The Encephalitis Society

The Encephalitis Society is an international charity and the only organisation of our kind in the world dedicated to supporting adults and children affected by Encephalitis. The Society provides support and information to all people affected by Encephalitis across the globe, and to a variety of professionals and organisations from health, social care and education. The Society works in conjunction with academic and clinical partners to promote and conduct high quality research into Encephalitis and its consequences, and promote high standards for patient diagnosis, management and care.

Professional Membership

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 Membership:

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, how the Society can work with professionals especially in relation to research and how it provides support to 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, great 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 of 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 01653 692583.

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Disclaimer
This Review has for the most part precis’d and reprinted sections of the original papers in order to retain accuracy and avoid editorial bias. 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.
Foreword

Prior to this Century, research into Encephalitis has lagged behind that of other diseases. Indeed, a few years ago there might not have been sufficient research and associated papers with which to create a review such as this one. Encephalitis was seen as a relatively rare condition, about which little could be done. Moreover there are conditions with lower incidences such as Bacterial Meningitis and Motor Neurone Disease, who receive much higher clinical and public profiles. Along with developments in our understanding of the condition, and the identification of new and emerging causes, The Encephalitis Society has striven to change this and is now more proactive than it ever has been in the field of research.

We promote, collaborate, conduct and fund research into Encephalitis. We appoint leading medical and health care professionals to the Society’s Professional Advisory Panel; conducting research and working in partnership with them and other researchers and research institutions. The Society also awards grants for research into Encephalitis and holds an annual essay prize and travel bursary for interested professionals.

This Research Review is the first of an annual archive we will continue to create, selecting key papers and books that have featured throughout the year on Encephalitis. The Review will be available both in hard copy and electronically along with the more detailed archive of papers we host on our website looking at everything from epidemiology to outcome.

As this review demonstrates there remains a dearth of research and focus on rehabilitation and social consequences, which unlike the medical and psychological fields, have remained of secondary importance. We can only hope that as this review builds we see an increase of papers in these areas.

We hope you enjoy having a resource which draws attention to key papers throughout the year. Unfortunately we couldn’t include all the research papers on Encephalitis.

We would be happy to receive your feedback and to include any other papers as part of our online archive. Just drop us a line…

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
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Encephalitis is a complex and severe illness often associated with neurological dysfunction and death, but understanding its epidemiology is still a challenge.

Granerod et al embarked on a journey of finding out if the incidence of Encephalitis in England is higher than previously estimated (1.5 cases per 100,000/per year in England for viral encephalitis in Davison et al, 2003). The study used two sources of data: routinely collected hospitalisation data between 2005 and 2009 and the largest population-based prospective cohort of encephalitis patients to date in England (part of a Public Health England (PHE) study). The authors linked the two data sources and performed capture–recapture analyses to estimate the number of encephalitis cases in England attributable to infectious and noninfectious causes.

Comparing the two sources used, the number of incident encephalitis admissions recorded in Hospital Episode Statistics (HES) was considerably higher than the number of cases included in the PHE study, even after restricting HES diagnoses to the primary diagnostic field. Conversely, nearly half of the PHE cases were not captured in HES. The poor agreement between these two data sources could have several possible reasons: testing in the PHE study went far beyond routine clinical practice, which highlighted the extent to which encephalitis can be underdiagnosed; patients with unusual signs and symptoms, such as those with N-methyl-D-aspartate receptor-antibody encephalitis, which typically causes psychiatric symptoms, might not have been classified as encephalitis case-patients in HES. Unmatched HES cases likely include true encephalitis cases not reported to the PHE study team and non-encephalitis cases misdiagnosed as encephalitis.

Incidence was estimated from unlinked hospitalisation data as 4.32 cases/100,000 population/year. Capture–recapture models gave a best estimate of encephalitis incidence of 5.23 cases/100,000/year, although the models’ indicated incidence could be as high as 8.86 cases/100,000 per year. A higher incidence (adjusted for year, age, and region) of encephalitis was observed among male patients. The study also highlights the higher incidence of encephalitis among patients <1 and >65 years of age. With a mean length of hospital stay of 34 days, an incidence of 5.23 cases/100,000/year (“best estimate”) equates to 90,852 bed-days of hospital occupancy. On the basis of a bed-day cost of £261, the cost to the National Health Service would be >£23 million per year. The actual cost is likely to be higher as patients often require intensive care, costly investigations, and in-patient rehabilitation. Additional costs include long-term care and loss of productivity among many working-age survivors.

This higher incidence has clinical, research, and public health implications. A diagnosis of encephalitis should be considered for patients with compatible symptoms, especially given the increased recognition of immune-mediated encephalitides for which treatment is available and effective if instigated early. Early recognition is important to help reduce the substantial economic and societal costs of encephalitis suggested by this study. Stand-alone HES data are used extensively for public health research; the study highlights the extent to which HES-only data might over- or under-ascertain cases of complex syndromes and the advantages of linking these data to other sources to improve incidence estimates. Encephalitis incidence in this study was higher than that of other neurologic conditions, such as meningococcal meningitis and motor neuron disease. This study highlights the importance of accurate diagnosis and coding for complex syndromes with multiple etiologies to obtain accurate estimates of incidence and to further explore the epidemiology and outcomes of this devastating neurological illness.

Bernard et al compare the results from a 2007 prospective study which describe the French epidemiology of infectious encephalitis with the French national hospital discharge 2007 database (PMSI). The aim of the study is to evaluate the reliability of PMSI as a tool to assess the trends of encephalitis in France for frequent, rare, and unknown aetiologies and their epidemiological characteristics, and for the detection of emergence or outbreaks. In France, infectious encephalitis is not mandatorily notifiable, but a few infections,
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Responsible for encephalitis are: listeriosis, tuberculosis, measles, and rabies.

Two hundred and fifty-three patients were enrolled in the prospective study. According to the case definition, patients were age ≥28 days, lived in mainland France, were hospitalised in public hospitals, were negative for HIV, and had remained in hospital for ≥5 days for surviving patients. The main strength of the prospective study was a single case definition and the investigation of a wide range of pathogens, but this type of study is too expensive to be conducted on a continuous basis for epidemiological surveillance.

A national hospital discharge database has the advantage of being continuous, exhaustive, and available at low cost. However, its accuracy is limited. In 2007, a total of 1,694 non-HIV patients presenting with acute encephalitis were recorded in the PMSI, in mainland France, making an estimated incidence of encephalitis of 2.6 cases/100,000 inhabitants.

No significant difference for global mean and median age was observed between the PMSI and the study population. Causative agents were identified in 52% of cases in the study, and 38% in PMSI (P<0.001). The most frequent aetiological agents associated with encephalitis (HSV and VZV) were the same in both databases, nevertheless the proportion of cases of encephalitis due to M. tuberculosis and L. monocytogenes were significantly lower in the PMSI than in the prospective study. There was also less similarity for rare pathogens such as arboviruses. The case-fatality ratios were similar, except for Listeria (46% in the study vs. 16%).

Conclusion: The PMSI could be a useful tool at a limited cost for following the epidemiological trends of encephalitis of most frequent origins (HSV, VZV), as well as the characteristics of the patients and the relative frequency of these agents in encephalitis of all causes. However, the PMSI lacks accuracy and sensitivity for rare pathogens without a specific encephalitis code like M. tuberculosis or L. monocytogenes. The PMSI should be used with caution for arboviruses with important implications for health authorities. The delay before database availability makes it useless for the detection of outbreaks. Introducing specific codes for encephalitis due to rare infectious agents, or agents rarely responsible for encephalitis might improve both the epidemiological accuracy of the PMSI, and its accuracy as an economic tool if the severity of encephalitis, according to the aetiological agent, is taken into account.

Kulkarni et al describe the epidemiology and disease burden associated with encephalitis in Canada and explores possible associations with arboviral causes. Despite the occurrence of numerous arboviruses in Canada that cause neuroinvasive disease, West Nile virus is the only arbovirus under national surveillance. This raises the potential for underdiagnosis of other arboviral infections, which may be contributing to an unrecognised burden of encephalitis in Canada. This study reviewed national hospitalisation discharge diagnoses over a 15-year period and assessed the association of demographic and geographical factors with different aetiological categories of encephalitis.

During the 15-year period from 1994 to 2008 there were a total of 24,028 encephalitis-associated hospitalisations in Canada, with an annual average rate of 5.4/100,000 population. Unexplained aetiologies accounted for the largest proportion of encephalitis-associated hospitalisations in Canada, comprising 49.8% (2.57/100,000 population). Viral aetiologies accounted for 31.9% of all hospitalisations (1.64/100,000 population). Of the viral encephalitides, the primary causative agents were zoster, accounting for 4,257 (17.7%) hospitalisations, and herpes virus accounting for 2,245 (9.3%) hospitalisations. Arboviruses, including tick- and mosquito-borne pathogens, were responsible for 733 (3.1%) of total encephalitis hospitalisations.

