, and 18 showed full recovery. At the end of the follow-up (2.5 years), all children with minor sequelae and two with moderate sequelae recovered fully; two children with severe sequelae died; nine children were still left with severe sequelae and the others had a degree of improvement (most improvement happened within the initial year of follow-up). Long-term sequalae included abnormal behaviour in ten, epilepsy in eight, cognitive in eight and motor difficulties in seven children. Although acknowledging their small size sample, the authors argued that residual neuro-psychiatric problems prevented a significant proportion of children from returning to normal life.

Dutta A., Nag S.S., Dutta M., Basu S. (2021) Long-term morbidity and functional outcome of Japanese encephalitis in children: a prospective cohort study. Indian Pediatr; 58(9): 846-849.

Wang X., Su L., Sun S., et al. (2021) Long-term neurological sequelae and disease burden of Japanese encephalitis in Gansu Province, China. Ann Glob Health; 87(1): 103. doi: 10.5334/aogh.3343.

Outcomes of anti-LGI1 encephalitis

Binks et al. (2021) aimed to quantify the residual deficits observed after anti-LGI1 encephalitis across several functional domains. Despite a considered good mRS, the authors noted several long-term residual deficits across cognition, mood and fatigue, with a significant effect on employment status. Fatigue was the most impaired domain in this cohort, a novel finding in anti-LGI1 encephalitis. This observation is closely reflected by the many patients at the authors' clinic consideration of fatigue as a major residual symptom. Also, it parallels findings in paediatric N-methyl-d-aspartate receptor antibody encephalitis, where fatigue is associated with quality of life. Overall, the authors continued to advocate early immunotherapy to achieve optimal clinical outcomes in patients.

Chen et al. (2021) evaluated the cognitive and neurofunctional outcomes in patients with anti-LGI1 encephalitis after a follow-up of median 33 months. Eight out of 86 patients died after discharge, 24.7% relapsed, 39.7% were left with cognitive deficits (especially elderly), 21.9% with neuropsychiatric symptoms and 11.0% with seizures. Although most patients were functionally independent at follow-up, not all returned to all premorbid activities.

Binks, S.N.M., Veldsman, M., Easton, A., et al. (2021) Residual fatigue and cognitive deficits in patients after Leucine-Rich Glioma-Inactivated 1 antibody encephalitis. JAMA Neurology. doi:10.1001/jamaneurol.2021.0477.

Chen W., Wang M., Gao L., et al. (2021) Neurofunctional outcomes in patients with anti-leucine-rich glioma inactivated 1 encephalitis. Acta Neurol Scand; 144(6): 632-639.

Sleep disturbances after tick-borne encephalitis (TBE)

Veje et al. (2021) presented a study in which 44 adults, 22 TBE patients, diagnosed in Region Vastra Gotaland, Sweden, between 2012 and 2015, and 20 controls without a known TBE history, underwent an overnight polysomnography (PSG). The cases and controls were similar regarding age, sex, obesity, concomitant diseases, smoking and alcohol habits. Despite similar PSG characteristics such as total sleep time and obstructive sleep apnea (OSA) severity indices, the TBE cases reported statistically more sleep-related functional impairment on the Functional Outcome of Sleep Questionnaire (FOSQ) compared with the controls (median scores 18.1 vs 19.9; $p<0.05$). In a multivariate analysis, TBE correlated significantly with the lower FOSQ scores (unstandardized β−1.80 [%95 confidence interval −3.02 - −0.58]; $p = 0.005$) independent of age, sex, total sleep time and apnea-hypopnea-index. TBE cases with OSA reported the lowest scores on the FOSQ compared with the other subgroups with TBE or OSA alone, and the ones with neither TBE nor OSA. TBE is associated with impaired functional outcomes, in which concomitant OSA may worsen the subjective symptoms. Further studies are warranted to determine the effect of treatment of concomitant OSA on functional outcomes with regard to optimal rehabilitation of TBE.

Veje M., Studahl M., Thunstrom E., et al. (2021) Sleep architecture, obstructive sleep apnea and functional outcomes in adults with a history of tick-borne encephalitis. PLoS ONE; 16(2): e0246767.

