Advances in Encephalitis
Research Summary
2015
Welcome to The Encephalitis Society’s Research Summary 2015

The Advances in Encephalitis 2015 presents a summary of research papers published in 2015. Regardless of the gaps that are still in the existent knowledge about encephalitis, the vast number of research papers from 2015 means that the medical community are working hard to unravel the mysteries surrounding this condition. The researchers have looked beyond national borders and tried to bring to everyone’s attention (doctors and public health authorities) a broad range of new viruses, existent viruses expanding in new regions and rare presentations of already established types of encephalitis.

There is a growing interest in autoimmune encephalitis especially regarding the identification of new specific antibodies or phenotypes of known antigens, new treatment regimens and the effects of these treatments. There is also the discovery that herpes simplex encephalitis is a trigger of synaptic autoimmunity and some patients may develop overlapping syndromes. Although the clinical spectrum of encephalitis is fairly extensive, prompt recognition and treatment often leads to notable outcomes.

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.

The Encephalitis Society is happy to confirm that Liverpool University is the chosen host for our 2016 PhD Fellowship on recovery and rehabilitation after encephalitis. We look forward to reporting the findings of this research project in a future edition of this summary.

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
CEO The Encephalitis Society

Disclaimer
This review has tried to provide a succinct summary of the original papers. The full papers 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.
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Epidemiology of encephalitis

"Due to the increasing global spread of arboviruses, the geographic extent of virus co-circulation is expanding. This complicates the diagnosis of febrile conditions and can have direct effects on the epidemiology." (Nikolay, 2015)

New emergences

Chikungunya virus (CHIKV) is an Alphavirus transmitted by Aedes mosquitoes. The clinical presentation includes sudden onset of high fever, skin rash and joint pain with or without swelling. Recently, more severe manifestations with neurological involvement and death have been reported. No specific treatment is available. Vector control by community-based intervention and personal protective measures are the only ways of prevention. The 2005-2006 epidemic on La Réunion Island affected 300,000 people. Out of 57 patients diagnosed with CHIKV-associated CNS disease, 24 had CHIKV-associated encephalitis. The cohort included 21 adults and 36 infants. The clinical presentation and three-year outcome of CHIKV-associated encephalitis were more severe in adults than in infants, except for one neonate. Infants were left with behavioural changes and neurocognitive impairment, while in adults the outcomes referred to cortical functioning and led to disabling sequelae. The case-fatality rate of CHIKV-associated encephalitis was 16.6% (Gerardin et al., 2016). Van Den Bossche et al. (2015) report the importing of CHIKV and West Nile virus (WNV) into Belgium over a six-year period from 2007 to 2012. Out of 1,288 returning travellers who were investigated for CHIKV infection, four were confirmed and one was diagnosed with a probable infection.

Mansfield et al. (2015) review the epidemiology, diagnosis and vaccine development of the Rift Valley fever virus. This virus is a mosquito-borne virus of the genus Phlebovirus. Presently there is no human vaccine available. Only a limited range of veterinary vaccines in the endemic areas are available. The virus is endemic throughout Africa. The authors argue that the emergence of RVFV in the Middle East, northern Egypt and the Comoros Archipelago may pose significant warning signs of a virus spreading towards Europe. Therefore, the development of a human vaccine, alternative veterinary vaccines and effective public health measures are required.

There are no reports of outbreaks of disease caused by mosquito-borne viruses in the UK. But the spread of mosquito-borne viruses in Europe raised concerns about potential outbreaks within the UK. Mackenzie-Impoinvil et al. (2015) investigated the competence of a (temperate) British mosquito species, Ochlerotatus detritus [=Aedes detritus] (Diptera: Culicidae) for transmission of the Japanese encephalitis virus (JEV) as a model for mosquito-borne virus transmission. The study revealed that Ochlerotatus detritus was susceptible to laboratory infection with JEV at 23°C and 28°C, and virus was detectable in the saliva of some individuals as early as seven days post-infection. In conclusion, a British mosquito species, O. detritus, is a potential vector of an exotic Flavivirus.