In general, rates of hospitalisation were significantly higher in summer (June–August) and autumn (September–November) than in spring (March–May), except for Quebec where differences in seasonal rates of hospitalisation were not significant. At the national level, women had a marginally higher risk of encephalitis-associated hospitalisation than men, however, this trend differed according to aetiological category, with the higher incidence of zoster encephalitis in women largely accounting for the difference.

West Nile virus was the leading causative agent of arboviral encephalitis nationally, accounting for 86.9% of the 733 arboviral encephalitis hospitalisations. Of the remaining arboviral hospitalisations, 10.1% were diagnosed as ‘other specified mosquito-borne viral encephalitis’ and a small number of cases (3%) as other mosquito-borne aetiologies, such as Japanese encephalitis, Western equine encephalitis, St Louis encephalitis and Venezuelan equine encephalitis, or ‘other tick-borne viral encephalitis.

At the national level, arboviral hospitalisations were significantly associated with age and sex. Men were at higher risk of arboviral infection than women, and adults aged ≥65 years were at greater risk than younger age groups, consistent with the expected trends for West Nile virus.

The authors argue that a better understanding of the aetiology of encephalitis in Canada is needed to enhance diagnostic capacity and define appropriate public health action. Inclusion of encephalitis as a nationally notifiable condition could help to standardise case definitions and diagnostic testing procedures. Syndromic surveillance for encephalitis could form a component of an arbovirus surveillance system through education of physicians in risk areas.


Bernard S, Mailles A, Stahl JP; Steering Committee and Investigators Group. Epidemiology of infectious encephalitis, differences between a prospective study and hospital discharge data. Epidemiol Infect. 2013 Nov; 141(11)


Is Japanese Encephalitis (JE) under control in Asia and Western Pacific? A report published in Morbidity and Mortality Weekly Report summarises the status of JE surveillance and immunisation programs in 2012 in Asia and the Western Pacific. Japanese encephalitis (JE) virus is a leading cause of encephalitis in Asia, causing an estimated 67,900 JE cases annually. To control JE, the World Health Organization (WHO) recommends that JE vaccine be incorporated into immunisation programs in all areas.

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where JE is a public health problem. Twenty-four WHO member states have areas of JE virus transmission risk. Risk areas are determined based on any evidence of JE virus transmission from human surveillance, mosquito or animal studies, or ecologic similarity to areas with proven transmission.

In 2012, eighteen (75%) of the 24 countries with areas of JE virus transmission risk conducted at least some JE surveillance, and eleven (46%) had a JE immunisation programme. Seven (29%) programs were implemented nationally or in all areas considered to have JE risk, and four (17%) were subnational and did not include all risk areas. Ten (42%) countries included JE vaccine in the routine vaccination schedule, and one country conducted annual vaccination campaigns. Three types of JE vaccine are used in national immunization programs. Despite the availability of paediatric clinical trial data and extensive post-licensure experience for several vaccines, until recently, no JE vaccine manufacturer had made a submission to WHO for prequalification of a JE vaccine, a process that reviews a vaccine’s quality, safety, efficacy, and programmatic suitability.

In 2011, 19 (79%) of the 24 countries reported a total of 10,426 JE cases. The 8,247 reported cases from India and 1,625 from China represented 95% of all cases; no other country reported >150 cases. Among five countries reporting zero cases, three had no surveillance programme.

Recent progress in surveillance and immunisation has been spurred by an increase in funding, availability of improved vaccines, and growing international attention to the disease. Further progress toward JE control requires increased awareness of disease burden at the national and regional levels, and international support for surveillance and vaccine introduction in countries with limited resources.


Is involvement of the Thalamus or Basal Ganglia (T/BG) in patients with Encephalitis an important etiological clue?
Beattie et al reviewed the etiologies and neuroimaging of patients with encephalitis who present an involvement of the thalamus or basal ganglia (T/BG) included in the California Encephalitis Project (CEP) in order to improve diagnostic testing of T/BG patients.

T/BG neuroimaging abnormalities were reported in 6% of 3296 CEP cases. By completion of T/BG review (with additional follow-up) an etiology was found in 76%: 37% infectious, 16% postinfectious, and 23% noninfectious. Viral pathogens were most commonly identified, followed by bacteria, prions, fungi, and protozoa. The most frequently identified infectious agents were respiratory viruses, accounting for 31%, predominantly in children. Other infections more common in the T/BG group included Creutzfeldt-Jakob disease (the most common infectious etiology in adults), arbovirus, and Mycobacterium tuberculosis. HSV-1 was rarely associated with T/BG lesions in the CEP cohort, only two individuals with herpes encephalitis and T BG neuroimaging abnormalities were identified and both were children. Infectious and postinfectious cases had higher median cerebrospinal fluid white blood cell count than noninfectious etiologies.

Conclusions. T/BG involvement in patients with suspected encephalitis was associated with specific etiologies. In addition to agents with established predilection for the T/BG such as M. tuberculosis and arboviruses, a surprisingly high number of cases were associated with respiratory viruses, especially in children. Neuroimaging abnormalities in such patients can aid clinicians in narrowing the etiological scope and in guiding testing.

“Respiratory viruses should be considered as potential etiologic agents in patients with T/BG encephalitis, especially among the pediatric population.” (Beattie et al)
Armangue et al conducted a study involving five prospectively diagnosed patients with relapsing post-HSV Encephalitis and thirty-four patients with definite or probable HSE. Serum and CSF samples of all five patients were available from the time of symptom relapse, and in four from the time of HSE. None of the patients had NMDAR antibodies during HSE, but all had high antibody titers, both in CSF and in serum, 3 to 5 weeks later by the time of relapsing symptoms. All five patients had IgG and IgM NMDAR antibodies, and two had mild IgA antibody reactivity. Antibodies to the other indicated antigens were not identified. Four of the five patients were children and all developed choreoathetosis. The adult patient developed abnormal behaviour and personality change.

Twelve of 34 patients whose archived serum/CSF samples were retrospectively studied, had antibodies against neuronal cell-surface antigens, two of them against NMDAR, nine against unknown antigens, and one against both. In the two patients with only NMDAR antibodies, the serum/CSF samples had been obtained after the first week of HSE (74 and 61 days). In the third patient, the NMDAR antibodies were identified on day 42. For all three patients, the antibody isotype was IgG (two also had IgM) against the GluN1 subunit of the receptor. The antibodies of the other nine patients (four detected during the first week of HSE and five afterward) were directed against cell surface antigens of unknown identity.

The conclusion of this study is that relapsing post-HSE is often anti-NMDAR encephalitis, that this immune response underlies different complications which may occur in (eg, choreoathetosis in children, abnormal behaviour in adults), contiguity or a few weeks after HSE, and that HSE is a trigger of cell-surface/synaptic autoimmunity.

The Armangue et al study of paediatric anti-NMDAR Encephalitis in a series of 20 patients included a two year old girl who developed anti-NMDAR encephalitis four weeks after HSE. Her symptoms were very much similar to the choreoathetosis and orofacial dyskinesias of some patients during the first month of onset of HSE. Based on the biphasic course of symptoms of this patient, the CSF findings (negative PCR HSV, positive NMDAR antibodies), no additional changes in the brain MRI, and lack of response to acyclovir but improvement after rituximab and cyclophosphamide, the study suggests that some patients with post-HSE choreoathetosis may in fact have anti-NMDAR encephalitis.

The Hacohen et al study of paediatric autoimmune encephalopathies presents two NMDAR antibody positive patients who were also positive for HSV PCR in the CSF. These two children continued to regress despite acyclovir treatment but improved following immunotherapy. The authors argue that it is possible that some patients have existing antibodies that gain access to the brain when there is a viral infection, or alternatively a para-infectious antibody-mediated process may begin during an acute infective process.

Leypoldt et al have also shown in their study that synthesis of NMDAR antibodies began after HSV Encephalitis, and that relapsing symptoms were due to steroid-responsive anti-NMDAR encephalitis. They report a 24 year old man who was diagnosed with HSV Encephalitis (HSV PCR in CSF was positive, Immunoglobulin G (IgG) NMDAR antibodies in serum and CSF were negative), treated with acyclovir for 21 days and recovered slowly being discharged to rehabilitation. Forty-one days post HSV Encephalitis was back in hospital with progressive mania, irritability, racing thoughts, and pressured speech suspected to be a relapse of HSVE. HSV-1 PCR was negative in CSF, and there was an increase of IgG HSV antibody index consistent with prior HSVE. He was started on a 14-day course of IV acyclovir. IgG NMDAR antibodies were detected in CSF and serum with specific antibody index of 24.78; no other neuronal antibodies were identified. Methylprednisolone 1,000 mg IV (day 48 post HSVE) was administered for five days followed by oral tapering. Memory improved within one week, and the patient went back to his daily activities. He was discharged 20 days after relapse. At a follow-up 119 days after relapse (160 days post HSVE), more improvement have been noticed. The IgG NMDAR antibody titer had decreased in CSF, but stayed the same in serum.

