Foreword

This is our second year producing this research review. The feedback received following the 2013 edition was overwhelmingly positive – a one-stop shop for key papers, articles and books that relate to encephalitis. We continue to promote, collaborate, conduct and fund research into encephalitis. The current year sees us involved in 13 encephalitis-related studies.

We have expanded our professional seminar and meeting to include a research exchange where those interested in research on encephalitis can come together to discuss their projects and studies, as well as new ideas.

We have embraced our membership (those affected by encephalitis and their families) into research in the field by supporting their presence on trial management and steering groups. More broadly the membership have been consulted to address ethical issues in research ensuring the patient’s voice is represented in decisions that will affect them.

We continue to pursue and participate in opportunities for patient and public involvement in research as World Encephalitis Day (22nd February) bore testament to. A highlights video and more details on the next World Encephalitis Day can be viewed here: www.worldencephalitisday.org

Finally, we continue to nurture young talent in the field with our Medical Student Essay Competitions and Travel Bursaries. In addition we have just launched an appeal for an academic partner prepared to collaborate on an encephalitis PhD fellowship.

This Review is available both in hard copy and electronically, along with a more detailed archive of papers we host on our website looking at everything from epidemiology to outcome.

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

Dr Ava Easton
Chief Executive
The Encephalitis Society

Acknowledgements
The Encephalitis Society is extremely grateful to Moore Blatch Solicitors for funding that enabled the publication of this Summary.

Disclaimer
This review has tried to provide a succinct summary of the original papers. The full paper references are included in order to acknowledge the source, and for those who would like to read the articles, papers and books in full. The information presented in this summary should not be relied on to suggest an appropriate course of treatment for a particular individual. We strongly recommend you to refer to the author’s original paper before altering practice in any way.
Contents

Epidemiology of encephalitis

Asia:
Japanese encephalitis (JE): forecast and surveillance ................................................................. 01
Acute encephalitis syndrome (AES) in India: a growing concern ................................................. 01

Europe:
Tick-borne encephalitis: a review ................................................................................................... 03
Viral meningo-encephalitis in England and Wales: population trends .......................................... 04

America (USA):
West Nile virus (WNV) encephalitis: why the surveillance and prevention programmes are important? .......................................................................................................................... 04
Encephalitis: a major public concern in the USA ........................................................................ 05

Australia:
Neonatal herpes simplex virus (HSV) infection: epidemiology and trends ................................ 05

Pathogenesis of encephalitis

Herpes simplex encephalitis (HSE) and toll-like receptor 3 (TLR3) deficiency ............................. 06
Japanese encephalitis (JE): pathogenesis still unfolding ............................................................... 06
Antibodies directed against neuronal cell surface antigens in the CNS: evidence for their pathogenicity ................................................................................................................................. 07
Amoebae encephalitis: a life-threatening infection for both immunocompetent and immunocompromised individuals ........................................................................................................ 07

Infectious encephalitis

Varicella zoster virus (VZV): immunisation, reactivation and central nervous system (CNS) complications ................................................................................................................................. 08
Herpes simplex encephalitis (HSE): uncommon presentation and empiricism ............................. 09
Herpes simplex encephalitis (HSE) and anti-NMDA receptor encephalitis: co-occurrence or trigger? ........................................................................................................................................ 09
Cryptococal meningoencephalitis: how to improve the outcome ................................................. 10
Autoimmune encephalitis

Autoantibodies and their associated syndromes: an expanding area of neurology

Testing for autoantibodies: serum versus cerebrospinal fluid (CSF)

Anti-NMDA receptor encephalitis: the impact of early treatment on the outcomes

Anti-NMDA receptor encephalitis: new features and exceptional circumstances

Teratoma-associated encephalitis: with and without anti-NMDA receptor antibodies

Voltage-gated potassium channel (VGKC)-complex antibodies: clinical relevance

Leucine-rich, glioma-inactivated 1 (LGI1) antibody associated encephalopathy: novel neurocardiac prodrome, association with cerebellar degeneration and natural course without immunotherapy

GlyR antibodies: an overview

GABA\textsubscript{\textalpha} encephalitis: a report of five cases in the Asian population

GABA receptor antibodies: a new epileptic disorder

Autoantibodies: a potential role in demyelinating syndromes

New autoimmune syndrome: autoimmune adult onset focal epilepsy and encephalitis

Rasmussen encephalitis (RE): pathogenesis and treatment

Diagnosis, treatment and outcomes of encephalitis

Limbic encephalitis (LE) associated with voltage-gated potassium channel (VGKC) complex antibody: cognitive impairments and predictors of outcome

Acute encephalitis: overview of causes, management and predictors of outcomes at discharge

Neonatal herpes simplex virus infection: the role of the magnetic resonance imaging (MRI) in assessing the course of the disease

Rituximab: efficacy and safety

Seizures: antiepileptic drugs and ketogenic diet

Recovery and rehabilitation

Transition to adult care for patients with Rasmussen encephalitis (RE)

Book review

The Thief in the Night by Catherine O'Toole Scott

A Single Swim by Kristina Circelli

The Encephalitis Society

Neuropsychology service

Professional membership
Epidemiology of encephalitis

“Understanding the epidemiology is important in order to identify which populations are most vulnerable, the treatment and prevention strategies that need to be developed and to identify key research priorities for the future”. (Kadambari et al., 2014)

Asia

Japanese encephalitis (JE) – forecast and surveillance

Japanese encephalitis is an important cause of viral encephalitis in Asia. There are around 67,900 cases every year in the JE-endemic countries. Around 20–30% cases are fatal and 30–50% of survivors are left with substantial neurological consequences (Campbell et al., 2011). Spatial distribution of JE has changed over the years because of various factors. Being able to forecast JE distribution and transmission is vital for adopting efficient and adequate public health strategies.

Wang et al. (2014) analysed the JE surveillance data in China over a six-year period (2005–2011) in order to describe the relationship between JE human cases and various factors such as minimum and mean temperature, elevation and population density. The authors considered these factors as being the main environmental drivers of JE cases during the study period. They also revealed that the majority of the JE cases (60%) were distributed in the predicted high-risk areas: southwestern and central China (6% of mainland China).

In conclusion, the authors argue that using current JE surveillance data and the environmental factors, one can forecast, short-term, the spatial distribution of JE. The areas with the highest risk should be prioritised for implementation of more effective prevention and control interventions against JE.

Handique et al. (2014) tried to forecast JE incidence from the historical morbidity patterns of JE incidence alone in one district in India by using four forecasting methods. The aim of the study was to assess the accuracy of these methods in forecasting JE at a district level. The methods used were: seasonal average ‘SA’ (historical average of each particular calendar month as forecast for the same month in the future); seasonal adjustment with last three observations ‘SAT’ (the seasonal average corrected using the mean deviation of three most recent observations from their expected seasonal values to generate forecasts for future months); modified method adjusting long-term and cyclic trend ‘MSAT’; autoregressive integrated moving average ‘ARIMA’. These methods were validated for five consecutive years from 2007 to 2012; their accuracy was assessed by determining the errors resulting from the difference between the observed and forecasted JE incidence.

The study took place in Dibrugarh, where the JE incidence is 37 cases per million population. The authors found that the JE incidence varied from season to season and year to year, but July was the month with the highest peak across all years. The most accurate forecasting method was MSAT followed by SAT and ARIMA, while SA resulted in the highest forecast error. The authors argue that adopted forecasting techniques could predict the presence of JE at primary health centre level without considering other variables.


Acute encephalitis syndrome (AES) in India: a growing concern

According to World Health Organization (WHO), a case of AES is defined as a person of any age, at any time of the year with the acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) and/or new onset of seizures (excluding simple febrile seizures).

The state of AES in India is summarised in a paper by Potharaju (2014). The author gives an overview of the epidemiology of encephalitis in India, describes the causes of high case fatality rate and suggests what can be done to avoid the huge burden caused by this disease. With three billion people living in endemic regions and 375 million people at risk of developing AES, this disease is a big challenge for the whole of India (government, medical professionals and the wider public).

“Understanding the epidemiology is important in order to identify which populations are most vulnerable, the treatment and prevention strategies that need to be developed and to identify key research priorities for the future”. (Kadambari et al., 2014)
There are many reasons for the high fatality rate such as:

- Incorrect data on the disease burden due to many cases of unreported AES and lack of cross-border reporting which leads to incorrect allocation of staff and finances.
- Environmental issues due to overcrowding, non-existent or malfunctioning drainage systems in hospital and rural areas, and the lack of biomedical waste management systems in hospitals.
- Diagnostic errors due to heavy workload during epidemics, lack of doctors in rural areas, media, political and public pressure.
- Delay in and ignorance about the importance of administering non-specific treatment (supportive, symptomatic and nursing care).
- Lack of facilities to administer timely necessary treatment and lack of training for health care professionals.
- Lack of public awareness about treatment facilities and the importance of the early treatment.
- Lack of an effective referral system.
- Inefficient administrative systems in hospitals and lack of accountability among staff.
- Lack of motivation among health care professionals.

Potharaju (2014) argues that India could fight AES using four main weapons: (1) vaccination, (2) environmental sanitation, (3) vector control, (4) health education and attention to prompt diagnosis and treatment in rural hospitals.

Two other studies report the epidemiology and clinical features of AES in different parts of India. Rathore et al. (2014) investigated AES in Eastern India looking at viral causes, case-fatality rates and level of recovery. They identified 526 patients who were admitted to tertiary hospitals in Odisha between April 2011 and July 2012. 85% of patients were from a rural areas, 61.9% were male and 72.3% were children under 15.

Blood and cerebrospinal fluid (CSF) were analysed. The results showed that 91 patients had a confirmed viral cause with 22 having been infected with two viruses. From all viral causes, herpes simplex virus (HSV) was found in 85 of cases, measles in 14, JE virus in eight, Dengue virus (DENV) in three, varicella zoster virus (VZV) in two and enteroviruses in one.

Patients presented with fever, which was associated with various other symptoms such as altered sensorium in 97.3%, convulsions in 46.7%, headache in 30.9%, vomiting in 32.6% and meningeal signs in different combinations in 26.2%.

Seven percent of all patients died. At follow-up (40 patients with viral aetiology and 40 with non-viral aetiology), from all patients with viral aetiology, 90% of them had a favourable outcome, while 10% died at home. Seventy-five percent of patients with non-viral AES had favourable outcome while 25% had poor outcomes (death or severe neurological disability).

The authors argue that, despite the study’s several limitations the results are important. They provide the first figures for viral encephalitis for this area and show HSV as the most commonly identified viral aetiology of sporadic encephalitis syndromes in India.

Runjan et al. (2014) conducted a study of AES cases in Gorakhpur between 2008 and 2011, aiming to investigate the epidemiology of AES in general and the efficacy of JE vaccination in particular. Mass JE vaccination was conducted in 2010 and the vaccine was introduced in a routine immunisation programme from 2011.

A total of 10,175 cases were included in this study and 852 cases (8.4%) were positive for JE (IgM antibodies against JE detected). The number of JE cases decreased from 1.9/100,000 in 2010 to 0.5/100,000 in 2012. The number of non-JE cases stayed the same. A higher incidence of both JE and non-JE was reported during August to October, among children under five and in males compared to females. Out of 852 JE patients, 16 had a history of JE vaccination.

The study concludes that the decline in JE incidence could be a result of vaccination. In addition, epidemiological pattern of non-JE AES (predominantly young age, high incidence during rainy season, wide geographical spread) suggests faecal-oral transmission by contaminated drinking water and the inefficiency of current control measures for the transmission of infection.