Hoffmann et al. (2015) describe three cases of a variegated squirrel bornavirus associated with fatal human encephalitis. Clinical manifestations included fever, shivers, progressive psychomotor slowing, confusion, unsteady gait, myoclonus, ocular paresis and coma. All three patients also experienced bilateral crural-vein thrombosis, which led to pulmonary embolism in two patients. CSF tests revealed pleocytosis and magnetic resonance imaging (MRI) showed edematous lesions in the cerebrospinal fluid areas and basal ganglia or meninges that were increasing in size, a finding specific for a viral infection. No infectious agent could be detected while the patients were alive. Metagenomic sequencing approach that incorporated next-generation sequencing and real-time reverse-transcriptase quantitative polymerase chain reaction (RT-qPCR) revealed the presence of a previously unknown bornavirus in a contact squirrel and in brain samples from the patients. Phylogenetic analyses showed that this virus, named variegated squirrel 1 bornavirus (VSBV-1), forms a lineage separate from that of the known bornavirus species. The authors argue that the finding of this study support VSBV-1 as the likely causative agent of this fatal encephalitis.

Concurrent outbreaks have been reported in some countries with implications regarding misdiagnosis and incorrect case management, but also alteration of the epidemiology of the viruses. Venkat et al. (2015) report the first known concurrent outbreak of St. Louis encephalitis virus (SLEV) and West Nile virus (WNV) disease in Arizona in 2015 and argue that clinicians should consider both WNV and SLEV infections in the differential diagnosis of cases of aseptic meningitis and encephalitis. Nicolay (2015) undertook a systematic review to compare the geographic, host and vector ranges of WNV and Usutu virus (USUV) in Europe. The author shows that co-circulation of these two viruses happens not only regarding the geographic areas [ten countries reported the presence of both viruses] but also among host [34 common bird species belonging to 11 orders] and vector species [four mosquito species].

Sporadic cases or public health threat?

- West Nile virus (WNV) neuroinvasive disease was reported in Portugal in September 2015 (Zé-Zé et al., 2015)
• WNV IgM antibody was found in the serum of three patients and CSF of one patient in Sri Lanka [Lohitharajah et al., 2015]

• A human case of WNV encephalitis was reported in Brazil [Veire et al., 2015]

• St Louis encephalitis virus (SLEV) genotype IV was discovered in mosquitoes from a region in Colombia, implicating the risk of human disease due to SLEV infection [Hoyos-López et al., 2015]

• SLEV was also found in Mato Grosso, Brazil in three patients co-infected with dengue serotype 4 (DENV-4) [Heinen et al., 2015]

• A case of DENV-3 from the CSF of a male patient with encephalitis with atypical symptoms in Vietnam in 2013 is reported by Phu Ly et al. (2015)

• Two cases of fatal granulomatous amoebic encephalitis (GAE) in India are reported by Khurana et al. (2015)

• A case of fatal meningoencephalitis caused by B. mandrillaris in a woman from the Netherlands who had visited The Gambia is presented by Van der Beek et al. (2015)

• Acanthamoeba is found in nasal swabs of cancer patients in hospitals in Tehran, Iran [Memari et al., 2015]


West Nile virus (WNV) development

“Identifying WNV endemic as well as infection-free areas is becoming a need for the development of human vaccines and therapeutics and the application of blood and organs safety regulations.” [Rizzoli et al., 2015]

Kleinschmidt-DeMasters and Beckham (2015) provide an overview of WNV encephalitis, highlighting the spread of the illness westward in North America and into Canada and through countries among the European Union. The transmission happens mostly via a mosquito bite, but there are cases when the transmission occurs after organ transplantation of WNV-infected organs, blood transfusion from asymptomatic WNV-infected individuals or breast-feeding. While 80% of infections are asymptomatic, 20% of infected individuals present with an acute febrile flu-like illness (fever, headache, fatigue, anorexia, nausea, myalgia and lymphadenopathy) and a maculopapular rash on the trunk and limbs in 25% to 50% of cases. Less than 1% of infected individuals develop a neuroinvasive infection manifested as meningitis (30-40%), encephalitis (50-60%), acute flaccid paralysis (5-10%) or a combination of these clinical syndromes. Neuroinvasive illness is more common in elderly and immunocompromised patients. There is also an improved recognition of this illness in children. Twelve percent of the patients with neuroinvasive WNV disease have a fatal outcome. There is not a great understanding of the sequelae people are left with, but problems such as fatigue, weakness, depression, difficulty walking, ataxia and memory loss are reported.