“The link between NMDAR antibodies and relapsing post-HSE is important in establishing the correct diagnoses and direct appropriate treatment approaches.” (Armangue et al)

Infectious Encephalitis
Does Herpes Simplex Virus (HSV) Encephalitis trigger brain autoimmunity?
“Herpes simplex virus encephalitis should be considered deliberately in patients with nonspecific, otherwise unexplained, clinical complaints, and even in children with normal cerebrospinal fluid studies.”

(Schleede et al)

The authors challenge the future research to find out if this postinfectious entity is caused by mechanisms of mimicry or breakdown of immunologic tolerance towards the NMDAR expressed by damaged neurons in an inflamed environment. The same question is asked by Höftbreger et al in their review of recent studies of relapsing HSV Encephalitis with anti-NMDAR antibodies. They conclude that patients with relapsing symptoms of HSVE whose CSF PCR studies are negative for HSV should be investigated for NMDAR antibodies in CSF and serum. If these antibodies are found, than the disorder is anti-NMDAR encephalitis and should be treated with immunotherapy.


Pediatric Herpes Simplex Virus (HSV) Encephalitis - nonspecific early symptoms, the role of imaging in the diagnosis, and early outcomes

Schleede et al present a retrospective multicenter experience of 6 neonates and 32 children diagnosed with HSV aiming to provide a more detailed description of early symptoms and complicated early clinical courses. The most frequent symptoms of non-neonatal patients noted prior to admission were nonspecific, including fever, headache, fatigue, vomiting, dizziness, diarrhea, and abdominal pain. At onset, only 38% of patients presented clear neurologic symptoms such as seizures, meningism, or disorientation. Only three neonatal patients showed neurologic symptoms at disease onset: seizures (3), impaired vigilance (1) and abnormal movement pattern (1).

The evolution of MRI changes showed a characteristic time-related pattern. Diffusion weighted imaging seems to be the most sensitive imaging method in the initial phase of this disease. In contrast, T1-weighted, T2-weighted, and contrast-enhanced imaging seem useful to describe the development of tissue lesions during follow-up. Eighteen non-neonatal children (75%) showed abnormal findings on at least one MRI obtained at any time during the course of herpes simplex virus encephalitis. Among non-neonatal patients with abnormal MRI findings, cerebral lesions commonly affected the temporal lobes, the insula, the basal parts of the frontal lobe, and the white matter. In contrast to adults, the cingulum was affected less frequently in non-neonatal patients. In neonatal patients, MRI lesions most commonly affected the parietal lobes, the occipital lobes, and the insula. One neonatal patient showed no MRI lesions at all.

After diagnosis 24% experienced clinical worsening after an initial phase of stability or recovery. The most common new symptoms characterising a relapse were abnormal movement patterns, impaired vigilance, seizures, hemiparesis, and cranial nerve palsies. Median time between diagnosis and early relapses was 16 days. In six of these patients, the relapses occurred during the first acyclovir treatment phase. One child experienced a late relapse occurring 396 days after the first episode.

Fourteen of the non-neonatal patients could be discharged with no apparent residual symptoms, whereas 18 showed residual deficits including abnormal movement patterns, cranial nerve palsies, tetra-/hemiparesis, and aphasia. Further neurologic symptoms were memory impairment, psychiatric symptoms, hyperreflexia, seizures, eye movement disorder, low muscle tone, sensory disturbance, and areflexia. Two of the six neonatal patients had no major neurologic sequelae at hospital discharge, whereas the remaining four showed abnormal movement patterns, low or high muscle tone, and hyperreflexia. No correlation between initial dosage of acyclovir therapy,
cumulative dosage of acyclovir, treatment duration, and outcome of patients was found.

The study concludes that herpes simplex virus encephalitis should be considered deliberately in patients with nonspecific, otherwise unexplained, clinical complaints, and even in children with normal cerebrospinal fluid studies. Early relapses, most likely caused by inflammatory mechanisms, were frequent and should be studied more intensively as these can affect outcome. The underlying inflammatory processes might even be common in herpes simplex virus encephalitis and could serve as a new starting point for an improved treatment. This treatment could include a more deliberate use of steroids, as increasingly proposed for adults, or prolonged acyclovir treatment.


Will West Nile Virus (WNV) continue to produce unpredictable local and regional outbreaks?

Chabierski et al studied the human antibody response to European WNV strains responsible for outbreaks in Italy and Greece in 2010, caused by lineage 1 and 2 strains. Unlike the epidemiology in America, where a lineage 1 WNV strain is exclusively detected, there are several strains belonging to different lineages that circulate in Europe. The authors describe a platform to investigate systematically antibody responses to WNV infections using a series of overlapping protein fragments spanning all structural proteins of the virus.

The study shows that several peptides of the capsid, the prM/M, and the E proteins of WNV are recognised by IgG antibodies from humans infected with newly emerging European strains of WNV. All WNV-positive sera bound strongly to at least one peptide (corresponding to the lineage 1 amino acid sequence) and no clear differences were observed between sera obtained from patients from Greece, Italy or the USA that were infected with lineage 2 or 1 strains. However, the data reveal substantial differences between individual sera in the patterns of the proteins and domains recognised, highlighting the heterogeneity of the human humoral immune response against WNV, which should be considered during the development of specific diagnostic tests.

Sambri et al review the current epidemic situation regarding WNV in Europe, emphasising the clinical, diagnostic and preventive measures available. The areas affected by WNV continue to expand in Europe and in the rest of the world, producing increasing numbers of outbreaks associated with human morbidity and mortality. In the last two years, WNV provoked outbreaks involving significant numbers of people in the Balkan area, Italy and Hungary. During 2012, relevant WNV activity was also identified in the Russian Federation, Ukraine, Israel, Tunisia, Algeria, and the Occupied Palestinian Territories. There are concerns regarding the potential emergence of strains with increased virulence, the rapid development of epimics and the limitations of current diagnostic tests in identifying novel and unexpected WNVs. The authors argue that timely surveillance for WNV infection is needed on an EU-wide scale including veterinary and entomological surveillance, as well as molecular surveillance of emerging strains.

Petersen et al reviewed the ecology, virology, epidemiology, clinical characteristics, diagnosis, prevention, and control of West Nile virus, with an emphasis on North America and found that West Nile virus has expanded its geographical range throughout the United States. The authors envisage other unpredictable local and regional outbreaks in the future; therefore sustainable, community-based surveillance and vector management programs are necessary especially in the areas with a history of West Nile virus and large human populations at risk.


Petersen L R, Brault AC, Nasci RS. West Nile virus: review of the literature. JAMA. 2013 Jul 17; 310(3)

Is the severity of influenza related neurological manifestation underestimated?

Goenka et al present the results of a surveillance study of 25 cases with acute neurological illness within one month of proven influenza infection. Cases were predominantly children (21 children), mainly those with a pre-existent neurological condition. None of the patients were vaccinated, even if many had recommendations for this. Four patients died. Encephalopathy syndromes such as Acute Necrotising Encephalopathy (ANE), Acute Infantile Encephalopathy Predominantly Affecting the Frontal Lobes (AIEF), Haemorrhagic Shock & Encephalopathy (HSE) and Acute Haemorrhagic Leukoencephalopathy (AHL) were identified mostly in children, being associated with a worse outcome. Acute movement disorders and Guillain–Barré syndrome were seen more frequently in adults. Influenza PCR was negative in all 10 CSF samples tested, and the CSF identified pleocytosis in three cases (18 tested). Influenza A was found in respiratory secretions (PCR) of 21 cases (20 had H1N1 strain) and influenza B in 4 patients.

The authors argue that influenza should be considered a cause of acute neurological syndromes in the winter months, especially in children with unexplained encephalopathy.

Autoimmune Encephalitis

Demographics, clinical and diagnosis features - important factors in early recognition and management of patients with anti-NMDAR Encephalitis.

Titulaer et al conducted a multi-institutional observational study of 577 patients with GluN1 antibodies. The study confirmed the female preponderance (81%) and the high frequency on children (37% of cases were younger than 18). 65% of adults presented with behavioural problems, while 50% of children under 12 presented with seizures or movement disorders. In adolescents, the disease presented with a combination of symptoms from these groups. Within the first four weeks most patients developed the same symptoms regardless of age, and in the first month, 87% of patients developed four or more symptoms (from these eight categories: behaviour and cognition, memory, speech, seizures, movement disorder, loss of consciousness, autonomic dysfunction and central hypoventilation). Only 1% of patients remained monosymptomatic. Armangue et al also found that development of a monosymptomatic illness is very rare in children (except in relapses). They recommend prudence in accepting the diagnosis of anti-NMDAR encephalitis in monosymptomatic cases or when symptoms do not fit the expected syndrome and suggest reassessment of CSF and serum for antibodies in these cases.