Europe

Tick-borne encephalitis: a review

The number of tick-borne encephalitis (TBE) cases is on the rise. New cases are reported in zones previously not considered endemic. Active vaccination is the most important prevention method.

The 16th Annual Meeting of the International Scientific Working Group on TBE (Kunze, 2014) published a review report after one year of having TBE included on the list of notifiable diseases in the European Union. In 2012, there were 2,605 cases reported with an overall notification rate of 0.65/100,000 population. The highest rates were reported in Lithuania, Estonia, Latvia, Slovenia and the Czech Republic. The report argued that TBE continues to be a disease neglected by travel medicine. Travel-associated cases were underestimated because of a lack of awareness and serology in the non-endemic countries. From 2011 to 2013, only four confirmed travel-related cases were reported in the UK. The review also shows that there is no reliable surveillance to identify TBE high-risk areas. The current surveillance based on the recorded human cases is not sufficient and other methods such as serological monitoring of rodents and other wildlife should be considered.

The results of a few studies were discussed during the meeting. One study emphasised the high risk of incomplete recovery of children affected by TBE with executive dysfunctions and working memory difficulties being the most commonly occurring consequence (Fowler et al., 2013). Another study reported a case series of five patients who presented with meningoencephaloradiculo myelitis with only one patient being able to return to independent life. Older age was related to more disabling and severe outcomes than younger age (Ponfick et al., 2012).

Beran et al. (2014) investigated the long-term persistence of TBE antibodies in adults and adolescents after a first booster dose with Encepur. According to the current vaccination protocol, a first booster vaccine is recommended at three years after a conventional regimen (two doses given one to three months apart and a third dose given nine to twelve months later for those who live /work in endemic area) or 12 to 18 months after a rapid regimen (three doses administered within three weeks for those who travel in endemic areas).

The study included 323 people aged 15 and over. They had a primary TBE vaccination three years before this study as part of a trial comparing different primary vaccination schedules with Encepur. They were followed up to five years after the booster. Immunogenicity and safety were assessed. Forty people out of the 323 had their booster before this study, so data about their safety was not collected.

All participants had a very good immune response to the first booster. Sixty-four percent of the participants reported at least one solicited adverse effect of which 56% were localised (pain, erythema, swelling), 30% were systemic reactions (myalgia, headache, malaise, arthralgia and nausea) and 5% were other reactions. Thirteen percent of the participants reported at least one unsolicited adverse effect. Four deaths were reported during the study period, but all were considered unrelated to the vaccination.

The study shows that a first booster vaccination following a primary vaccination resulted in high and long-lasting immunity (five years). Consequently, the period between the first and second booster vaccination could be extended. The participants of the current study are included in a second extension study for the following five years.

Dorko et al. (2014) reported a total of 102 cases of TBE in Slovakia in 2012 with two local outbreaks after the ingestion of raw milk and dairy products. The annual incidence had increased since 2009 when there were 76 cases and this rate was attributed to a 50% decrease in the active vaccination (children under 15 years of age) in 2012 compared with 2009. The disease affected all age groups apart from infants. Fifty-eight patients reported tick bites, 18 patients reported ingestion, five cases inoculation and three patients bites by other insects. The remaining 22 cases were of unknown aetiology. None of them were vaccinated. The highest incidence months were June and October. There was only one reported case of travel related TBE. The authors argue that the rise in the TBE reported cases has several reasons such as changing climate, social, political, ecological, economic and demographic factors.


Viral meningo-encephalitis in England and Wales: population trends

Kadambari et al. (2014) analysed population trends in laboratory-confirmed, viral meningo-encephalitis reports in England and Wales between 2004 and 2013. Over the 10-year period, 9,941 laboratory-confirmed cases of viral meningo-encephalitis were reported with more than six-fold increase in numbers from 2004 (0.6/100,000) to 2013 (3.9/100,000). Thirty-one percent were children younger than 15. The highest incidence was among infants younger than three months. In 2013, the incidence for this age group was 329/100,000.

Fifty-two percent of all cases were caused by enteroviruses with high incidence among infants younger than three months. Twenty-nine percent of all cases were caused by herpes simplex viruses, which were the causative agent for half of the cases in adults aged 45 or older. Thirteen percent were caused by varicella zoster, which also showed a predilection for the older age. There were only 27 cases of mumps and one of measles.

The results of the study reflect a massive improvement in the diagnosis rates, the authors arguing that this is due to an increase in the use of polymerase chain reaction (PCR) testing for viruses and better reporting by NHS hospital laboratories. The authors conclude that the enterovirus meningo-encephalitis burden is high especially among young infants. There is an increase in HSV meningo-encephalitis cases and therefore early empirical diagnosis and treatment is necessary in order to minimise the risk of death and neurological sequelae. The number of varicella zoster virus (VZV) meningo-encephalitis especially among older adults which was not reported before is increasing and needs to be assessed in the future especially in regards to introduction of routine zoster vaccination for older adults.


America (USA)

West Nile virus (WNV) encephalitis – why the surveillance and prevention programmes are important?

Staples et al. (2014) reported data on initial hospital costs and lost-productivity costs for 80 people hospitalised in Colorado during 2003 with different clinical presentations of WNV disease (acute flaccid paralysis-AFP, meningitis and encephalitis). Thirty-eight people were followed for five years and long-term medical care and lost-productivity costs were assessed. The authors extrapolated data to estimate the total costs of all reported hospitalised cases associated with WNV infections in the USA between 1999 and 2012.

The study showed that costs varied greatly between the different presentations of the WNV disease. Initial costs were higher for patients presenting with AFP (median $25,117) and encephalitis (median $20,105), while the long-term costs were highest for patients with AFP ($22,628) and meningitis ($10,556). The cost for lost productivity was lower for encephalitis cases and this was explained by the fact that encephalitis was mostly affecting older adults who were already retired at the time of the disease.

There were 37,088 reported cases of WNV disease between 1999 and 2012. Four percent died and 49% were hospitalised. The estimated cost for them was $778 million (95% confidence interval $673 million-$1.01 billion) or an average of $56 million/per year. $449 million were from lifetime lost productivity caused by WNV disease. Initial hospital costs were $252 million (95% confidence interval $158-$459 million), Long-term medical and long-term productivity costs were $54 million (95% confidence interval $25-$104 million). The authors concluded that although the study had a small sample of patients representing one year and one state in the USA, the results could be used in assessing the cost-effectiveness of various preventive and surveillance programmes aimed at WNV.

Hadler et al. (2014) described the results of an assessment of national capacity for surveillance, prevention and control of WNV and other arbovirus infections in the USA. This assessment was carried out in 2012 and the results were compared with surveillance and prevention provision from 2004 when all programmes were managed through CDC Epidemiology and Laboratory Capacity (ELC) cooperative agreements with all 50 states and six large cities/counties. The need for assessment resulted from two important facts: ELC funding for surveillance decreased by 61% in 2012 compared with 2004 and 2012 was the most severe WNV season since 2003.

The findings showed that there was a reduction in the surveillance capacity as follows: the jurisdictions assessed were less likely to have an active component of human surveillance; they were less likely to report contacting neurologists or infectious disease specialists to encourage disease reporting; mosquito surveillance capacity decreased; the number of staff working on surveillance decreased. There was also a reduction of prevention activities concerning raising awareness about WNV: less availability of information on local authorities’ websites; less formal plans for killing adult mosquitoes in the case of an outbreak and supporting larviciding in the local health departments.

“Increasing use of molecular testing has led to a 7-fold increase in laboratory confirmed, viral meningo-encephalitis reports”. (Kadambari et al., 2014)
Overall, the findings of the assessment suggest that there is a reduction in early detection capacity compared with the provision in 2004, which prompts a need for each jurisdiction to review the current surveillance systems and ensure they are efficient and in concordance with CDC guidance. This will help with early detection of WNV and other arboviruses and prompt preventive measures.


Encephalitis – a major public concern in the USA

Two studies aimed to explore the burden of encephalitis in the USA, one looking at the general population and one at American Indian and Alaska Native populations. Vora et al. (2014) retrospectively studied hospital discharge data for the general population over a 12-year period from 1998 to 2010. There were an estimated 263,352 encephalitis-associated hospitalisations during this period corresponding to an encephalitis-associated hospitalisation rate of 6.9/100,000 population. Death occurred in 5.8% of all cases.

50.3% of cases had a known aetiology with 20.3% having a viral cause (most of them were infants younger than one year with herpes virus meningoencephalitis), whereas 49.7% had an unspecified cause. Herpetic meningoencephalitis was the most common viral aetiology followed by other specified non-arthropod-borne viral encephalitis and WNV Encephalitis.

The rate of cases with known cause increased over the study period, while the rate of unspecified aetiology cases declined.

The rate for female hospitalisation was higher than for the males. There were more cases of encephalitis-associated hospitalisation for people over 65 years of age compared with younger people. The western region of the country had the lowest rate of all regions. The costs for encephalitis-associated hospitalisations for 2010 were an estimate of $2.0 billion.

Mehal et al. (2014) described encephalitis-associated hospitalisations among American Indians (AI) and Alaska Natives (AN). Over a 12-year period (1998–2010) there were 436 cases of encephalitis with a death rate of 4.1% and an average annual hospitalisation rate of 3.1/100,000 population. The findings were consistent with the findings from the above study: higher rates among infants, herpetic meningoencephalitis was the most identifiable cause and more than half of the cases (53.9%) had an unknown cause.

The authors try to explain the lower general rate of hospitalisation compared with the general USA population through the low number of encephalitis cases among adults aged 65 and over due to the lower life expectancy for AI/AN populations and possibly differences in genetic material or immune function. In addition, geographical factors (population distributed over vast areas) or a shortage in medical staff (neurologists) may influence the diagnosis and reporting of cases.


Australia

Neonatal herpes simplex virus (HSV) infection - epidemiology and trends

Jones et al. (2014) looked at data from the Australian Paediatric Surveillance Unit regarding confirmed cases of neonatal HSV disease between 1997 and 2011 aiming to ascertain the epidemiology and clinical characteristics of this disease.

Pathogenesis of encephalitis

Herpes simplex encephalitis (HSE) and toll-like receptor 3 (TLR3) deficiency

TLR3 is a toll-like receptor with a role in pathogen recognition and activation of innate immunity, whose deficiency is associated with HSE. Lim et al. (2014) aimed to establish the proportion of children diagnosed with HSE who present TLR3 deficiency and analyse their clinical features and TLR3 allelic heterogeneity.

This study included 120 children with HSE. They identified six children who carried one of five unique or extremely rare missense TLR3 alleles. One of the patients had two missense mutations. Four of the five mutant alleles (G743D+R811I, D592N, M374T and L360P) have not been reported before, while the fifth one (R867Q) was reported in public databases before. Computational analysis and in vitro study showed that three of these five mutations could have the potential to affect TLR3 function. There was high allelic heterogeneity, with three forms of autosomal dominant partial defect by negative dominance or haploinsufficiency, and two forms of autosomal recessive defect with complete or partial deficiency.

Four out of six children had at least one late relapse of HSE. The percentage of these relapses (66%) was considered high, especially when compared with the percentage of all relapses in the studied cohort (10%). The authors argued that their study demonstrated that inborn errors of central nervous system (CNS)-intrinsic TLR3 immunity might be the basis of the pathogenesis of HSE in the course of primary Herpes Simplex virus (HSV) 1 infection at least in some children. Children with HSV due to TLR3 deficiency should be followed-up because of the high risk of relapses.