Predictors of outcomes in autoimmune encephalitis (AE)

Broadley et al. (2021) examined the utility of the peripheral blood neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-lymphocyte ratio (MLR) as biomarkers of prognosis in seropositive autoimmune encephalitis (AE).

ABSTRACT

Methods: In this multicenter study, we retrospectively analysed 57 cases of seropositive AE with hospital admissions between January 2008 and June 2019.

Results: During initial hospital admission 44.7% of patients had unsuccessful first line treatment. After a median follow-up of 700 days, 82.7% had good functional outcome (mRS ≤2) while five patients had died. On multivariable analysis, high NLR was associated with higher odds of first line treatment failure (OR 1.32, 95% CI 1.03-1.69, $p = 0.029$). Increased MLR was not associated with any short or long-term outcome.

Conclusions: NLR on initial hospital admission blood tests may be provide important prognostic information for cases of seropositive AE. This study demonstrates the potential use of NLR as a prognostic marker in the clinical evaluation of patients with seropositive AE.

Levraut et al. (2021) reported the concentrations of CSF sIL-2R, IL-6, IL-8, IL-10 and IL-17A and to correlate it with acute disease severity and the 1-year outcome in non-NMDAR AE.

ABSTRACT

Methods: We measured the CSF concentration of each cytokine in 20 AE patients and compared IL-6 and IL-17A concentrations

with 13 patients with CNS demyelinating diseases and 20 non-inflammatory controls. Patients were > 18yr and had at least 1-year clinical follow-up. Intracellular and NMDAR antibody (Ab) -mediated encephalitis were excluded. A mRS ≤ 2 was retained as a 1-year good outcome.

Results: The IL-17A concentration in CSF was higher in AE patients than in both control groups ($p<0.01$). No difference was observed in CSF concentration of IL-6 between groups. At disease onset, a high CSF IL-17A concentration correlated with a high modified Rankin Scale ($p<0.05$), a high Clinical Assessment Scale for Autoimmune Encephalitis score ($p<0.001$) and ICU admission ($p<0.01$). There was no correlation between the concentration of all CSF cytokines and the 1-year clinical outcome.

Conclusion: Our results show that CSF IL-17A could be interesting to assess initial severity in non NMDAR AE. Thus, CSF IL-17A could be an interesting therapeutic target and be useful to assess early selective immunosuppressive therapy.

Broadley J., Wesselingh R., Seneviratne U. (2021) Peripheral immune cell ratios and clinical outcomes in seropositive autoimmune encephalitis: a study by the Australian autoimmune encephalitis Consortium. Front Immunol; 11: 597858. doi: 10.3389/fimmu.2020.597858.

Levraut M., Bourg V., Capet N., et al. (2021) Cerebrospinal fluid IL-17A could predict acute disease severity in non-NMDA-receptor autoimmune encephalitis. Front Immunol; 12: 673021. doi: 10.3389/fimmu.2021.673021.

Patient experience of recovery

McKeon et al. (2021) investigated patients' perceptions of the factors affecting their recovery from anti-N-methyl-d-aspartate receptor (anti-NMDAR) encephalitis. The study included seven patients, with a mean age of 26.4 years, one male and six female, who completed semistructured interviews exploring their experience of recovery. The estimated time from symptom onset to treatment with immunotherapy ranged from one month to 20 years. At the time of the study, patients were between seven and 41 months posttreatment. The patients identified as factors that facilitated recovery support from family and friends, kindness of hospital staff and a range of interventional, educational and rehabilitation treatments. Barriers to recovery included perceived psychiatric stigma, insufficient illness education and lifestyle disruptions to accommodate ongoing treatment. Participants described persisting functional impairment following resolution of the acute phase including physical, psychological and neurocognitive symptoms as well as social and daily-living skills impairment. The authors concluded that anti-NMDAR encephalitis contributes to persistent burden on patients, their families and health services after the resolution of acute symptoms.