In the Titulaer et al study the tumour predominated in patients between 12 and 45 years, with 94% being ovarian teratoma. Asian and African-American patients were most likely to have a teratoma than Caucasian and Hispanics. The frequency of an underlying teratoma was significantly greater in females aged 12 years or older than in young children and males. The authors argue that if a tumour is not found, the extent and frequency of tumour screening should take into consideration the patient’s age and gender. Young et al report nine cases of critically ill patients with anti-NMDA Encephalitis which includes four cases of ovarian teratoma detected after intensive investigations. In one case, this diagnosis was only confirmed after laparoscopic removal of macroscopically normal ovaries.

There is a broad spectrum of movement disorders associated with anti-NMDAR Encephalitis. Baizabal-Carvallo et al studied the movement disorder of nine children with confirmed anti-NMDAR Encephalitis. All patients presented with at least one movement disorder including chorea, stereotypic movements, ataxia, limb dystonia, limb myorhythmia, oromandibular dystonia, facial myorhythmia, blepharospasm, opisthotonus, athetosis, and tremor. All patients had movement disorders involving their limbs, and five also had cranial involvement. More than a single movement disorder was observed in six of these patients.

NMDAR antibodies were detected in CSF of all patients and serum of 85% of them in the study conducted by Titulaer et al. The same findings came from the Armangue et al study; NMDAR antibodies were identified in the CSF of all patients (20) and serum of only nine (out of 11 available).

A high number of cases with anti-NMDAR Encephalitis are admitted to Intensive Care Unit (ICU). Young et al highlight a number of important learning points that may aid clinicians in the management of patients with anti-NMDAR encephalitis when they encounter them in clinical intensive care practice. The patients’ abnormal movements were particularly problematic and difficult to control, with 26 different medicines used (for nine patients), none were found to be particularly effective. To overcome the difficulty of distinguishing seizures from other abnormal movements, the optimal management is probably urgent investigation with video EEG before commencement of antiepileptics. Autonomic dysfunction was commonly reported; fever was a universal feature, and one patient dying from complications of hyperthermia (fever might have been an iatrogenic complication of treatment rather than a manifestation of the anti-NMDAR encephalitis itself). Four of nine patients had hypersalivation which led to tracheostomy complications.

Recovery of patients with anti-NMDAR Encephalitis can be a slow process, and not always straightforward. It took more than 18 months for patients to improve in the Titulaer et al study. This slow recovery time may also suggest the possibility of an occult malignancy, and systematic searches need to be carried out (Vincent). Leyboldt et al argue that recovery can happen years after disease onset (three years in his study of a patient with anti-NMDAR encephalitis) therefore communicating.

“Recognition of the symptoms should prompt testing for antibodies leading to an early diagnosis and the search for a tumour” (Titulaer et al)
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a negative prognosis needs not to be rushed. Armangue et al argue that one of the findings of their review, constant detection of factor antibodies. Knowledge of antibodies identified in all nine patients studied, supports the ide postulated in previous studies that the long duration of the disease and slow response to immunotherapy are due, in part, to the production of antibodies within the central nervous system as well as systemically.

Spontaneous recovery can happen. Titulaer et al report six patients out of 29 who had a spontaneous recovery without treatment. They also present a new onset or worsening of symptoms occurring after at least two months of improvement or stabilisation in 45 patients who had one or multiple relapses (representing a 12% risk within two years); 67% of relapses were milder than the initial presentation. Kayser et al report 40 patients out of 67 having relapses of encephalitis. The authors found that for patients with a history of NMDAR encephalitis, any behavioural changes might represent relapse. They suggest that patients who relapse need to be screened for tumour especially teratoma of the ovary because of the strong link between relapse and the presence of a previously unidentified or recurrent tumour.


Differential Diagnosis of anti-NMDAR Encephalitis. A challenge for psychiatrists, internists and medical toxicologists

Kayser et al studied the frequency and type of isolated psychiatric symptoms at either disease onset or relapse in a large cohort of patients with anti-NMDAR encephalitis (571 patients). There were 23 patients with isolated psychiatric symptoms, five on initial presentation (in retrospect families of two of them reported excessive blinking and hypersalivation) and eighteen at relapse (28% of all relapses were pure psychiatric episodes). Delusional thinking, mood disturbances and aggression were the preponderant symptoms. The authors argue that some cases of anti-NMDAR encephalitis can be mistaken for a primary psychiatric disorder; therefore, patients presenting to a psychiatrist with new onset psychosis or mania, may need to have their CSF and serum analysed depending on the history of their illness and other clinical data.

Maraka et al also argue that prompt clinical recognition of this syndrome is vital because the treatment (early and adequate) can influence the outcomes despite the severity of the symptoms. They report the case of a 33 year old woman with anti-NMDAR encephalitis wrongly diagnosed for psychiatric disorder after presenting with agitation and psychotic symptoms following a four-day history of flu-like illness.

Ryan et al suggest that psychiatrists should consider anti-NMDA Encephalitis in patients presenting with psychosis as well as dyskinesia, seizures, and/or catatonia, especially if there is no history of a psychiatric disorder. They present a case of a 37 year old woman with agitation and exhibited bizarre behaviour and firstly misdiagnosed as acute psychotic episode. Van de Riet et al also describe two patients admitted to the psychiatric hospital with severe first onset psychosis diagnosed at a tertiary hospital with anti-NMDAR Encephalitis and state that a diagnosis of anti-NMDAR encephalitis should be taken into consideration in agitated and psychotic patients with catatonia.

Lim et al report an 18 year old man with anti-NMDAR Encephalitis who was found to have an increased intracranial pressure which presented both a diagnosis and treatment challenge. They argue that it is important for internists to consider anti-NMDAR encephalitis in the differential diagnosis of encephalopathy. Punja et al describe two patients initially evaluated for neuroleptic malignant syndrome (NMS) and ultimately diagnosed with anti-NMDAR Encephalitis.
Anti-NMDAR Encephalitis in children and adults – a comparison

Studies confirmed that anti-NMDAR Encephalitis in children varies than in adults. The ratio female/male varies according to age, with male preponderance only seen in the age group below 12 and above 45. The initial symptoms of paediatric anti-NMDAR encephalitis vary from those of the adults with more neurologic and less psychiatric symptoms in children (Titulaer et al, Armangue et al). The MRI and EEG findings are mostly similar to those reported in adults. Armangue et al report a unique EEG pattern (“extreme delta brush”) in one of the paediatric patients in their study.

Most children with anti-NMDAR encephalitis do not have an underlying tumour. No tumour was present in the Baizabal-Carvallo study (nine children, age between 3 and 14). Armangue et al report only two patients out of 20 (median age 13) who had tumours, both between age 12 to 18 and none under 12.

There are also differences between NMDAR Encephalitis in adults up to 45 and adults over 45. Titulaer et al (2) investigated clinical features and outcomes of 31 patients over 45 and compared with those of 338 patients age 18-44 previously reported. Older patients were more often male (45% vs 12%). They had less tumours (23% vs 51%), mostly carcinomas. They had longer median time to diagnosis and treatment (eight weeks vs four weeks) and the outcomes were poorer. The symptoms were less severe in older adults; seizures happened less frequently in patients ≥45 years of age, but memory loss was more common in the same patients. At 24 months follow-up, 60% of the patients had good outcome (mRS 0–2) compared with 80% of young adults. The authors conclude that overall anti-NMDAR encephalitis is less severe in patients older than 45, but the outcome is poorer. The symptom presentation makes the diagnosis difficult; there are longer delays in the diagnosis and treatment and age-related factors influence both the presentation and the outcomes. A prompt diagnosis and treatment may improve the outcomes.

“Clinical presentation in children is often different from that of the adults.” (Titulaer et al)

Immunotherapy versus antiepileptic drugs in faciobrachial dystonic seizures

Irani et al undertook the first prospective study of faciobrachial dystonic seizures with serial assessments of seizure frequencies, cognition and antibodies in 10 cases confirms positive for voltage-gated potassium channel-complex antibodies. In all cases, AEDs were the initial treatment and were administered alone for between 11 and 200 days. During this period, in only one patient was the frequency of faciobrachial dystonic seizures reduced by >20%. AEDs were followed by corticosteroid administration in all cases with additional intravenous immunoglobulins (n = 4) and plasma exchange (n = 1). Faciobrachial dystonic seizures were controlled more effectively with immunotherapy than anti-epileptic drugs. The cessation of the very frequent faciobrachial dystonic seizures was achieved in all cases after immunotherapy was added to AEDs and this often occurred rapidly after corticosteroid administration. The cessation of faciobrachial dystonic seizures was commonly observed before substantial reductions in serum VGKCcomplex/LGI1 antibody titres. Relapses of faciobrachial dystonic seizures were seen in four of ten cases. Voltage-gated potassium channel-complex antibodies persisted in the four cases with relapses of faciobrachial dystonic seizures during corticosteroid withdrawal. Interestingly, the patient who stopped corticosteroids and AEDs once the antibodies were negative did not relapse. There were also two patients in who VGKC-complex/LGI1 antibodies returned without a relapse of faciobrachial dystonic seizures or cognitive impairment.