Japanese encephalitis (JE): Pathogenesis still unfolding

Shimojima et al. (2014) aimed to determine the relationship between JE virus infection and three lectins: dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN), its related molecule (DC-SIGNR) and liver sinusoidal endothelial cell lectin (LSECtin). They established that DC-SIGN expression caused moderate JE virus proliferation; DC-SIGNR expression caused robust JE virus proliferation in a lymphoid cell line, Daudi cells; and LSECtin expression had minor consistent effects in all cell types used in JE virus preparation. The authors argued that this was the first report on the use of LSECtin in mosquito-borne flavivirus infection.

Japanese encephalitis (JE): Pathogenesis still unfolding

Gupta et al. (2014) analysed the functional modulation of dendritic cells (DCs) after exposure to the JE virus and the consequences on CD4+ T-lymphocyte functions. The study used human monocyte-derived DCs, which were infected with 1MOI of live virus, UV-inactivated virus, or were mock infected. The results confirmed a direct modulation of DCs and proposed an indirect modulation of helper T lymphocytes by JE virus. The authors conclude that the JE virus evades the hosts’ immune system by modulating the crosstalk between DCs and T lymphocytes via the PD-L1 axis.

Gupta et al. (2014) analysed the functional modulation of dendritic cells (DCs) after exposure to the JE virus and the consequences on CD4+ T-lymphocyte functions. The study used human monocyte-derived DCs, which were infected with 1MOI of live virus, UV-inactivated virus, or were mock infected. The results confirmed a direct modulation of DCs and proposed an indirect modulation of helper T lymphocytes by JE virus. The authors conclude that the JE virus evades the hosts’ immune system by modulating the crosstalk between DCs and T lymphocytes via the PD-L1 axis.

Thounaojam et al. (2014) assessed the involvement of miR-155 in modulating JE virus-induced neuroinflammation. The authors argue that the results of their study suggest that miR-155 modulates the neuroinflammatory response during JE virus infection via negative regulation of SHIP1 expression, and therefore modulation of miR-155 may be a therapeutic target to develop antivirals in JE.

Zhang et al. (2014) investigated the role of oxidative stress in the pathogenesis of JE viral infection and the antiviral effect of antioxidant agents (minocycline, arctigenin, fenofibrate, and curcumin) in inhibiting JE virus production. The authors certify that JE virus infection induces the generation of oxidants and exhausts the supply of antioxidants, which activates specific signalling pathways. The study suggests that antioxidants could probably be developed into antiviral agents for the treatment of JE.
Antibodies directed against neuronal surface antigens in the CNS: evidence for their pathogenicity

Van Coevorden-Hameete et al. (2014) reviewed the evidence for neuronal surface antibodies’ pathogenicity. They distinguished three types of evidence: clinical and circumstantial (symptoms similarity in response to genetic or pharmacological disruption of the antigen and immunotherapy response); in vitro evidence; and in vivo evidence. This evaluation discussed the different types and subtypes of antibodies related to the above categories of evidence. The authors concluded that strong evidence for the antibodies’ pathogenicity was still lacking for many of the antibodies subtypes.

This review also tried to provide solutions for the possible cellular and molecular mechanisms by which the antibody-antigen interaction could affect the function of the target protein by reviewing the pathophysiological mechanisms in each distinct antigen. The results show that antibodies to neuronal surface antigens are often directed at conformational epitopes located in the extracellular domain of the antigen. The conformation of the epitope can be affected by specific posttranslational modifications. In addition, the study suggests that the patients may have a heterogeneous antibody population targeting multiple epitopes from an immunogenic region resulting in multiple pathophysiological effects in the same patient. All these findings may explain the differences in clinical phenotype. Future research should focus in establishing the primordial mechanisms in each distinct antigen and tailor the therapeutic options accordingly.

The authors conclude that cytokines have no substantial effect on Balamuthia binding and cytotoxicity to HBMEC and amoebic proteolytic activity. The cytokines ability to limit amoebic number and bacterial intake may be an indicator of the virulence potential of the amoeba and a reason why both immunocompetent and immunocompromised individuals are affected.

The authors analysed each drug by establishing their mode of action and level of amoebicidal effect. Overall, from all the tested drugs, two of them – digoxin and procyclidine - had a killing effect on Naegleria fowleri and one of them (amlodipine) showed more than 80% amoebicidal effect. The authors conclude that their study is important for the future developments in treatment of Naegleria fowleri.

Baig et al. (2014) investigated the effects of clinically available drugs on Naegleria fowleri in vitro. The current treatment protocol involves the use of various drugs, including antimicrobial and experimental anti cancer drugs. Nevertheless, mortality remains high. The authors used a clinical isolate of Naegleria fowleri from the CSF of a patient who died of primary amoebic meningoencephalitis (PAM) and seven drugs: procyclidine, digoxin, amloidipine, haloperidol, apomorphine, loperamide and amiiodarone. Amoebicidal assays were performed to ascertain the lytic effects of these drugs on Naegleria fowleri.

The authors found that Balamuthia clearly manifested more than 90% binding and more than 70% cytotoxicity to HBMEC, but the cytokines did not influence these processes, apart from lipopolysaccharide (LPS) which reduced Balamuthia-mediated HBMEC cytotoxicity and also reduced amoebic numbers within 24 hours. With regard to the cytokines’ ability to influence bacterial ingestion by Balamuthia, the study shows that all cytokines tested could have an inhibitory effect on amoebic ability for bacterial uptake, with maximum inhibition by LPS. However, cytokines do not have any effect on proteolytic ability of Balamuthia.

The authors conclude that cytokines have no substantial effect on Balamuthia binding and cytotoxicity to HBMEC and amoebic proteolytic activity. The cytokines ability to limit amoebic number and bacterial intake may be an indicator of the virulence potential of the amoeba and a reason why both immunocompetent and immunocompromised individuals are affected.


Infectious encephalitis

Varicella zoster virus (VZV): immunisation, reactivation and central nervous system (CNS)

The use of VZV vaccine has been recommended in Canada since 1999 and the universal varicella vaccination began in Ontario in 2004. Science et al. (2014) undertook a study of 84 children aged between one month and 18 years who were hospitalised with neurological manifestations associated with VZV rash or a confirmed laboratory test at the Hospital for Sick Children between January 1999 and December 2012. The aim of this study was to describe the CNS complications of VZV and the impact of recent vaccination.

The rate of admission to hospital with VZV related CNS complications was 55/100,000 before full vaccine coverage and 20/100,000 after the full coverage. Four out of the 84 cases were vaccinated. Encephalitis was diagnosed in 17 children and acute disseminated encephalomyelitis (ADEM) in two children. Three children with encephalitis died. Patients with encephalitis and ADEM were reported to have the most severe outcomes out of all patients with non-stroke CNS VZV complications.

The study revealed a low vaccine coverage in this location although the vaccination was available. The authors warn neurologists that neurological symptom onset can precede the VZV exanthema and in some cases, it can appear without the exanthema.

Halling et al. (2014) present an unusual case of VZV reactivation in a young adult of 23 without a rash or radicular pain. The episode of focal VZV encephalitis was diagnosed after performing an excision and examination of a suspected brain tumour. The patient presented with headache and seizures. He had a recent history of two varicella vaccinations (a requirement for new employment as he had negative VZV antibody titre). A Magnetic Resonance Imaging (MRI) revealed a single hyperintense lesion in the left temporal lobe and the provisional diagnosis was brain tumour. The lesion was resected after an MRI guided left temporal craniotomy was performed. The pathology report showed no tumour in the resected tissue, but VZV immunostaining was positive. Wild type VZV sequences were detected. The patient started treatment with valacyclovir although his condition had improved. Further hematologic screening showed positive results for VZV. The authors note that the patient had a documented herpes zoster diagnosis at 27 months of age and his older sister had varicella when he was six months of age. Follow-up at one year showed no neurological symptoms.

The authors attempt to make sense of the case by suggesting that: the patient had varicella at six months and herpes zoster at 27 months. At 23 years of age, he developed a second reactivation of the VZV. Because he was a healthy young person, he developed a rapid immune response against VZV, which prevented further inflammation (helped as well by the neurosurgical excision of the inflammatory area in the temporal lobe).

Schäbitz et al. (2014) report the first case of VZV encephalitis, which may have triggered NMDA receptor encephalitis. The 76-year-old patient presented with hypoglossus paresis, dysphonia due to hypophonic vocal cord paresis, left velum paresis, right oculomotor paresis, saccadic eye movement, horizontal nystagmus and left hemihypesthesia. The polymerase chain reaction (PCR) of cerebral spinal fluid (CSF) was positive for VZV. NMDA receptor antibodies were present in both serum and CSF, but the specific antibody index for anti-NMDA receptor was < 1, therefore there was no evidence for intrathecal NMDA receptor antibody production. The MRI showed inflammatory lesions in the left brainstem and several enhancing cranial nerves. There were no signs of skin VZV disease.

The first diagnosis was VZV brainstem encephalitis combined with polynyuritis cranialis and the patient received ceftriaxone, acyclovir, ampicillin and steroids. After a partial recovery, the patient developed hallucinations, illusions, cognitive impairment and disturbances of orientation. The second diagnosis of anti-NMDA receptor encephalitis emerged and the patient received six sessions of immunoadsorption (the patient continues to be on oral prednisolone). The symptoms started to improve and the anti-NMDA antibodies titres declined. The authors argue that the mechanism of this new entity (VZV encephalitis-trigger of anti-NMDA receptor encephalitis) is not yet established. It is likely that other viruses, together with already established herpes simplex virus (HSV) could produce the same pathology.

Herpes simplex encephalitis (HSE): uncommon presentation and empiricism

Iyer and Ramalingam Ramakrishnan (2014) reported an unusual case of HSE who presents with epilepsia partialis continua (EPC) of the tongue. A five-year-old boy developed a two-day history of involuntary tongue movements non–responsive to lorazepam, phenytoin or levetiracetam. MRI, electroencephalography (EEG) and CSF (third day of the illness) were normal. Consequently, he developed intermittent drooling and swallowing difficulties. As a diagnosis of viral encephalitis was considered, the patient received acyclovir. A repeated CSF PCR showed HSV deoxyribonucleic acid (DNA). The child recovered without any neurological deficit. The authors emphasise that HSE has sometimes, uncommon presentations and initial investigations such as MRI, EEG and CSF may not be very helpful in diagnosing it. They argue that identifying EPC, as a possible feature of HSE may be very helpful in evaluating further and empirically treating for this diagnosis.

Gaensbauer et al. (2014) had a slightly different approach and asked if doctors are testing (using PCR) and administering acyclovir without a need in non-neonates.

The study looked at identifying patterns in HSV empirical treatment at US paediatric hospitals by using the Paediatric Health Information System (PHIS). In addition, they analysed the profile of patients tested for HSV in a single institution (Children’s Hospital, Colorado) over a six-year period between 1 January 2007 and 30 June 2013. For the first part of the study, 15 hospitals were included in the study (hospitals with complete data for the study period: 1 January 1999 and 31 December 2012). They identified 743 cases of invasive HSV infection with 52% of cases in patients 30 days and older. There was no significant change in the number of cases over time, but the use of acyclovir increased from 7.6% in 1999 to 15.6% in 2012.