McKeon G., Parker S., Warren N., Scott J.G. (2021) The patient experience of recovery following anti-NMDA receptor encephalitis: a qualitative content analysis. J Neuropsychiatry Clin Neurosci; 33(1): 57-63.

About the Encephalitis Society

How we can help you and your patients

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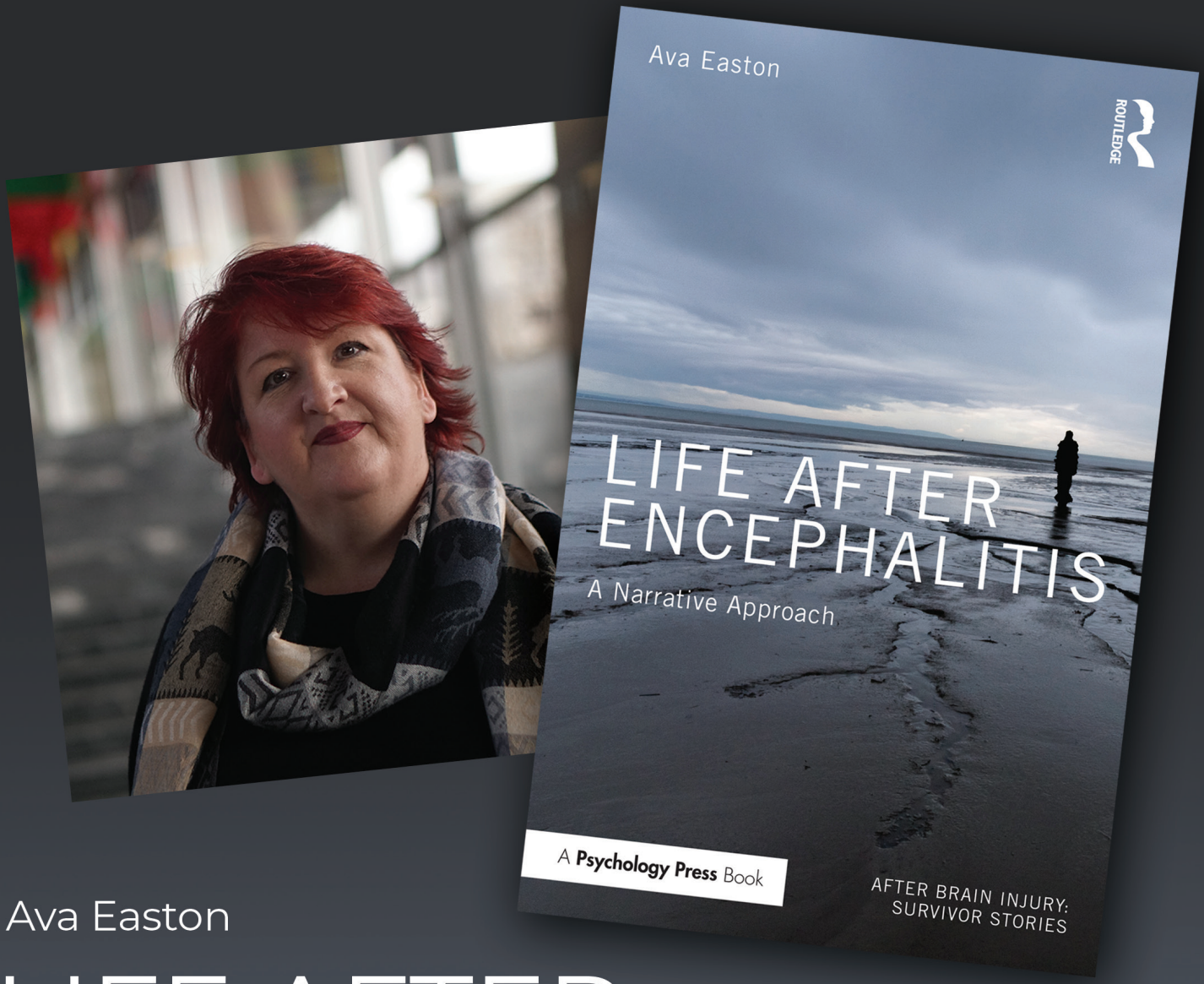

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