Time to recovery of baseline function was positively correlated with time to immunotherapy but not time to anti-
epileptic drug administration. Five cases had cognitive impairment when first seen. The other five were initially seen with faciobrachial seizures and no detectable cognitive impairment. At this stage all five cases were administered AED and three progressed to develop cognitive impairment at 45, 60 and 89 days, respectively. The two cases who did not develop detectable cognitive impairment were additionally given steroid therapy at days 30 and 79 into their illness.

The authors argue that the findings of this study provide strong evidence that immunotherapy, particularly when given early, may confer multiple benefits in the treatment of faciobrachial dystonic seizures. In some cases, where close antibody monitoring is considered useful, it may be worth measuring LGI1 antibodies rather than VGKC-complex antibodies, because the latter are often low or negative while LGI1-antibodies were still detectable.


The role of the immunotherapies in Autoimmune Encephalitis

In patients with anti-NMDAR encephalitis, immunotherapy results in substantial neurological improvement (Titulaer et al; Armangue et al). Immunotherapy had also produced the resolution of the abnormal movements in all patients who received it in the Baizabal-Carvallo et al study.

Second-line immunotherapy was used in the Titulaer study and reported being an additional factor of good outcome. In a study conducted by Armangue et al all seven patients who received rituximab responded to treatment without further relapses, including one patient who had had five previous episodes. None of the patients in their study had significant side effects of the treatment. However the side effects of these drugs need to be considered, Suleiman et al suggesting that a “risk versus benefit” assessment is necessary.

There are forms of Limbic Encephalitis (LE) with other antibodies such as those to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA-Ab) or gamma-aminobutyric acid (GABA) B receptors which usually respond well to immunotherapies, despite the tumour association although with a tendency to relapse. These forms are much less common, although they are important because the patients have a high probability of tumours. LE associated with antibodies to glutamic acid decarboxylase (GAD) tend to occur in young adult females with temporal lobe epilepsy. This form is relatively resistant to immunotherapies and antibody titres do not decrease substantially following treatments (Vincent).

Hacohen et al report the clinical and investigative features of children with a clinical diagnosis of probable autoimmune encephalopathy, both with and without antibodies to central nervous system antigens. Overall, 46% of patients were antibody positive to either NMDAR, 27%; VGKC complex, 17% and one to GlyR antibodies. No significant clinical differences were found between the antibody positive and negative groups. Prodromal symptoms, with either fever and/or associated infectious episodes, were noted in 56% of patients. The most common presenting features included seizures (83%), behavioural changes (63%) and confusion (50%). 56% of patients had neuropsychiatric symptoms and 38% developed a movement disorder. 52% of children required intensive care admission for seizure control or reduction in conscious level. At presentation brain imaging was normal in 73% and EEG showed encephalopathy in 70% of patients. Both antibody positive and negative patients responded to immunotherapies with improvements in the mRS scores and complete recovery in 42% overall at the latest follow-up (mean 24 months). In this cohort, worse outcomes were seen in patients who did not receive any immunotherapy, and delay to therapy was likely to have influenced outcome, as seen in the two patients who received immunotherapy late and did not respond. Nevertheless, four patients who did not receive immunotherapy made a complete recovery.

Najjar et al describe a case of a 21 years old girl who suffered from psychosis and encephalopathy for six years before she underwent treatment with immunotherapy. Based on the findings of this study and a literature review, the authors conclude that autoimmune panencephalitis seronegative for VGK-complex, NMDAR and GAD autoantibodies is a subtype of autoimmune encephalitis that can present with pure neuropsychiatric characteristics and a normal brain MRI. They suggest the new entity needs to be added at the differential diagnosis of psychosis with prominent negative symptoms, even in the absence of seizures or serologic, CSF and MRI abnormalities and a response to conventional treatment. Patients with a delayed diagnosis and treatment can suffer refractory psychiatric disturbances and permanent neuropsychiatric sequelae.


Baizabal-Carvallo JF, Stocco A, Muscat E, Jankovic J. The spectrum of movement disorders in children with anti-NMDA receptor encephalitis. Mov Disord. 2013 Apr; 28(4)


Vincent A. Developments in autoimmune channelopathies. Autoimmun Rev. 2013 Apr; 12(6)


Najjar S, Pearlman D, Devinsky O, Najjar A, Nadkarni S, Butler T, Zazag D. Neuropsychiatric autoimmune...
Hashimoto’s Encephalopathy (HE) in children

To identify the clinical findings of Hashimoto’s Encephalopathy (HE) in children and assess their neurological outcome, Mamoudy et al compared biological, EEG and brain MRI characteristics of eight children with HE with those of 34 children suffering from a suspected encephalitis clinically expressed as acute neuro-behavioural symptoms. All eight children had high levels of anti-thyroid antibodies, in particular thyroglobulin antibodies (TPO) antibodies at onset despite normal T4 and TSH levels in six of them. The main clinical differences were that all eight HE children were girls and all had personal or familial histories of auto-immune disease. CSF analysis gave similar results for the two groups of children, although the HE group exhibited a trend toward high protein concentrations in the CSF. All HE children had abnormal EEG compared with 61% in the other group and brain MRI was abnormal in 50% of them compared with 62% in the other group.

Relapses were observed in five children with a second relapse, despite steroid therapy, occurring sooner after the previous episode. Immunosuppressive therapy was started in all five children and two developed sequelae by the last follow-up visit (after 4 ± 1.3 years). High dose IV methylprednisolone appears to be insufficient to prevent relapses in some patients, and such patients may benefit from early treatment with more aggressive immunosuppressive drugs. At the end of follow up, persistent clinical signs (headache, memory impairment, hand tremors, cerebellar syndrome) were reported in four of the eight patients with HE and were sufficiently severe to affect daily life in two cases. Only 50% of HE children in this series responded to steroid treatment, the inclusion of steroid responsiveness in the diagnostic criteria of HE should be carefully reassessed, as similar therapeutic responses can occur in any auto-immune or non-auto-immune inflammatory encephalitis.

Hacohen et al describe three children presenting with limbic encephalitis with elevated thyroid antibodies that did not respond to corticosteroids alone and required more aggressive immunotherapy, mirroring the slower treatment response that is more frequently seen in other immune-mediated forms of limbic encephalitis. The clinical and radiological presentation of these three cases is similar to those described both in the adults and the paediatric groups with limbic encephalitis. The raised level of antithyroid antibodies and the absence of any other identifiable central nervous system directed autoantibodies, alongside a response to immunotherapy support a diagnosis of immune-mediated limbic encephalitis with similarities to some cases of Hashimoto’s encephalopathy. The authors argue that in patients with limbic encephalitis associated with elevated antithyroid antibodies, immunotherapy should not be abandoned following failure of response to steroids as these patients often respond to further and more aggressive immunotherapy, similar to patients with other central nervous system autoantibody mediated limbic encephalitis.


Proposed modified guidelines for identification of children with neural surface antibodies syndromes (NSAS)

Suleiman et al used a sample of children with suspected autoimmune epilepsy (13 patients) to test the utility of modified Zuliani guidelines (Zuliani et al, 2012) which were designed to classify adults with neuronal surface antibody syndromes (NSAS). Seven patients of the 13 children (11 were female, age range 1 to 13 years) with suspected autoimmune epilepsy were positive for neuronal surface antibodies (NMDAR, n = 3; VGKC-complex, n = 3; and GABA, n = 1), immunotherapy was given to nine cases, and a positive response was more common in patients with positive neuronal surface antibodies (5/5) compared to those with negative antibodies (2/4).

Based on antibody testing and the response to immunotherapy (when given), they proposed five categories for classification on disease (and likelihood of autoimmunity epilepsy) including definite, probable, possible, unlikely, or unknown autoimmune epilepsy. Applying the proposed guidelines, the classification of autoimmune epilepsy was definite in five, probable in one, possible in three, unlikely in two, and unknown in two patients. The authors argue that the proposed guidelines can be useful in the recognition of children with seizures of autoimmune etiology. Neuronal surface antibodies and GAD antibodies are present in a proportion of children with suspected autoimmune epilepsy and may define a treatable subgroup of childhood epilepsy. The recognition of immune mechanisms in neurologic disorders is important as this can prompt early treatment and may lead to better outcomes. Although helpful, the guidelines are not perfect and represent only an attempt to identify and classify these patients. These guidelines do not predict treatment responsiveness or outcome. Future studies may improve the understanding of clinical phenotypes of autoimmune epilepsy in children and help further develop syndrome-specific and treatment-oriented guidelines.