At The Children’s Hospital in Colorado, 3006 HSV PCR tests were performed. Forty-six percent of children were older than 30 days. Only three children had a positive result with two cases of HSV encephalitis. Both cases of HSV encephalitis met the study criteria for typical HSV encephalitis compared with only four percent of the negative-tested patients who met the same criteria.

Recently, anti–NMDA receptor antibodies have been reported in patients with HSE. DeSena et al. (2014) present two cases (one infant and one adult) of HS confirmed encephalitis who went on to develop confirmed anti-NMDA receptor antibody Encephalitis. The first case is a male child whose history showed an eye infection (HSV unspecified type confirmed) when he was born that was successfully treated with acyclovir. The current illness developed with worsening mental status and persistent twitchy movements for several months and seizure one day before admission to hospital. PCR findings confirmed HSV 2 in his CSF sample. He was administered IV acyclovir, but his condition continued to deteriorate (non-verbal, longer periods of non-responsiveness, orofacial dyskinesia). After more than 21 days of acyclovir, his second Lumbar Puncture (LP) was negative for HSV and a third LP (a week later) was positive for anti–NMDA receptor antibodies and negative for HSV.

The authors mention that the first two LPs have not been analysed for anti-NMDA receptor antibodies, as his presentation was typical for HSE. The treatment protocol included IV immunoglobulin (with no
improvement) followed by plasma exchange. His condition started to improve. The second case is a young man in his twenties who presented to hospital with headache, malaise, one week of confusion and fever. PCR was positive for HSV and he was treated with acyclovir for 21 days. Anti-NMDA receptor antibodies have not been checked. After an initial improvement, his condition worsened with speech and behavioural changes. His second LP was negative for HSV, but a serum anti-NMDA receptor antibody was positive. A third CSF sample confirmed anti-NMDA receptor encephalitis and the patient was administered plasma exchange, which resulted in a speech improvement, followed by IV immunoglobulin and then cyclophosphamide. The patient made further recovery.

The authors argue that this association of HSE and anti-NMDA receptor antibody encephalitis may be more common than previously thought. Future research should focus on the question as to whether HS infection triggers anti-NMDA receptor encephalitis. If so then clinicians should consider both diagnoses, especially when encountering atypical cases of viral Encephalitis.

Wickström et al. (2014) describe a case of an 11-month-old girl who first presented with HSE, but went on to develop NMDA receptor antibodies at relapse. Clinical manifestation at initial presentation and EEG suggested HSE and prompted acyclovir treatment. PCR of the CSF was positive for HSV 1. As she was included in an encephalitis study, she was sampled according to the study protocol including anti-NMDA receptor antibodies in serum and CSF, which were negative at that time. Repeated EEG showed persisting delta activity over the left temporal lobe. Another PCR of CSF performed on day 12 was negative for HSV 1, but the LP showed persisting monocytic pleocytosis. Her condition deteriorated (fever, behavioural changes, dystonia and choreoathetosis). A third PCR was negative for HSV 1, but IgG for HSV 1 were found in CSF. Immunotherapy was commenced and she started to improve. An MRI after one month showed changes typical for HSV. Antibody testing was negative on day 12, but on day 21, she had antibodies both in serum and CSF and on day 36 only in serum. After three years, at follow-up, she displayed delay in cognitive and speech development, hyperactivity and intractable epilepsy.

The authors argue that this represents a case of viral infection as trigger of anti-NMDA receptor encephalitis. Relapses or persistent symptoms in HSE could be an immune-mediated response. Testing for anti-NMDA receptor antibodies may influence the treatment protocol.


Cryptococcal meningoencephalitis: how to improve the outcome

Recently, anti-NMDA receptor antibodies have been reported in patients with HSE.

Skripuletz et al. (2014) investigated the use of CSF parameters as possible prognostic markers in cryptococcal meningoencephalitis. Twenty-one patients (16 males) diagnosed with cryptococcal meningoencephalitis between 1999 and 2013 were analysed retrospectively.

Seventeen patients had a HIV infection, seven being diagnosed before the presentation of meningoencephalitis. Fifteen patients improved after the antifungal therapy and six patients died.

Several advanced CSF markers such as CSF cell counts, CSF-serum albumin quotient (QAlb) and intrathecal synthesis of the immunoglobulins IgG, IgA and IgM were evaluated prior and during the therapy. The authors found that parameters of CSF prior to antifungal therapy are not different between different types of outcomes, so they are not useful as markers of the outcome. During antifungal therapy, CSF cell counts decreased for all patients irrespective of outcome, so it cannot be a useful tool to assess the efficacy of the treatment.

Opposed to this result, QAlb was found to be related to the outcomes during the treatment, in the way that a decrease of QAlb was consistent with a good outcome and conversely a raise of QAlb value was associated with death. In addition, the study established that intrathecal synthesis of IgM was present in five patients prior to therapy. Three had a good outcome and two died. A new intrathecal synthesis of IgM was observed in two patients with good outcome, while in two patients with fatal outcome it disappeared.

The authors concluded that among the various CSF parameters, the course of QAlb could be a marker of antifungal treatment efficacy.

Autoimmune encephalitis

“As these disorders continue to reach mainstream neurology and even psychiatry, more cell-surface-directed antibodies will be discovered, and their possible relevance to other more common disease presentations should become more clearly defined”. (Irani et al., 2014)

Autoantibodies and their associated syndromes: an expanding area of neurology. Clinical features, diagnostic protocol, treatment, outcomes and dilemmas

Leypoldt and Wandinger (2014) reviewed the current understanding and advances related to paraneoplastic neurological syndromes and associated autoantibodies. Paraneoplastic neurological syndromes are defined as being immune-mediated syndromes affecting different levels of nervous system (central, peripheral and autonomic) associated with cancer. The study classifies these syndromes into classical (high probability of an underlying cancer) and non-classical (low probability of an underlying cancer) syndromes.

The authors argued that the diagnosis protocol for paraneoplastic syndromes should include the following steps: proving the immune-mediated nature and excluding other diseases such as meningeal disease, metastasis, toxic or metabolic causes by using magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF); testing for antibodies and interpreting their results in association with clinical manifestations; and tumour screening. There are two types of antibodies described: paraneoplastic or onconeural (high specificity of underlying cancer) and neuronal cell-surface (with or without underlying cancer).

Because of the difficulty associated with finding the tumour in some cases, the advice given is to investigate the presence of tumour based on the clinical picture and antibody existence. When searching for the tumour, the authors describe three possible clinical scenarios: classical or non-classical syndrome with antibody present (onconeural or neural cell-surface); classical syndrome with no antibody found; non-classical syndrome and no antibody found. In the first two scenarios, the probability of a tumour is very high; therefore, the work-up to find a tumour should follow recent European guidelines (Titulaer et al., 2011). In the last scenario, the probability of a tumour is low; the advice given is to repeat tumour screening and seek an alternative diagnosis.

Furthermore, the study summarises the treatment, which consists of removal of the tumour and immunosuppressive therapy. Although most of the paraneoplastic syndromes have a poor response to treatment, the ones with neuronal cell-surface antibodies have a good outcome.

Irani et al. (2014) reviewed the current knowledge regarding cell-surface central nervous antibodies (NGSAbs) and assessed the antibody testing methodology and the immunosuppressive therapy used for these antibody-associated syndromes.

The study describes the neuronal or glial surface directed antibodies target as being recently discovered antibodies that target the extracellular domains of cell-surface antigens, usually integral membrane proteins. They are potential pathogenic, modulating the function of the target protein and are associated with clinical syndromes which often respond well to immunotherapy. The most commonly identified autoantibodies are anti-NMDA receptor antibody and VGKC complex antibody which includes leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein 2 (CASPR2) and contactin-2.

The authors summarise the clinical manifestations that should raise the suspicion of antibody presence. Patients who present with cognitive impairment, psychiatric manifestations, epilepsy, movement disorder and/or demyelinating disease should be tested for one of the syndromes associated with NGSAbs. The paper describes each one of these clinical manifestations in regard to onset, clinical features, and MRI/CSF findings and pairs them with the associated antibodies. The authors note that one common characteristics of all these presentations is the rapid onset, often within days to a few weeks.

The binding of serum or CSF immunoglobulin G to live cells that express the native antigen on their surface is considered the most accurate method to detect the antibodies. The downfall is that these live cell assays are time-consuming and costly. Commercial kits with fixed brain tissue and fixed antigen-expressing cells are commonly used but their limitations need to be taken into account. Furthermore, the authors argue that low-levels of autoantibodies may be present outside the NGSAbs associated syndromes representing secondary immunisation after neuronal damage and either have no effect or could alter the course of the illness. Thus, the benefits of an early aggressive treatment need to be weighed against the adverse effect of an unnecessary immunosuppressant treatment.

The review of current treatment approaches highlights that the treatment should aim to control the symptoms, reduce the levels of existing antibodies, suppress the future antibody production, remove the tumour...
and withdraw potential toxic medication. The current treatment protocol includes various combinations of corticosteroids, immunoglobulin (IG) and plasma exchange (PLEX). For some treatments, there is evidence of their benefit (corticosteroids), for others the evidence is not always there, even though they are very popular due to rapid onset of action and accessibility. The authors state that early treatment gives better chances of recovery. Nevertheless, decisions about treatment should be based not only on symptomatology, but also on the cause of these symptoms. For example, worsening in a patient with NGSAbs-associated encephalitis could be a result of prior antibody action or ongoing central nervous system (CNS) disease activity.

Varley et al. (2014) discussed dilemmas surrounding autoantibodies and suggest future directions in research. The first controversy appears in the field of antibody levels and assay methodologies, namely the fact that some studies report higher levels of antibodies in serum than in CSF at the onset of the illness, while other studies report the presence of antibodies in CSF but not serum. This difference in reporting is explained by the differences in assay methodologies. The authors suggest that in order to overcome this dilemma, both CSF and serum should be sent to laboratories if possible. Leypoldt and Wandinger (2014) who suggest that testing both CSF and serum may prevent false-negative and false-positive results have expressed the same opinion.

The presence of NGSAbs in other neurological illnesses and the healthy population is the object of another discussion. Varley et al. (2014) suggest that clinical syndrome classification is essential for defining disease-relevant autoantibodies with pathogenic potential.

Recent reports of the pathogenic potential of IgA and IgM, despite the fact that antibodies of the IgG class associate with all of the neuronal surface-directed antibody-mediated disease, make the subject of another dilemma in the Varley et al. (2014) study. Finally, there is a controversy about what triggers antibody production, specifically concerning tumours, infection and neurodegeneration. The authors suggest that multiple factors could trigger antibody production and their pathogenicity capacity could be influenced by the concentration, access to the brain/CSF, the duration of antibody production and inherent individual patient thresholds.

Varley et al. (2014) conclude their paper by highlighting the need for more research regarding pathophysiology, management of diseases, best treatment, prognosis, assay methodology, low-level antibodies in patients with non-classical syndromes and discovering new phenotypes. They call for an effective collaboration between clinical work and research as the best way to further advance the knowledge of these devastating syndromes and ultimately improve the patient outcomes.


Testing for autoantibodies: serum versus CSF

Gresa-Arribas et al. (2014) conducted a study to assess the sensitivity and specificity of serum and CSF antibody testing in patients with anti-NMDA receptor antibody encephalitis. They also aimed to determine the relation between titre, relapses, outcome and epitope repertoire.