Lindsey et al. (2015) report the surveillance data provided to Centre for Disease Control and Prevention (CDC) in 2014 for WNV and other notifiable Arboviruses, excluding dengue. They reported 2,205 cases of WNV disease, of which 61% were WNV neuroinvasive disease (e.g. meningitis, encephalitis, acute flaccid paralysis), for a national incidence of 0.42/100,000 population.

Rizzoli et al. (2015) summarise the current knowledge on WNV in Europe. The virus continues to spread and has been introduced in new areas with sporadic outbreaks of WNV central nervous system (CNS) infection. The challenges associated with WNV include the lack of safe vaccines and specific therapeutic treatments for humans, the high costs due to the need to guarantee the safety of blood transfusions and organ donation, the increased resistance to many commercial insecticidal products used to suppress mosquito populations and the different strains of WNV (up to seven different genetic lineages). Analyses of full genome sequence data have shown that the virus can adapt to new ecological niches through mutation and selection events.

Recent developments regarding the epidemiology, outcomes, and prognostic factors for acute encephalitis. Based on the US Nationwide Inpatient Sample (NIS), a nationally representative database of hospitalisations, the encephalitis hospitalisation rate is of approximately 7/100,000 which is similar to previous reported figures suggesting an occurrence of approximately 1.8/100,000. Aetiology is established agents.

The authors suggest the aged is known in approximately half of all the cases with viral encephalitis and more specifically herpes simplex encephalitis (HSE) being the most common cause followed by enteroviruses, West Nile virus (WNV) and varicella zoster virus (VZV). In the autoimmune encephalitis field, ongoing identification of newer autoantibodies is reported, more recently antibodies against the GABA_A receptor and the glycine receptor. An increase in acute flaccid paralysis (AFP) cases has been temporally linked to an outbreak of enterovirus-D68 respiratory infections throughout the United States, but a conclusive link between enterovirus-D68 and AFP is still yet to be proven. Mortality rates in encephalitis are between 5–15% and are associated with several potentially reversible conditions such as cerebral oedema, status epilepticus, and thrombocytopenia. Those who survive are left with substantial physical and cognitive sequelae. Poor outcomes in HSE have been associated with older age, altered level of consciousness at the time of initiation of therapy, and a delay of greater than two days between hospital admission and initiation of acyclovir. Delay in treatment and admission to intensive care unit (ICU) were markers for a poor prognosis in anti-NMDA receptor encephalitis patients. The author urges for robust global surveillance measures for both infectious and autoimmune causes to define and update encephalitis epidemiology following recent emergence of new syndromes and clinical phenotypes associated with established agents.
Pathogenesis of encephalitis

“More experimental and observational studies are important to do, not only to enhance our knowledge of basic pathogenetic mechanisms of disease, but also to provide the experimental background on which to devise novel therapeutic agents for these infections and other diseases.”(Kennedy, 2015)

Novel antibodies: how pathogenic are they?

The autoimmune encephalitis associated with antibodies to dipeptidyl-peptidase-like protein 6 (DPPX) was recently identified. There are 27 patients reported in the literature to date and half of them presented with gastrointestinal symptoms. Piegras et al. (2015) investigated the pathogenic effects of antibodies to DPPX, on gut and brain neurons. They used serum and purified immunoglobulin G (IgG) from a new patient with anti-DPPX encephalitis and serum of a previous patient with anti-DPPX encephalitis and analysed the effects on the activity of enteric neurons by voltage-sensitive dye imaging in guinea pig myenteric and human sub mucous plexus preparations. This study supports a pathogenic role of anti-DPPX antibodies in this novel form of autoimmune encephalitis.