Future prospects in Autoimmune Encephalitis

Future investigations of the antibody negative group may lead to the definition of new antigenic targets. The similarities between patients with and without identified antibodies indicate a need to search for new antigenic targets that could be helpful in future diagnosis; in the meantime diagnostic and management strategies that are often based on antibody evaluation, and directed by one of a specific antibody, may need to be re-evaluated (Hacohen et al).

Vincent also argues that it is likely that further antibody-mediated CNS diseases will be identified in the future, and it is also evident that some patients with more common diseases such as idiopathic forms of epilepsy, psychosis, dementia or movement disorders will have an antibody-mediated condition. Although most of the autoimmune forms of encephalopathy do respond...
“In the majority of cases the patients improve substantially with immunotherapies” (Vincent)

to current immunotherapies, the responses can be slow and the therapies have unwanted side effects. Treatments that target more specifically those B cells or plasma cells that produce the specific antibodies would clearly be preferable. There is a need for better and faster diagnosis which requires development of commercial assays that can be used locally.


Vincent A. Developments in autoimmune channelopathies. Autoimmun Rev. 2013 Apr; 12(6)

Brainstem Encephalitis (BE)-etiology, diagnosis and outcomes

A retrospective review by Tan et al of 81 non–HIV infected patients (adults and children) diagnosed with BE looked at their clinical presentations, etiologies, response to treatment, and predictors of outcome. An etiology was identified in 71.6% of cases, most of which were confirmed or probable inflammatory/autoimmune conditions. Of the remaining 23 cases in which a specific diagnosis remained undefined, clinical presentation, CSF, neuroimaging studies, and outcomes were similar to the inflammatory/autoimmune group. Brain biopsy identified a specific diagnosis in 50% of patients. 75% of patients had abnormal CSF examinations as defined by CSF pleocytosis, elevated protein or decreased glucose. Imaging abnormalities involving the brainstem were evident in most patients.

Antimicrobial therapy was utilised in all patients in the infectious group, and in a minority of individuals with inflammatory/autoimmune or undefined BE. Corticosteroids were used more frequently in the inflammatory/autoimmune group (81.5%) as compared to the undefined group (56.5%) and were typically used as frontline treatment. In individuals with inadequate response, second-line immunotherapies including plasmapheresis, intravenous immunoglobulin, cyclophosphamide, mycophenolate mofetil, were used. These therapies were utilised at about the same rate in both the inflammatory/autoimmune and the undefined group. Fifteen patients (18.5%) either died or had a poor outcome. Although outcomes of BE are variable and can be devastating, the majority of the patients with inflammatory/autoimmune and undefined causes of BE recovered with favourable outcomes.

In summary, BE has distinct clinical characteristics and etiologies as compared to encephalitis in general. The majority of etiologies in the cohort were of non-infectious, inflammatory causes. Brain biopsy and histopathological diagnosis may play a role in the management of selected patients and can be useful in guiding treatment decisions.
Advances in diagnosis and management of Encephalitis

Venkatesan et al present a consensus document representing a synthesis of the discussions of the International Encephalitis Consortium meeting 2012 and supported by literature, that proposes a standardised case definition and diagnostic guidelines for evaluation of adults and children with suspected encephalitis. Areas of research priority, including host genetics and selected emerging infections, were also debated.

The proposed definition of encephalitis and encephalopathy of presumed infectious or autoimmune etiology includes two criteria. The Major Criterion (required) represents patients presenting to medical attention with altered mental status (defined as decreased or altered level of consciousness, lethargy or personality change) lasting ≥24 h with no alternative cause identified. The Minor Criteria (2 required for possible encephalitis; ≥3 required for probable or confirmed encephalitis) includes: documented fever ≥38°C within the 72 h before or after presentation; generalised or partial seizures not fully attributable to a preexisting seizure disorder; new onset of focal neurologic findings; CSF WBC count ≥5/cubic mm; abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from prior studies or appears acute in onset; abnormality on electroencephalography that is consistent with encephalitis and not attributable to another cause.

The proposed algorithm for diagnosis intends to provide a practical tool for medical professionals worldwide in the initial evaluation of suspected encephalitis and a standardised approach for use in collaborative, multicentre research studies. There are two algorithms developed, one for adult and one for pediatric population directed toward identification of specific infectious and autoimmune causes of encephalitis and therefore do not include a broad evaluation for mimickers of encephalitis or other causes of encephalopathy. The algorithm recommends testing for most common causes, along with selected, treatable conditions, in all individuals. Obtaining a comprehensive case history, including recent and remote travel, animal contacts and insect exposure, and carefully characterising presenting symptoms, signs, and laboratory and neuroimaging findings are crucial to inform additional testing. Neuroimaging (preferably magnetic resonance imaging [MRI]), electroencephalography (EEG), and lumbar puncture (LP) are recommended in all individuals unless contraindicated because such testing may confirm the diagnosis of encephalitis and establish the etiology. The authors argue that the proposed guidance is general, for initial evaluation of encephalitis, but rapid advances in autoimmune encephalitis coupled with the emerging nature of infections warrant ongoing evaluation of testing paradigms.

Analysis of the cerebrospinal fluid (CSF) obtained at lumbar puncture (LP) is pivotal to establishing the diagnosis and guiding management of acute central nervous system (CNS) infections. Michael et al developed a Lumbar Puncture (LP) pack for patients with a suspected CNS infection. They also assessed its impact on diagnosis by comparing practice six months before and after its introduction to the medical admissions unit of a large inner city teaching hospital. The aims of the study were to increase the proportion of patients having an LP for a suspected CNS infection for whom the appropriate samples are taken and the proportion of patients for whom a pathogen was identified. The authors modified an existing LP pack for subarachnoid haemorrhage (SAH), to create an LP pack, which would guide clinicians on the appropriate investigation for both a suspected CNS infection and/or a suspected SAH. The modified flowchart describes clinical features directing investigation for a CNS infection or an SAH, and guides when to perform a CT or an LP first. It also indicates which samples should be taken, the volumes required, the bottles to fill, where to send and how to transport them. The pack also contains numbered bottles for CSF and blood, which correspond to the flowchart. The authors found that the LP pack reduced major errors in CSF sample collection and improved the diagnosis of acute CNS infections; among those patients who had a CSF pleocytosis, the proportion with a viral or bacterial pathogen identified by PCR was increased after introduction of the pack.

“Algorithms for the diagnosis of encephalitis may serve many purposes, including aiding clinicians in management of patients, standardizing evaluations for research, and facilitating public health disease surveillance” (Venkatesan et al)
Abuhandan et al conducted a cross-sectional study on 26 patients, aged 9 to 13 years, diagnosed with SSPE who were undergoing regular follow-up between January to December 2011, and a control group of 18 subjects (similar age group with normal results from cranial MRI) to evaluate the contribution of diffusion-weighted magnetic resonance imaging in diagnosis and staging in SSPE. Clinical staging was determined by Risk and Haddad classification; 12 patients at Stage II and 14 at Stage III. Diffusion weighted magnetic resonance images were taken of six areas (frontal, parieto-occipital, cerebellar, deep white matter, thalamus and basal ganglia) and by calculating the apparent diffusion coefficient (ADC) values, and a comparison was made between the stages and with the control group. The ADC values of all the areas of the SSPE patients were found to be significantly higher compared to the control group (p < 0.05). While the mean ADC values of the deep white matter, basal ganglia, frontal and parieto-occipital areas of the Stage II patients were found to be significant compared to the control group (p < 0.05), there was no significance in the other areas (p > 0.05). The ADC values of all the areas of the Stage III patients were found to be significantly high compared to the Stage II values (p < 0.05).

The authors argue that diffusion weighted magnetic resonance imaging can be used with other diagnostic criteria to confirm diagnosis of SSPE and to reveal differences between the stages.


The role of viral infections in children with CNS infections from a malaria endemic area in Malawi

Mallewa et al conducted a prospective cohort study in Malawi and enrolled 513 children aged between 2 months and 15 years who were admitted to hospital with suspected non-bacterial CNS infections from March 1, 2002, to Aug 31, 2004 aiming to investigate whether viruses could also be an important cause of their CNS infection, and examine the relative contribution of viral pathogens and malaria parasitaemia.

18% of children died. 71% of them made apparent full recoveries, and 11% had neurological sequelae at discharge (including motor and cognitive deficits). HIV status was established for 140 children (27%), of whom 49 (35%) were HIV positive. 32% of children had P falciparum parasitaemia, of whom 21% died compared with 17% of those without parasitaemia. There was no association between the density of parasitaemia and outcome. Children with parasitaemia were more likely to present in deep coma (48% vs 19%). Fundoscopy was done in 90 children. 49% of children had parasitaemia, of whom 45% had evidence of malaria retinopathy. None of 46 patients without parasitaemia had retinopathy.