Samples from 250 patients with anti-NMDA receptor antibodies encephalitis and 100 control participants were examined using different techniques (brain immunohistochemistry, CBA with live cells and CBA with fixed cells). All patients with anti-NMDA receptor encephalitis had antibodies in their CSF, but only 85.6% had antibodies in their serum. None of the 100 control patients had antibodies in their CSF or serum.

For the second part of the study, they examined, at three or more timepoints, samples from 45 patients who presented with different outcomes: relapses (10 patients), good outcomes (25 patients) and poor outcomes (10 patients) and investigated the relationship between the outcomes and antibody titres in serum and CSF. Thirty-two out of 45 patients had available both serum and CSF samples, only CSF was available for eight patients and only serum for five. Higher antibody titres in both CSF and serum were found in patients with poor outcome or teratoma. Conversely, lower titres were reported in patients with good outcomes or no tumour. Relapses were more associated with titre change in CSF than in serum. By the last follow-up
most patients had a decrease of serum and CSF titres regardless of outcome, but most patients still had antibodies in serum and CSF after recovery.

The findings suggest that the sensitivity of NMDA receptor antibody testing is higher in CSF that in serum. In addition the study ascertained that all patients’ antibodies targeted a main epitope region at GluN1 (amino acid 369) irrespective of the outcome. The authors conclude by emphasising the importance of the antibody testing and in particular the CSF antibody testing for diagnosis and assessing the course and outcomes of the disease.


Anti-NMDA receptor encephalitis: the impact of early treatment on outcomes

Byrne et al. (2014) tried to ascertain if early treatment improves the outcomes in anti-NMDA receptor encephalitis. They analysed the outcomes of five children (two males and three females) with ages between four and eight, who were given immunotherapy within three to six days from the onset of neurological or psychiatric symptoms at two hospitals in Dublin between 2007 and 2012. The immunotherapy was initiated before the results of antibody testing as the clinical picture (neuropsychiatric manifestations, movement disorder, seizures, dysautonomic features) suggested an autoimmune encephalitis. They were followed for 24 months (median length). Four children had a full recovery with a modified Rankin Scale (mRS) score of 0. One child was left with seizures and cognitive and behavioural problems. The authors argue that the results of this study, compared with other studies with a longer median time from symptom onset to immunotherapy initiation, and poor outcomes, suggest that treating empirically for NMDA receptor encephalitis within a short period of presentation can influence the outcomes.

Early diagnosis and early treatment had an influence on the outcomes in Wright et al. (2014) study on paediatric NMDA receptor antibody-mediated neurological disease, when 78% of early-diagnosed patients made a full recovery compared to only 13% of patients who were diagnosed later. Furthermore, this study also showed that PLEX during the initial treatment led to a quicker recovery.


DeSena et al. (2014) described different presentations of some already known features of anti-NMDA receptor encephalitis: ‘light switch’ mental status changes and irritable insomnia. Their study includes four children who presented with these symptoms, identified from 12 children with anti-NMDA receptor encephalitis observed over a two-year period at one hospital. ‘Light switch’ mental status changes involve very rapid on-off state between responsiveness and non-responsiveness not linked to seizure activity. Irritable insomnia involves insomnia associated with extreme irritability which appears very early in the patient’s course. The authors argue that

“Antibody titres in CSF and serum were higher in patients with poor outcome or teratoma than in patients with good outcome or no tumour. The titre change in CSF was more closely related with relapses than was that in serum”. (Gresa-Arribas et al., 2014)
the presence of these two symptoms could suggest an anti-NMDA receptor encephalitis diagnosis, especially when they appear in the early course of the disease.

A study of 31 children by Wright et al. (2014) with anti-NMDA receptor encephalitis reported a typical course of this disease in 24 children and a partial phenotype without encephalopathy in seven children including predominantly psychiatric in four and movement disorder in three. The authors conclude that anti-NMDA receptor encephalitis can present with a single feature predominating.

Cobo-Calvo et al. (2014) reported a first case of optic neuritis in an adult with anti-NMDA receptor encephalitis. No tumor was found. Anti-NMDA receptor antibodies were detected in CSF. In addition, antibodies to myelin oligodendrocyte glycoprotein (MOG-Ab) were identified in serum and CSF. After immunotherapy with IV Immunoglobulins (IVIG), the patient made a significant recovery, being free of visual and neurological symptoms two months after the initiation of treatment.


“Taken together, careful use of treatment regimes and supportive therapies are essential to maximise patient care in this difficult-to-treat condition”. (Wright et al., 2014)

This review conclude that the incidence of this condition is higher than previously estimated and it is likely to increase with more awareness and improvements in healthcare especially in countries that have not reported many cases.

Armanegue et al. (2014) compared patients with teratoma-associated encephalitis with anti-NMDA receptor antibodies with those with teratoma-associated encephalitis without anti-NMDA receptor antibodies. From a cohort of 249 patients with teratoma-associated encephalitis, 211 were positive for anti-NMDA receptor antibody, whilst 38 were negative.

There were no differences between the two groups regarding age and gender. The main features that distinguished the second group from the first group were: common brainstem cerebellar dysfunction at initial presentation; lack of psychosis and behavioural abnormalities at initial presentation; uncommon development of dyskinesia in the first month; common tendency to develop brainstem-cerebellar symptoms, sometimes with opsoclonus in the first month.

Within the negative-antibodies group, the authors focus on the patients with brainstem cerebellar dysfunction (22 patients). Twenty of them were females with ovarian teratoma and two were male with testicular teratoma. Their clinical manifestations include various symptoms: ataxia in 86% of the patients, opsoclonus-myoclonus in 45%, dysarthria in 36%, decreased level of consciousness in 32%, diplopia/ophthalmoparesis in 18% and seizures in 18%. Neurological symptoms developed before finding the tumour in 18 patients and after diagnosing the tumour in the other four. The patients with opsoclonus were all young women and had a good response to treatment.
The treatment consisted of immunotherapy with tumour resection in 13/19 cases followed-up, only immunotherapy in two and only tumour resection in two. Two patients did not receive any treatment. The follow-up of these patients showed that 14 patients had a full recovery, three had a partial recovery and two had no improvement (one of them was not treated). Relapses happened in three cases: two with complete recovery (two and seven years after disease onset) and one with partial recovery.

The authors conclude by suggesting that any teenager/young adult especially if female, who presents with subacute brainstem-cerebellar symptoms or opsoclonus-myoclonus suspected to be immune-mediated, should be investigated for a teratoma. If teratoma is identified, then the treatment should include tumour resection and immunotherapy.

The patients with low levels of antibodies included: four definite autoimmune (one with a paraneoplastic cerebellar syndrome, one with acquired neuromyotonia and two with Morvan’s syndrome); 13 possibly autoimmune (three had tumours at the time of testing); and 15 unlikely or undetermined. Many of these patients had a history of symptoms over many months before the antibody testing took place. The two patients with Morvan’s syndrome had immunotherapies, but only one had a substantial improvement.

The patients with high levels of antibodies included: 11 definite autoimmune (10 with limbic encephalitis and one with a tumour); nine possible autoimmune; and three unlikely autoimmune. The median time from the emergence of first symptoms to antibody testing was 30 months. Eight patients with encephalitis were tested for LGI1 antibody and contactin antibodies and six of them were positive. All patients with encephalitis received immunotherapies with a good response.

Overall, the authors suggest that high level of antibodies should prompt a diagnosis of VGKC complex related disease especially when tested within a few months of onset. On the other hand, a low level of antibodies should be treated with care: they may be secondary to other disease pathologies or just present in healthy individuals where they may rise to detectable levels under certain circumstances. Patients with definite or possible autoimmune syndrome need to be screened for cancer. The two patients with VGKC complex antibodies who were negative for LGI1 or CASPR2 antibodies suggest that there may be other antibody targets within the VGKC complex.


Leucine-rich, glioma-inactivated 1 (LGI1) antibody associated encephalopathy: novel neurocardiac prodrome, association with cerebellar degeneration and natural course without immunotherapy

Naasan et al. (2014) reported three cases of LGI1 antibody associated encephalopathy who presented with episodic bradycardia two months before the onset of the encephalopathy. Two men, aged 53 and 54, and one woman, aged 64 were identified among 14 patients with LGI1 antibody encephalitis. None of the patients had cardiac problems prior to this illness. Their clinical manifestations included amnesia, seizures and serum hyponatremia, but no faciobrachial dystonic seizures, tumours or contactin-associated protein-like 2 Abs. At the time of the episodic bradycardia, the antibody was not tested, but at the time of encephalitis, all three cases had serum VGKC-complex Abs and LGI1-Abs. None of the cases experienced any other symptomatic bradyarythmias in the follow-up (18 months to seven years).
The authors argued that episodic bradycardia that resulted in a pacemaker implantation in all three cases in this study, was a distinctive prodrome of VGKCc/LGI1-Ab encephalitis. They associate this feature with the temporal lobe and insular involvement, which regulates cardiac autonomic function and suggest an epileptic cause secondary to focal encephalitis of these brain regions. The authors conclude by emphasising the importance of recognising this feature in association with other limbic manifestations (amnesia or seizures) as prodrome of LGI1 antibody encephalitis, and starting immunotherapy early to prevent progression to encephalopathy.

Steriade et al. (2014) reported a first case of LGI1 autoantibodies associated with cerebellar degeneration. The patient was an 18-year-old male who had a two months history of headache, progressive clumsiness and difficulty walking. At presentation, he had gaze-evoked nystagmus, dysarthria, bilateral appendicular ataxia and truncal ataxia. MRI showed multiple T2-hyperintense lesions isolated to cerebellar hemisphere. Microbiological studies on CSF were negative. No tumour was found despite various investigations performed. In the following days, his condition deteriorated, becoming apathetic with disinhibited behaviour and visual hallucinations. Antibodies were tested and a biopsy of the cerebellum was performed. The results of biopsy showed relatively widespread mixed lymphocytic infiltrates and Purkinje neuronal loss with patchy severe loss of granular neurones. The serum was positive for LGI1 antibodies. Immunotherapy was started and the patient began to improve. At nine months follow-up, he had no clinical evidence of ataxia or cognitive dysfunction.

At follow-up, both patients had a relatively good outcome with no seizures or psychiatric symptoms and only mild/moderate cognitive impairment (memory and verbal fluency). MRI findings in one case showed early hippocampal sclerosis and global atrophy.

The authors argued that this report suggests the possibility of an LGI1 encephalitis with a monophasic and benign course, which may improve spontaneously without immunotherapy. Nevertheless, the authors suggest that early immunotherapy should be initiated in order to achieve a substantial and fast recovery.


**GlyR antibodies: an overview**

Carvajal-Gonzalez et al. (2014) described clinical presentation, treatment and outcomes of 45 patients positive for GlyR antibody selected from 779 sera samples. The authors also analysed retrospectively serum/CSF samples of a series of patients with stiff person syndrome, progressive encephalomyelitis with rigidity and myoclonus (PERM) or related disorders from Heidelberg, Germany, looking for the presence of GlyR antibody.

First part of the study included 24 males and 21 females with median age of 50. GlyR antibody levels varied significantly between individuals in serum and CSF. In 11-paired samples, serum levels were higher or equal to CSF levels and intrathecal synthesis of GlyR antibodies was reported. The antibody test was performed at an interval varying from one to 96 months since the emergence of symptoms although most of the patients (71%) had a rapid onset.
One patient had a lymphoma and three had thymomas identified during the neurological illness. The most common symptoms at presentation were spasms (painful) and stiffness and rigidity of neck, trunk or limb muscles. Excessive startle, eye movement disorder, difficulty opening the mouth, and swallowing and speech problems were also frequently reported. Twenty-nine percent of the patients had cognitive difficulties and 13% had seizures. Clinical features at the peak of the illness were reported for 30 patients and included spasms, stiffness, rigidity, eye movement disturbance, facial/bulbar motor disturbance. Cognitive disturbances, encephalopathy, seizures, hyperekplexia and muscle weakness were also more frequent.

There were various investigations undertaken, some of them being uninformative. MRI was abnormal in 10 out of 36 patients and spinal cord MRI abnormal in five out of 23 patients. Electroencephalogram (EEG) showed irregularities in 15 out of 21 and CSF in 18 out of 30 patients. Serum GAD antibodies were found in nine patients, but only four had a high titre (more than 1000U/ml). VGKC-complex antibodies high titre was reported in one patient and low titre (less than 200pM) in two. Three patients had NMDA receptor antibodies and six had thyroid antibodies.

The patients were diagnosed as follows: 33 with progressive encephalomyelitis with rigidity and myoclonus (PERM), two with stiff person syndrome, five with LE or epileptic encephalopathy, two with brainstem features mainly, two with demyelinating optic neuropathies and one had an unclear diagnosis.

Four patients died, but most of them had improved following immunotherapy treatment. The patients were followed up for two to seven years and the outcomes were very good for most of the patients with the mRS scores ranging from a median of five to a maximum severity to one. Relapses happened in five cases.

Looking retrospectively at the patient cohort (47 cases) from Germany, the authors discovered that 30 patients were positive for GAD antibodies. GlyR antibodies were found in six sera and four CSF samples.

The authors argue that this study shows that GlyR antibodies are usually present independently from GAD antibodies (although they can co-exist) and are associated with a good response to immunotherapy. They could be an important factor in diagnosing patients who present with ocular motor and other brainstem dysfunction, hyperekplexia, stiffness, rigidity, myoclonus and spasms. Although the antibodies are usually detected in sera, CSF samples can also be useful for comparison and in cases where serum levels are low. Long-term follow up is needed, as relapses are possible.

Kim et al. (2014) report five cases of GABA_β_ encephalitis: report of five cases in an Asian population

Kim et al. (2014) report five cases of GABA_β_ antibody encephalitis advertising their clinical features, treatment and outcomes. The patients were identified among 631 patients in Korea suspected of having autoimmune encephalitis of unknown origin, who were screened for autoantibodies against neuronal surface proteins.

Three patients were female and two were male. Their median age was 63. Their clinical manifestations included memory difficulties, behavioural disturbance and seizures. MRI showed abnormalities of the median temporal lobes in two patients, while EEG revealed abnormalities in all five patients. Brain FDG-PET showed abnormalities in three patients with two temporal hypermetabolism and one cortical hypometabolism (first report of this kind in the authors’ opinion).

Four patients had small-cell lung cancer; in three of them, the diagnosis of cancer was made after the one of encephalitis. Two of the patients had anti-Hu antibodies, but the authors argue that their symptoms were related to GABA_β_ antibody encephalitis rather than anti-Hu syndrome. This finding prompts them to suggest that in patients with lung cancer, LE and anti-Hu antibodies, it may be necessary to investigate the presence of other antibodies such as GABA_β_.

Their treatment included both immunotherapy and/or chemoradiotherapy. Two patients (one without cancer) have recovered fully and three partially after receiving immunotherapy and cancer treatment. The authors argue that this type of encephalitis appears to be associated with a rather partial response to treatment.


GABA receptor antibodies: new epileptic disorder

Petit-Pedrol et al. (2014) report a new epileptic disorder, which manifests with refractory seizures, status epilepticus and antibodies to unknown neuropil antigens, and aim to establish the clinical features, the identity of the antigen and the effects of patients’ antibodies on neuronal cultures. They obtained samples (serum and CSF) from 140 patients who had met the inclusion criteria: the presence of antibodies to unknown neuropil antigens, encephalitis and seizures or status epilepticus (SE).

They analysed the samples using immunoprecipitation, mass spectrometry, cell-based assay and analysis of antibody effects in cultured rat hippocampal neurons with confocal microscopy. They also compared the samples with those of 75 healthy individuals and 416 control patients with various neurological diseases.

The authors identified a novel target antigen of autoimmune encephalitis: GABA<sub>A</sub> receptor. In this study, six patients had high titres of serum of GABA<sub>A</sub> receptor antibodies and antibodies detectable in CSF. Twelve people from the control group had low titres of GABA<sub>A</sub> receptor antibodies associated with a wider range of symptoms, but no antibodies detectable in CSF.

The six patients included one female and five males with ages ranging from three to 63 years. All six patients experienced rapidly progressive encephalopathy and their refractory seizures were preceded or associated with changes in behaviour or cognition. They all had abnormal MRI and the seizures were reflected in the EEG in all cases. Three patients had thyroid peroxidase antibodies, one had GAD65 antibodies and two had GABA<sub>B</sub> receptor antibodies. One patient had a history of Hodgkin’s lymphoma and one had idiopathic thrombocytopenic purpura. Four of the six patients were placed in a pharmacologically induced coma. At follow-up, one child who received levetiracetam but not immunotherapy had a significant recovery although remained on antiepileptic treatment three years after onset; two of the patients who received immunotherapy and antiepileptic drugs died of sepsis during status epilepticus; three other patients who also received immunotherapy and antiepileptic drugs made a complete or partial recovery.

Among the people with low titres of antibodies, six had encephalitis with seizures, four had stiff-person syndrome and two had opsoclonus-myoclonus. Five patients also had GAD65 antibodies and one had NMDA receptor antibodies. At follow-up (nine patients), seven patients received immunotherapy with full recovery in one, partial recovery in five and one patient died. Two patients received a symptomatic treatment for stiff-person syndrome.

The results of the study suggest that high titres of serum and CSF GABA<sub>A</sub> receptor antibodies are associated with a severe form of encephalitis, which manifests with seizures, refractory status epilepticus, or both. It is difficult to recognise this disease due to rapid onset of seizures and coexistence of autoimmune disorder, but once diagnosed, it can be treatable. The authors also found that patients’ GABA<sub>A</sub> receptor antibodies determine a selective decrease of synaptic GABA<sub>A</sub> receptors.

Autoantibodies: a potential role in demyelinating syndromes?

Autoantibodies in demyelinating diseases are the subject of investigation in a few studies trying to establish their presence and role in the demyelinating syndromes, the question being: are they directly involved in the demyelinating process or are they a secondary response to demyelination?

From a cohort of children (65) with a first episode of acquired demyelinating syndrome, Hacohen et al. (2014) identified 15 children under the age of 16, whose sera was positive for at least one antibody. Three children had AQ4 antibodies, two with neuromyelitis optica (NMO) and one with isolated optic neuritis (ON). Seven children had myelin oligodendrocyte glycoprotein (MOG) antibodies, two with acute disseminated encephalomyelitis (ADEM), two with ON, one with transverse myelitis (TM) and two with clinically isolated syndrome (CIS). Two children had anti-NMDA receptor antibodies, one with ADEM and one with ON. Three children had VGKC complex antibodies, one with ADEM, one with ON and one with CIS. One patient had GlyR antibodies with TM.

The authors notice the low prevalence of each individual antibody and the absence of differences based on demyelinating phenotype between the antibody-positive and the antibody-negative children in this study, which questions the clinical relevance of the antibodies in demyelinating syndromes.

Titulaer et al. (2014) identified 23 patients with anti-NMDA receptor encephalitis and additional symptoms or episodes suggesting a demyelinating disorder in a large cohort of patients with anti-NMDA receptor encephalitis. The patients’ diagnosis of
Anti-NMDA receptor encephalitis was based on clinical manifestations and antibody testing (sera and/or CSF). The demyelination episodes were diagnosed based on clinical and/or MRI findings. These patients presented with extensive or multifocal T2-FLAIR abnormalities. Twelve patients developed the demyelinating episode as a different entity to the anti-NMDA receptor encephalitis, which preceded or followed. Remaining patients (11) presented with both disorders in the same time indicating the co-existence of two simultaneously active immune mechanisms. Seven of these patients had NMDA receptor antibodies and AQP4 or MOG antibodies.

The authors argue that it is important to recognise the overlap of these syndromes as the treatment protocol is different for each. The patients are more difficult to treat and the outcomes are less favourable for patients presenting with both syndromes than for patients with anti-NMDA receptor encephalitis alone. In conclusion, the authors emphasise that there are patients with anti-NMDA receptor encephalitis who may develop a demyelinating episode (concurrent or independent). However, there are also patients with demyelinating disorders with unusual symptoms who may have anti-NMDA receptor antibodies.

New autoimmune syndrome: autoimmune adult onset focal epilepsy and encephalitis

Ramanathan et al. (2014) propose a new category within the autoimmune syndromes called autoimmune adult onset focal epilepsy and encephalitis.

This proposal is based on the analysis of six adult patients (five female and one male) who presented with recurrent seizures with focal frontotemporal onset, refractory to anticonvulsants at four tertiary hospitals in Australia between 2008 and 2011. All patients had a history of a viral prodrome, but no fever. An explosive onset of multiple daily seizures of frontotemporal semiology was characteristic. None of them had risk factors for epilepsy. Focal imaging abnormalities and an associated encephalopathy were present. CSF analysis showed variable lymphocytosis and/or positive oligoclonal bands.

The treatment consisted in pulsed steroids in five patients and only anticonvulsants in one. Two patients were given immunosuppression with remarkable recovery. Three patients with only pulsed steroids and the one with only anticonvulsants did not achieve seizure cessation and were left with cognitive impairment (two of them died of sudden unexpected death in epilepsy).

Subsequently, their serum samples have been tested for neuronal cell-surfaces antibodies and three of them were positive for anti-NMDA receptor encephalitis and LGI 1.

The authors argue that recognising this syndrome could improve the chances of an adequate treatment. Testing for all known cell-surfaces antigens and tumour screening with a whole body positron emission tomography–computed tomography (PET-CT) scan and a pelvic MRI (if anti NMDA receptor encephalitis is suspected) are recommended. Initiation of immunotherapy may improve their long-term outcomes.

Rasmussen encephalitis (RE): pathogenesis and treatment

Varadkar et al. (2014) summarised the current knowledge regarding RE and review both the main advances and difficulties related to this condition.

The authors describe the three stages of RE as being: prodromal stage with non-specific, low seizure frequency and mild hemiplegia; acute stage with frequent seizures, often epilepsy partialis continua, progressive hemiparesis, hemianopia, cognitive deterioration and aphasia (if dominant hemisphere affected); residual stage with permanent and stable neurological deficits and continuing seizures. They argue that diagnosis of RE should be based on association of various features regarding the clinical presentation, EEG, MRI and/or histopathology.

This review also summarises the main advances in RE pathogenesis and diagnosis. Firstly, RE may be driven by a T-cell response to one or more antigenic epitopes with additional contribution by autoantibodies. Secondly, initial damage to the brain may be mediated by T-cells and microglia. Thirdly, MRI findings of the progression of the inflammatory process could be a reliable biomarker of the illness.
The difficulties associated with RE are related to making an early diagnosis, understanding the underlying process, causes and triggers and the decision of when to have hemispherotomy.

The paper concludes by suggesting that future studies should focus on the more recent clinical features, the disease course in relation to the use of immunosuppressive therapy, pathobiology, the role of CNC autoantibodies in the pathogenesis of RE and primordially the main pathology.