The children were tested for 15 different viruses. At least one virus was detected in the CNS in 26% of children. The range of infections in this study was different than the studies in Europe, America and Asia. The most commonly detected virus was adenovirus (accounting for about a third of cases of viral CNS infection), followed by mumps virus, human herpes virus 6, and rabies virus. 33% of children with a CNS virus died compared with 13% of no CNS virus detected. The highest mortality was for rabies virus, followed by cytomegalovirus. About a quarter of children with adenovirus infection died. 9% of the children had both a viral CNS infection and malaria parasitaemia. No specific virus was associated with parasitaemia. A third of the children who met the case definition for cerebral malaria had viral infections, including a quarter of the children who had the characteristic retinal changes thought to be diagnostic of cerebral malaria. Although fewer patients had viral infection than parasitaemia, more children with viral infection died, even when patients with rables—which is uniformly fatal—were excluded. Children with malaria parasitaemia and viral co-infection were more likely to present with seizures or a more severe disease than were those with either infection alone or neither infection, raising the possibility that both pathogens contribute to the pathogenesis in patients with dual infections. How viruses and malaria parasites might interact is unknown. Overall viral infections were associated
with more fatal cases than was malaria parasitaemia. The authors also found that viral CNS infection was equally common in children with parasitaemia with or without retinal changes of cerebral malaria, suggesting that some of the patients could have had viral CNS infection with coincidental parasitaemia, while others had viral CNS infection and cerebral malaria, as defined by fundoscopy. The study concludes that Viral CNS infections are an important cause of hospital admission and death in children in Malawi, including in children whose coma might be attributed solely to cerebral malaria. Interaction between viral infection and parasitaemia could increase disease severity.


Can the outcome of Encephalitis cases be predicted? Thakur et al conducted a retrospective review of 103 patients with acute encephalitis and assessed the outcome at hospital discharge of patients with acute encephalitis who received treatment and supportive care in the ICU aiming to identify which factors were predictive of outcome at hospital discharge.

18.45% of patients died. Mortality was associated with cerebral edema, status epilepticus (SE) and thrombocytopenia. 95% of the patients who died during hospitalisation required endotracheal intubation with ventilator support. Older age (>65) and immunocompromised status were not statistically significant to be considered factors predictive of death. Of the surviving patients, 44.04% had favourable outcome and 55.96% had poor outcome. 25% of the surviving patients were discharged home, 58.33% discharged to rehabilitation, 11.9% to a nursing home, and 4.67% to another hospital. In those patients who survived to hospital discharge, viral, nonviral, and unknown causes of encephalitis were all less likely to be considered prognostic of poor outcome compared with the autoimmune etiology.

Speers et al conducted a review of nine (seven adults and two children) laboratory-confirmed cases of Murray Valley encephalitis (MVE) from Western Australia between 2009 and 2011 aiming to find factors that may help clinicians predict the outcome of MVE. One adult patient died, one child made a full recovery and the other seven patients were left with significant difficulties. The MRI data showed that patients who had widespread abnormalities involving the thalamus, midbrain, and cerebral cortex or the cerebellum had severe neurological outcomes compare with patients whose MRI showed absence of thalamic MRI hyperintensity during the acute illness, with or without leptomeningeal enhancement.


The Functional, Social and Economic Impact of Encephalitis in Children Griffiths et al conducted a study to assess the wider impact of Japanese Encephalitis (JE) and Acute Encephalitis Syndrome (AES) in children. This is the first study to examine the functional, economic and social impact of AES in parallel following hospital discharge. Children (aged 1 month–14 years) with AES were assessed 5–12 months after discharge from two Nepali hospitals. Children were classified as JE or ‘other AES’ based on anti-JE virus antibody titres during acute illness. Seventy-two children were included. At follow-up, six children had died and 48% of survivors had impaired function. Impairment was more common in JE than ‘other AES’ cases (68% versus 40%); the types of impairment were similar in children with confirmed JE and other AES. Behaviour, language or limb impairments were common.

Encouragingly, almost half the children reported improved function at follow-up compared to hospital discharge. The economic impact was substantial: $1151 US dollars (10 times their monthly income) among families with children suffering severe/moderate impairment. Acute admission represented 74% of total costs. The substantial economic costs to families suggest rationalisation of acute care costs may be warranted. Although attempts to rationalise acute hospital treatment should be balanced against the needs of patients and medical staff to explore all reasonable avenues of treatment, a more detailed analysis of acute costs may help determine where hospital treatment could be streamlined. In turn, this could significantly reduce the economic impact to families. The relatively low post-discharge out-of-pocket costs to families may reflect limited access to services for children following encephalitis.
Few families reported limitations in their child’s social participation. The functional problems experienced by these children highlights their need for long-term medical support. Families reported their child maintaining social participation, implying a positive attitude to social engagement. The majority (84%) of school age children, including half of the children with moderate or severe functional impairments continued to attend full-time education.

The study found that children with high functional ability following AES illness also tend to have a high level of social participation with exception of children who suffered behavioural disturbance, visual impairment or changes in their external environment (such as family financial difficulties).

Fowler A et al evaluated 55 children with TBE with central nervous system involvement infected during 2004–2008 in Stockholm, 2-7 years later using the Rivermead post-concussion symptoms questionnaire and the Behavior Rating Inventory of Executive Functioning for parents and teachers. General cognitive ability was investigated in a subgroup using the Wechsler Intelligence Scale for Children, 4th edition. The aim of this study was to examine the long-term outcome of TBE infection in children in order to design optimal vaccination strategies for children in areas in which TBE is endemic.

In the present study, only children with CNS involvement were included. At long-term follow-up, two-thirds of the children reported persistent problems such as headache, fatigue, irritability and cognitive problems. The cognitive problems were seen in areas of executive function and working memory. More than one-third of the children were reported by parents or teachers to have problems with executive functioning on the Behavior Rating Inventory of Executive Functioning, mainly in areas involving initiating and organising activities and working memory. Children who underwent Wechsler Intelligence Scale for Children, 4th edition testing had a significantly lower working memory index compared with reference norms. No prognostic factors in the acute phase of CNS illness in children, were identified, in whom severe TBE is associated with greater rates of long-term sequelae. There was no correlation between age at illness and severity of symptoms at follow-up, indicating that even young children may experience an incomplete recovery that manifests later as they become older. Girls had significantly more symptoms at follow-up compared with boys. Apart from sex, no single factor studied in the acute phase was predictive of outcome.

The authors conclude that a large proportion of children experience an incomplete recovery after TBE with central nervous system involvement. Cognitive problems in areas of executive function and working memory are the most prevalent. Even if mortality and severe sequelae are low in children after TBE, all children should be followed after TBE to detect cognitive deficits.

Als et al conducted a prospective observational case-control study to assess short-term neuropsychological function and academic performance in school children following admission to intensive care and to explore the role of critical neurologic and systemic infection. A sample of 88 children aged 5–16 years who were admitted to intensive care with meningoencephalitis, septic illness, or other critical illnesses were assessed 3 to 6 months following discharge, and their performance was compared with that of 100 healthy controls. Patients were without prior neurologic or neurodevelopmental disorder.

The follow-up of children after critical-illness should form part of the “global standard” of critical care delivery.” (Als et al)

The children admitted to PICUs significantly underperformed on neuropsychological measures in comparison to healthy controls. The PICU cohort performed significantly worse than controls on measures of verbal and visual recall and recognition memory, spatial working memory and working memory capacity, and visual sustained attention. Reduced performance was most prevalent in the meningoencephalitis group, and this group performed significantly worse than healthy controls in IQ and memory, including verbal recognition, pattern recognition, visual recall and spatial working memory.

Teachers deemed more children admitted to PICUs than controls as performing educationally worse and having problems with school work, as well as performing below average on aspects of executive function and attention. Analysis of the effect of illness type on outcome revealed that aspects of neuropsychological function, such as memory function, and

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teacher-rated academic performance were most reduced in children with meningoencephalitis and septic illness. In the PICU group, multivariable linear regression revealed that worse performance on a composite score of neuropsychologic impairment was more prevalent when children were younger, from a lower social class, and had experienced seizures during their admission.

In conclusion admission to intensive care is followed by deficits in neuropsychologic performance and educational difficulties, with more severe difficulties noted following meningoencephalitis and septic illness.

Hoffman and Paschal conducted a study of 48 adult patients with West Nile Virus admitted to a rehabilitation facility to describe the functional impairments upon admission and the functional outcomes at discharge. The study focuses on physical therapy intervention only. Patients had important comorbidities (HTA, type diabetes mellitus, acute respiratory failure, ventilator dependency and pneumonia). The rehabilitation hospital length of stay varied from 2 to 304 days. The WNV affected each patient in different way. Their admission Functional Independence Measure (FIM) scores varied from 13 to 116 and discharge FIM scores from 18 to 121. The authors found that the advanced age and the higher number of comorbid conditions were linked to serious presentation and complications. None of the patients had complete recovery to their premorbid functional status. The majority of patients were discharged home or to a nursing facility (46%), with skilled or extended care (38%) with a need for continued rehabilitation services including physical therapy.