Amrom et al. (2014) describe four patients with RE and a comorbid autoimmune disease. In three cases, RE started in childhood with a rapid-progressive course, while in the fourth case RE had a late onset and slow progressive course. The patients were also diagnosed with Hashimoto thyroiditis, ulcerative colitis, Crohn’s disease and lupus systemic erythematosus. The time between the RE diagnosis and the emergence of the autoimmune disease was between 6 to 19 years. In an attempt to explain RE pathogenesis, the authors wonder if this association could suggest an immunogenic predisposition that could interact with some environmental (yet to be discovered) factors or simply represent an unfortunate coincidence. They call for initiation of an international RE registry in order to facilitate further studies on pathogenesis.

Granata et al. (2014) presented long-term outcomes after disconnective surgery in 16 patients with RE. The patients’ median age at the time of the surgery was 23.5 years and at the time of the illness was 5.8 years. Median time from seizure onset to surgery was 3.8 years. The patients were followed for three to 20 years.

After surgery, seizure cessation occurred in all but three patients (three of the patients became seizure-free after a secondary operation to complete disconnection). Hemiparesis remained the same after surgery. One patient who had a mild motor deficit before the surgery developed hemiparesis after the surgery. Postural control improved in all patients. Patients who were bedridden/wheelchair bound before the surgery, were able to walk. All patients presented with hemianopia. Improvement in cognitive skills was associated with the disease duration: patients with shorter time from disease onset to surgery had better cognitive outcomes. Language improved in three patients with early RE onset and operated by the age of six. At the latest follow-up, 10 patients were having no antiepileptic drugs (AED), while the other six were having one or two drugs.

The authors argue that the results of this study favour an early hemispherotomy in young patients with RE in order to achieve a control of seizures and good motor and cognitive improvement.


Diagnosis, treatment and outcomes

“Despite broad cognitive dysfunction in the acute phase, patients with VGKC-LE often make a substantial recovery with immunotherapy but may be left with permanent anterograde amnesia”. (Butler et al., 2014)

Limbitx encephalitis (LE) associated with voltage-gated potassium channel (VGKC) complex antibody: cognitive impairments and predictors of outcome

Butler et al. (2014) assessed cognitive outcomes in 19 patients with VGKC-LE using comprehensive neuropsychological tests that examined premorbid intelligence, memory, executive function processing speed, language and perceptual organisation.

First assessment took place before or immediately after the immunotherapy initiation, following 16 to 377 days after disease onset. It showed significant impairment on the index of verbal memory (story immediate recall, delayed recall, word list learning immediate and delayed recall) and executive function (letter fluency, category fluency and Trails B). Performance on the digit-symbol coding task was low, with one patient categorised as impaired. Language and perceptual organisation performances were not significantly affected.

Second assessment took place at a median interval of 254 days after the first and showed a persistent group level impairment on the index of verbal memory and specific impairments regarding delayed recall of the story and word list. Comparing the two assessments, there were substantial improvements on the index scores for verbal memory and executive function revealed in the second assessment. The authors acknowledged that, unfortunately, there was no evidence that this improvement was a result of autoimmune treatment, as the study did not include patients who had no treatment.

In addition, the study tried to identify markers of a good outcome and found that antibody titre at presentation were important in predicting the verbal memory index value at the second assessment. The authors concluded that VGKC complex antibody associated encephalitis results in a more focal cognitive impairment than other types of autoimmune encephalitis with cognitive impairment being restricted to amnesia. Antibody titre is an important marker of the disease outcome.


Acute encephalitis: overview of causes, management and predictors of outcomes at discharge

Singh et al. (2014) analysed the causes, clinical manifestations, treatment and outcomes in a large cohort of patients (198) with acute encephalitis who presented at the Mayo Clinic Rochester over a 13-year period (January 2000 to December 2012). The patients were older than 16 years. Acute encephalitis was defined as presentation with altered mental status lasting more than 24 hours and at least three of the following: fever 38°C or higher within 72 hours before or after presentation, generalised or partial seizures, new onset of focal neurological findings, cerebrospinal fluid (CSF) white blood count ≥5/mm³, abnormality of brain parenchyma on neuroimaging and electroencephalography (EEG) abnormality. According to aetiology, the patients were included in one of the three groups: viral encephalitis, autoimmune encephalitis and unknown/other origins.

The median duration of symptoms before hospitalisation was five days. 29.8% of patients had no cause discovered, while 22.2% had an autoimmune cause and 48% had a viral cause. From all viral causes, herpes simplex (HS) virus was identified in 38.9% of patients, varicella-zoster virus in 23.2%, West Nile in 18.9%, Epstein-Barr in 6.3%, HIV in 3.2% and other viruses in 9.5%. The most common antibody identified was anti-NMDA receptor antibody (24.4%) followed by VGKC complex antibody (24.4%).

38.4% of patients were admitted to the Intensive Care Unit (ICU) and 25.4% required ventilation. On Magnetic Resonance Imaging (MRI) examination, 52.3% had FLAIR/T2 abnormalities, 26.4% had unilateral involvement, 43.4% had bilateral involvement, 19% had diffusion abnormalities and 42.7% had cortical involvement.

Most patients with viral encephalitis (72.6%) received antiviral drugs. Autoimmune cases were treated with steroids (90.9%) for a median time of five days, and also IV immunoglobulin (IVIG) (20.5%) and plasma exchange (PLEX) (18.2%). Unknown aetiology encephalitis patients were treated with steroids (27.1%), antivirals (15.3%), IVIG and PLEX (small number).

Overall, the outcomes were good with 2/3 of patients having minor or no disability at one year. PLEX was an indicator of good outcome. There were no major differences regarding outcomes in patients with different aetiologies. At discharge, approximately half of each category had a
good outcome and around 9% of patients from each category died. At one-year follow-up, approximately 60% of patients had a good outcome and an additional 7.8% (viral encephalitis), 12.2% (autoimmune encephalitis) and 5.4% (unknown cause) of patients died.

The following factors were associated with poor outcome in all three categories: age 65 years and over, immunocompromised state, coma, mechanical ventilation and acute thrombocytopenia. An additional marker of poor outcome in viral encephalitis was CSF polymorphonuclear cell count (p= 0.0027). Imaging findings and development of seizures were not correlated with the outcomes.

Michaeli et al. (2014) conducted a review of 46 children with acute encephalitis between 2000 and 2010 at Meyer Children’s Hospital (Haifa-Isreal) aiming to evaluate the long-term motor and neurocognitive outcomes by using neurologic examinations and neurocognitive assessments.

Encephalitis was defined as at least one symptom/sign of cerebral dysfunction (altered mental status, motor or sensory deficits or seizures) and at least one of the following signs of inflammation: fever >38°C, white blood cell count >15 x10³ cells/µL, C-reactive protein level >10mg/L and CSF cell count >6 cells/µL. Meningoencephalitis, demyelinating diseases and any underlying neurologic, systemic or metabolic diseases were excluded. Half of patients (23) had a cause identified. The most common pathogens were enterovirus in nine and HSV in six patients.

Fifty percent of children were reported to have persisting symptoms at follow-up: behavioural difficulties in 52%, recurrent headache in 22%, tic disorder in 22%, sleeping problems in 19%, epilepsy in 11% (mostly intractable seizures) and 9% residual motor deficits (spastic hemiparesis). All the motor difficulties occurred in children with HSV encephalitis. Half of children were diagnosed with attention-deficit/hyperactivity disorder (ADHD) and 20% had learning disorders. One patient died.

Overall, good recovery was achieved in 37% of patients, moderate outcomes in 35% and the remaining 28% had poor outcomes. The poor long-term outcomes were associated with cases with known aetiology. The patients with HSV had the highest rate of neurological sequelae.

Poor long-term outcomes were associated with long hospital stay, abnormal neurologic examination results at discharge, abnormal results on neuroimaging studies and confirmed pathogen. Long-term outcomes were not correlated with outcomes at discharge from hospital. From 27 children who were considered to have a good outcome at discharge, only 13 had a good long-term outcome. Of the 13 children with severe sequelae at discharge, six had improved and three had fully recovered.

The authors conclude that encephalitis in children could lead to substantial long-term consequences, especially reduced neurocognitive performance, behavioural problems, ADHD and learning disabilities. Neuropsychological testing is recommended for all those who had encephalitis in childhood, as the outcomes at discharge are not predictive of long-term outcomes.


Neonatal HSV Infection: the role of the MRI in assessing the course of the disease

Bajaj et al. (2014) conducted a retrospective review of 29 infants with neonatal encephalitis looking at their clinical, neuroimaging and outcomes features.

The infants were divided into three groups: group 1 (skin, eye, mouth with positive surface cultures), group 2 (disseminated, with positive blood herpes simplex virus polymerase chain reaction (HSV PCR) and/or viral culture and visceral involvement with or without central nervous system (CNS) involvement) and group 3 (encephalitis with CNS signs alone and positive CSF HSV PCR). Twenty-eight percent of patients from group 2 and 3 died; all of them had disseminated disease.

MRI with diffusion-weighted imaging (DWI), at the onset of the illness, showed more widespread areas of diffusion restriction than detected on T2-weighted imaging. Specific for this group of infants was a diffuse predilection, rather than involvement of a specific temporal lobe. In addition, there was frequent involvement of the thalamus, corticospinal tract, and posterior limb of the internal capsule. MRI abnormalities were associated with poor outcomes in eight infants. The authors argue that the finding of this study showed that MRI, including DWI, could be used as a prognostic factor in neonatal HSV infection.


Rituximab: efficacy and safety

Irani et al. (2014) looked into the efficacy and safety of rituximab for patients with VGKC complex/leucine-rich, glioma-inactivated 1 (LG11) antibody associated encephalopathy. Rituximab is a monoclonal antibody against the protein CD20 used in treating various illnesses. This study included five adult patients, whose serologic and long-term clinical outcomes were assessed. The age of the patients ranged from 48 to 73 years. Median time from first symptoms to first rituximab administration was 414 days. All patients had VGKC complex and LG11 antibodies and presented with the antibody associated encephalopathy.

Rituximab had a significant effect in one patient on both modified Rankin Scale (mRS) score and fachiobrachial dystonic seizures (FBDS) frequency two years into the illness. This patient suffered a rituximab-responsive clinical relapse. In another patient, rituximab possibly improved verbal learning and memory one year into the illness. A clear effect was not visible in the other three patients. The authors tried to explain this result through possible late administration, imprecise assessment of the
clinical outcomes or the effects of individual drugs (due to the observations being retrospective). The authors conclude that rituximab may be useful in some patients with leucine-rich, glioma-inactivated 1 (LGI1) antibody associated encephalopathy even if it is administered late in the illness. Rituximab appears to be well tolerated by the older adult population of this study.

Dale et al. (2014) retrospectively reviewed the use, utility and safety of rituximab in children with autoimmune and inflammatory disorders of the CNS. The study included 144 children and adolescents. The median age was eight years and 103 were females. Rituximab was administered after an interval of 0.05 and 9.5 years since the initiation of the illness. 134 patients were followed for longer than six months.

Most patients had received other immunotherapies before rituximab: corticosteroids in 138, IVIG in 104, cyclophosphamide in 43 and PLEX in 21. The most commonly used regimen of rituximab administration was 375mg/m2 weekly for most commonly used regimen of rituximab cyclophosphamide in 43 and PLEX in 21. The corticosteroids in 138, IVIG in 104, most patients had received other long-term medications (except for corticosteroids). The risk of having infusion AE or infection AE was not correlated with age, except a possible increase in hypogammaglobulinemia in young children under five.