Post-encephalitis Presentations

- Inappropriate Behaviour & Poor Social Skills
- Loss of Taste and Smell
- Problems with Pain & Other Sensations
- Memory Problems
- Physical Difficulties
- Problems with New Learning
- Cognitive (thinking) Problems
- Emotional Problems
- Personality Changes
- Problems with Daily Living Skills
- Fatigue/Sleep Disturbance
- Epilepsy
- Hormone Problems
- Sexual Dysfunction
- Inability to Understand
- Loss of Taste and Smell

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Barbara Wilson describes the developments related to the rehabilitation of adults with non-progressive brain injury, referring also to people with dementia and children. This paper is an update of the article ‘Cutting edge developments in neuropsychological rehabilitation and possible future directions’, published in 2011. The present review describes some recent developments in assessment and treatment strategies, as well as studies looking at the effectiveness of rehabilitation. Wilson has chosen 10 topics corresponding to 10 areas of development and lists them in a reverse order of importance:

- compassion focused therapy (CFT) which may help to refocus emotional responses from self-critical to more positive ones. One simple CFT approach is to identify self-criticism and help people refocus on self-compassion and develop self-validation and acceptance through producing feelings of kindness and warmth.

- neurological music therapy with a neuroscience model in which music engages brain and behaviour functions. It has been used to improve gait, attention, memory and executive functions, and speech (through melodic intonation therapy [MIT]). It has also been used to reduce unilateral neglect, anxiety, depression, and hostility.

- virtual reality assessments whose ultimate goal is to make it possible for clients to become more able to participate in community life. Wilson concludes that it seems highly likely that VR assessments and treatment approaches will become the norm in neuropsychology and rehabilitation within the next decade.

- restitution of working memory (WM) deficits. There is good quality evidence in support of computerised WM training from several different studies, from different centres, and from different populations. There is also evidence of generalisation to other tasks or everyday behaviours.

- errorless learning (ER) for people with language deficits. The value of ER compared with EL (errorful learning) is discussed.

- problem-solving therapy for people with executive deficits which has a significant beneficial effect for people with executive deficits.

- support in the early stages of dementia. The value and importance of psychosocial (‘non-pharmacological’) interventions to help maintain or support functioning in early stage dementia is recognised.

- recognition of the need to evaluate rehabilitation in more appropriate ways-focusing on a single-case experimental design (SCED) as a way to assess the efficacy of NR as opposed to RCTs.

- SenseCam/Vicon revue by looking at the impact on people with memory difficulties’ lives as well as other potential applications.

- evidence for the effectiveness of holistic rehabilitation. Studies have looked at comprehensive-holistic rehabilitation, and the findings suggest that these programmes can improve community integration, functional independence, and productivity.

Wilson argues that unfortunately, many survivors of brain injury do not receive appropriate rehabilitation despite the fact that there is strong evidence for its benefits. One of the main goals of clinical neuropsychologists in the immediate future – in the author’s view is to persuade health-care purchasers that rehabilitation makes clinical and economic sense.


ED- SenseCam/Vicon is now called The Autographer. The Encephalitis Society offers a restricted number of bursaries each year to purchase cameras for people affected by Encephalitis who will benefit from them but who cannot afford them. If you would like more information please visit our website www.encephalitis.info
Recovery and Rehabilitation Books

Narrative Approaches to Brain Injury:
edited by Stephen Weatherhead and David Todd

This book brings together narrative approaches and brain injury rehabilitation, in a manner that fosters an understanding of the natural fit between the two. We live our lives by narratives and stories, and brain injury can affect those narratives at many levels, with far-reaching effects. Understanding held narratives is as important as understanding the functional profile of the injury. This book explores ways to create a space for personal stories to emerge and change, whilst balancing theory with practical application. Despite the emphasis of this book on the compatibility of narrative approaches to supporting people following brain injury, it also illustrates the potential for contributing to significant change in the current narratives of brain injury.

This book takes a philosophically different approach to many current neuro-rehabilitation topics, and has the potential to make a big impact. It also challenges the reader to question their own position, but does so in an engaging manner which makes it difficult to put down.

There is a thread to the internal narrative of the book as a whole. It begins with an exploration of narratives within brain injury broadly, then moves to considering professional interactions with those narratives. Once the context has been set, the authors move to look at focusing clinical work through goal-setting, and thinking about the issues clinicians or therapists might meet, such as trauma, communication difficulties, working with carers, families, and other forms of indirect work. It concludes with a chapter looking at the journey of our work through the process of gathering outcome evidence.

Life after Brain Injury:
Survivor’s Stories by Barbara Wilson, Jill Winegardner & Fiona Ashworth

This is the first book of its kind to include the personal accounts of people who have survived injury to the brain, along with professional therapists’ reports of their progress through rehabilitation. The paintings and stories of survivors combine with experts’ discussions of the theory and practice of brain injury rehabilitation to illustrate the ups and downs that survivors encounter in their journeys from pre-injury status to insult and post-injury rehabilitation.

Wilson, Winegardner and Ashworth’s focus on the survivors’ perspective shows how rehabilitation is an interactive process between people with brain injury, health care staff and others, and gives the survivors the chance to tell their own stories of life before their injury, the nature of the insult, their early treatment and subsequent rehabilitation. Presenting practical approaches to help survivors of brain injury achieve functionally relevant and meaningful goals, Life After Brain Injury: Survivors’ Stories will help all those working in rehabilitation understand the principles involved in holistic brain injury rehabilitation and how these principles, combined with theory and models, translate into clinical practice.

This book will be of great interest to anyone who wishes to extend their knowledge of the latest theories and practices involved in making life more manageable for people who have suffered damage to the brain. Life After Brain Injury: Survivors’ Stories will also be essential for clinical psychologists, neuropsychologists and anybody dealing with acquired brain injury whether they be a survivor of a brain injury themselves, a relative, a friend or a carer.
It started with a headache. Then within days, twenty-four-year-old New Yorker Susannah Cahalan was experiencing hallucinations, paranoia, seizures and violent psychosis. Was she mad?

This is the story of one woman’s descent into an insanity for which there seemed to be no cure. In her story, Brain on Fire, she pieces together the terrifying lost month of her life, asking what happens when your identity is suddenly destroyed – and how you get it back.

A gripping medical mystery with a unique personal voice, Brain on Fire is also the story of how one brilliant man, Syria-born Dr Najar, finally proved - using a simple pen and paper - that Susannah’s psychotic behaviour was caused by a rare autoimmune disease attacking her brain. His diagnosis of this little-known condition, anti-NMDA-receptor autoimmune encephalitis, saved her life and possibly the lives of many others. Susannah was only the 217th case ever to be diagnosed; now there are thousands.

Susannah Cahalan, a reporter on the New York Post and the recipient of the 2010 Silurian Award of Excellence in Journalism for Feature Writing, takes readers inside this newly-discovered disease through the progress of her own harrowing journey, piecing it together using memories, journals, hospital videos and records. Written with passionate honesty and intelligence, Brain on Fire is a searingly personal yet universal book.

Susannah Cahalan is Ambassador for The Encephalitis Society.

Dr. Ava Easton, The Encephalitis Society, shares her view of the book:

This is a remarkable book about a relatively newly identified type of Encephalitis called NMDA-receptor Encephalitis. Susannah survives not only this devastating condition but also not uncommon mid-diagnoses, and their potential for admission to psychiatric institutions. Susannah recovers well thanks to the astute observations and ongoing professional development of a doctor, one of many in a team trying to diagnose and manage this young woman spiralling into a world of madness and mayhem.

Susannah’s book is the first account (to my knowledge) of this type of Encephalitis. She successfully interweaves her own narrative with the observations of others and the expert and clinical explanations of her condition as would be expected of a journalist and writer of her calibre. This results in a book that makes us empathise with her experiences but also leaves us with an evidence-based education in relation to this condition.

The book is an absolute must-read not only for anyone affected, their families and friends but also for professionals working in, or with an interest in, neurology. Reading this book will undoubtedly save lives and prevent inappropriate admissions to psychiatric units of people whose condition is neurological and not psychiatric. The book does of course leave us wondering how many un-diagnosed NMDA-receptor Encephalitis patients remain in psychiatric institutions.
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Chair of Neurological Science  
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Support when you have needed 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 12 years, offering legal services and advice to its members and associates.

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- Education law
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If you or your loved ones need any form of legal advice or support, simply call us today on the number below and ask to speak directly to Tim Spring, Head of Clinical Negligence and Healthcare.

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