At the time of rituximab administration, only 17.4% of patients had a mRS score of 0–2, while 73.9% had the same score at outcome. Improvement was correlated with the length of time from the disease onset to rituximab initiation, being greater in patients treated early in the disease course compared with those treated later.

According to treating clinicians’ opinions, rituximab had a definite benefit in 45 patients, probable benefit in 49, possible benefit in 31, no benefit/unclear in 17 and two patients got worse. At follow-up, the mortality was 2% and neurological sequelae were present in 70% of patients, suggesting that this series of patients had severe and often refractory disease.

The authors conclude by acknowledging not only the benefit of rituximab of improving neurological outcomes but also the significant risk of infectious complications and thus the suggestion for using rituximab in disorders with substantial morbidity and mortality.

Infusion adverse effects (AE) (adverse effects during the infusion: allergic, hypersensitive or other unwanted effects) were reported in 18 patients. Three patients had a grade 4 reaction (anaphylaxis) which resolved without complications. One patient’s treatment was suspended after the fourth-incomplete dose due to progressively worse hypersensitivity reactions. There were no differences between patients who received antihistamine prophylaxis, and those who did not.

Eleven patients were reported as having infection side effects in the follow-up, two of whom died and with two children developing a life-threatening or disabling adverse effect at an interval between three and 38 days after rituximab initiation. The other seven patients developed a grade 3 infectious adverse effect (requiring hospitalisation or IV antibiotics). There was no difference regarding the infectious adverse effects between children with antibiotic prophylaxis and those without. Instead, infection adverse effects were present in 3.4% of children who received cyclophosphamide compare with 7.6% of children who did not. The risk of having infusion AE or infection AE was not correlated with age, except a possible increase in hypogammaglobulinemia in young children under five.

At the time of rituximab administration, only 17.4% of patients had a mRS score of 0–2, while 73.9% had the same score at outcome. Improvement was correlated with the length of time from the disease onset to rituximab initiation, being greater in patients treated early in the disease course compared with those treated later.

According to treating clinicians’ opinions, rituximab had a definite benefit in 45 patients, probable benefit in 49, possible benefit in 31, no benefit/unclear in 17 and two patients got worse. At follow-up, the mortality was 2% and neurological sequelae were present in 70% of patients, suggesting that this series of patients had severe and often refractory disease.

The authors conclude by acknowledging not only the benefit of rituximab of improving neurological outcomes but also the significant risk of infectious complications and thus the suggestion for using rituximab in disorders with substantial morbidity and mortality.


Seizures: antiepileptic drugs and ketogenic diet

Pandey et al. (2014) aimed to assess the efficacy and safety of antiepileptic drugs used for the primary and secondary prevention of seizures in viral encephalitis by reviewing randomised and quasi-randomised controlled trials in which patients were assigned to a treatment or control group (placebo or no drug). They searched various databases, but unfortunately, they did not find any high quality clinical trials that fitted the study’s criteria.

The authors argue that this study proves the lack of evidence to support the use of antiepileptic drugs for the primary or secondary prevention of seizures in viral encephalitis, highlighting the acute need for future studies to explore this subject.

Thakur et al. (2014) investigated the use of ketogenic diet (KD) for adults in super-refractory status epilepticus (SE) focusing on demographic features, clinical manifestations, diagnosis, EEG data, antiepileptic treatment (AEDs) and timing and duration of KD.

Ten patients were identified. The median age was 33 years and four patients were male. Seven patients had encephalitis of whom three had antibody-positive paraneoplastic encephalitis. Two of these patients had received IVIG and/or PLEX before commencing the KD. Six patients had a history of seizures and five were taking AEDs before admission (median number of drugs was 7). Nine patients had a Glasgow Coma Score (GCS) score lower than eight when KD started. Nine patients were placed on a 4:1 KD ratio (fat to carbohydrates and protein grams) and one on 3:1 ratio. The median length of time on the KD was 17.5 days.

Nine patients achieved ketosis and had resolution of SE within a median time of three days. Seven patients had clinical and/or electrographic seizure resolution within one week and nine within one month. On discharge, six patients had a GCS of ≥12. Minor complications of KD such as transient acidosis and hypertriglyceridermia were reported in three patients. Two patients died due to causes unrelated to KD. This study proved that KD led to resolution of the SE in Intensive Care Unit patients.


Recovery and rehabilitation after encephalitis

“In Rasmussen encephalitis, transition may be particularly complex for those with adolescent onset”. (Thiele et al., 2014)

Transition to adult care for patients with Rasmussen encephalitis (RE)

Thiele et al. (2014) analysed the difficulties associated with transition to adult care for children with RE. The authors differentiated between childhood-onset RE and adolescence-onset RE. This review was based on the authors’ observations of 21 patients older than 14 years, selected among the 27 patients at the National Neurological Institute, Milan, Italy.

Childhood-onset RE means that at the time of adolescence the child may have had the surgery, be seizure and drug free, and have a hemiparesis resulting from the operation that is stable. The overall quality of life could be good. It is suggested that the focus should be on dealing with the impact of motor disability directly on the individual, but also indirectly through the perception of peers. Low self-confidence, social withdrawal, self-marginalisation, anxiety disorders, aggressive behaviour against parents and doctors who decided for the hemispherotomy are frequent symptoms. The coping strategies should be directed towards alleviating these symptoms.

Adolescent-onset RE poses more challenges due to the insidious course of the illness, the difficulty in making therapeutic decisions and the fact that the person affected has a greater awareness of the disease. The impact of seizures and motor difficulties should be considered within the wider context of adolescence including increased independence and the emergence of emotional relationships. Loneliness and anxiety for what the future brings add at the burden of the disease. Efficient communication among all involved and involvement of the young person and multidisciplinary expertise in treatment decisions are essential. In this cohort of patients, transition to adult care did not happen due to the inexperience of adult services and the family’s reluctance to move to adult care. In a few cases where transition did happen, it failed, with a return to paediatric care.

In the authors view, the ideal transition process should distinguish between the outcomes. The patients with good outcome could stay under the original case manager and be referred to adult care only in the case of new issues. The patients with a poor outcome should be gradually transferred to specialised adult services who have the expertise to deal with various disability associated difficulties.

Books featuring experiences of encephalitis

The Thief in the Night by Catherine O’Toole Scott

“Catherine’s story is important. It is her narrative, and is important for that alone. However, it is important for a number of other reasons. It is an honest and candid account of her outcomes following encephalitis and the impact it has had both upon her and her family. It will help others to feel better understood and less alone. It also demonstrates that the outcomes of Encephalitis, in those likely to be considered mildly or moderately affected in a clinical sense, can in fact find life on a day to day basis extremely difficult and at times hopeless. The labels we rely upon, and to some extent impose upon survivors of this devastating condition can, at times, serve only to confuse and perhaps dismiss their experiences.

We have called encephalitis ‘A Thief’ for many years at The Encephalitis Society. It robs people of abilities we take for granted every day: thinking, memory, concentration, inhibitions. For some families it robs them of their loved one and even in those families where the person affected survives, it can rob them of the person they once knew.

It is my pleasure to know Catherine both as a member of our Society and as one of our dedicated and highly valued regional volunteers. The ability to write is a gift and this book is a gift to the many survivors (and their family members and friends) who will read it and will feel someone does understand, and they are not so alone”.

Reviewed by Dr. Ava Easton, Chief Executive, The Encephalitis Society

A Single Swim by Kristina Circelli

“Only five days after that innocent swim in the water, Courtney began experiencing one of the first symptoms of the amoebic meningitis. Eight days later, she passed away after being diagnosed with a disease that, until the diagnosis had been made, no one in her family even knew was a threat”.

On August 13, 2011, sixteen-year-old Courtney Nash passed away after contracting Naegleria fowleri, a brain-eating amoeba that lurks in warm waters. This is her story.

A Single Swim follows Courtney’s life and death, while taking a closer look into an amoebic infection very few people ever hear about - until it’s too late. Tracing as far back as 1960s, Naegleria fowleri and the resulting infection of this parasite have taken more than a dozen lives, with a fatality rate of nearly 100%.

Through an examination of Courtney’s case along with stories of other victims across the United States, A Single Swim offers a glimpse into our waters’ rare silent killer. From ecology to symptoms, hospital care to awareness, find out what can happen ... after a single swim.


The book is available from Amazon (www.amazon.co.uk) or Kristina Circelli’s website (www.kristinacircelli.com)
The Encephalitis Society

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

- Supporting adults, children, families and carers of those affected by encephalitis
- Producing evidence-based, quality information about encephalitis accredited by the NHS England Information Standard
- Raising awareness about encephalitis, its consequences and the need for improved services
- Conducting research and working in partnership with other researchers. This includes appointing leading medical and health care professionals to our Professional Advisory Panel, awarding grants for research into encephalitis and holding annual competitions for medical and neuropsychology students.

The Encephalitis Society Neuropsychology Service

The Encephalitis Society Neuropsychology Service (ESNS) is a UK-centric service that aims to help adults (aged 16 and above) who have been ill with encephalitis, and their carers gain access to neuropsychological support by:

- Providing help with accessing neuropsychological support through local statutory services and/or
- Offering a range of neuropsychological assessment and therapy services more directly such as cognitive assessment, cognitive rehabilitation, therapy, behaviour management, capacity assessment and consultation.

For further information about this service or if you would like to make a referral, please visit our website at www.encephalitis.info/support/neuropsychology-service

Professional Memberships

Professional Membership with the Society is open to all professionals worldwide. Membership is free and it takes only two minutes to complete online.

Benefits of Professional Memberships:

Free place at our Annual Professional Seminar

Held once a year, the Seminar presents current research advances and debates salient issues in the field of encephalitis. Professionals with various interests from epidemiology and virology, through clinical casework to rehabilitation and the social impact of the illness are taking part.

Membership Pack

Containing information about the Society and how the Society can work with professionals, especially in relation to research and supporting people affected by this condition.

Free subscription to our Newsletter

The Newsletter is produced four times a year and covers a range of topics including the Society’s members’ fundraising efforts, personal stories of encephalitis, latest news about the Society’s work, articles on neurological issues, book reviews and useful resources for both lay and professional people.

Research articles and books

The Society’s website www.encephalitis.info holds a database of research articles and books related to encephalitis and every year we produce a summary of the most important publications and research studies.

Support with collecting necessary data for research studies

The Society has an extensive database of over 5,000 people affected by encephalitis. We work in partnership with researchers putting them in touch with people who meet the criteria for their studies as well as collaborating on research projects.

For more information about Professional Membership or if you would like to become a Member please visit our website www.encephalitis.info or contact us at admin@encephalitis.info or +44 (0)1653 692583.
Support when you need it most

The Encephalitis Society works hard every day to develop understanding and support for patients across the country.

It's for this very reason that Moore Blatch has proudly supported the Encephalitis Society for over 15 years, offering legal services and advice to its members and associates.

- Clinical negligence
- Court of protection
- Deputyship
- Education law
- NHS continuing health care
- Powers of attorney
- Wills

If you or your loved ones need any form of legal advice or support, simply call Tim Spring, Head of Clinical Negligence on 023 8071 8138.

MOORE BLATCH solicitors

www.mooreblatch.com

Richmond • London • Southampton • Lymington