Peng et al. (2015) investigated the mechanisms by which a patient’s anti-D-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR) encephalitis antibodies affect synapses and neurons leading to this type of autoimmune-mediated encephalitis. The authors revealed that patient antibodies caused a selective decrease in the total surface amount and synaptic localisation of GluA1- and GluA2-containing AMPARs, through increased internalisation and degradation of surface AMPAR clusters, but did not change the density of excitatory synapses, N-methyl-D-aspartate receptor (NMDAR) clusters, or cell viability. The authors investigated if commercially available AMPAR antibodies directed against extracellular epitopes have the same effect as the patient’s antibodies, but they discovered that they do not have the same effect, thus emphasising the specific effects of patient’s antibodies. The authors conclude that their findings demonstrate that antibodies from patients with anti-AMPAR encephalitis selectively eliminate surface and synaptic AMPARs, causing a homeostatic decrease in inhibitory synaptic transmission and increased intrinsic excitability, which may cause the memory deficits and epilepsy, significant features of this condition.

Fouka et al. (2015) investigated the pathogenicity of antibodies against Glutamic-acid-decarboxylase (GAD65). Their presence is associated with various disorders including stiff-person syndrome, cerebellar ataxia, encephalitis and epilepsy. This study tries to establish if distinct epitope specificities or other co-existing antibodies may account for each disorder. Twenty-seven patients were tested and irrespective of clinical phenotype, the epitope recognised by all the patients, corresponded to the catalytic core of GAD. No co-existent autoantibodies were found. The authors argue that no GAD specific epitope defines any neurological syndrome but other antibody specificities may account for certain phenotypes.


Apoptosis and neuroinflammation

Kennedy (2015) reviews the knowledge on apoptosis and its relation to neuroinflammation. Apoptosis is a biological process of programmed cell death which can be triggered by various stimuli. Some of them are represented by viruses such as herpes simplex virus (HSV), varicella-zoster virus (VZV), rabies virus, human immunodeficiency virus (HIV) and reovirus. Current understanding is that apoptosis is beneficial to the host mainly because the apoptotic cells are anti-inflammatory. Recent findings suggest that this role is wider, and comprises other effects such as resolution of inflammation, prevention of autoimmunity and induction of tissue repair.

The author discusses both mechanisms (apoptosis and neuroinflammation) in different pathological scenarios (HSV infection, VZV infection, HIV infection, human African trypanosomiasis-HAT). The effects of apoptosis on central nervous system (CNS) can vary and apoptosis can be seen as both beneficial and harmful depending on which perspective is considered: host or virus. Apoptosis is also linked to various neurodegenerative illness and psychiatric disorders such as Parkinson’s disease, HIV-associated dementia, multiple sclerosis and schizophrenia, but its role in the aetiology of these diseases hasn’t yet be proved. Furthermore, the role of inflammation in a neurological disease is reviewed. While historically, inflammation was considered a ‘bad’ thing (a host immune response to an insult or infection), recently, not all inflammation has been regarded as harmful. The controlled inflammation is now seen as necessary both for cell repair and to dampen down inflammatory responses. Further studies are needed to explain fully the role of apoptosis in the mechanisms of the disease and the relation between the apoptosis and neuroinflammation.

Infectious encephalitis

“The only unchanging finding is that high immunization rates are currently the most important factor in preventing this disease (SSPE).”
(Süter et al., 2015)

Relevance of imaging and electroencephalography (EEG) in diagnosing herpes simplex encephalitis (HSE)

Renard et al. (2015) investigated the relevance of diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) imaging performed within 60 days in diagnosing HSE in non-neonatal HSE patients. Eleven patients with HSE were included in the study. In nine patients with magnetic resonance imaging (MRI) performed within two weeks, DWI detected 11% more areas involved than FLAIR. The only brain substructure better visualised on FLAIR than on DWI was the thalamus. In patients with early MRI and equal number of involved brain areas on FLAIR and DWI, lesions were often better seen (especially in the brain cortex) on DWI than on FLAIR. In two patients with late MRI, FLAIR was superior to DWI with essentially white matter involvement. The authors argue that the importance of this study rely in the identification of typical lesion distribution and progression in HSE which helps differentiate it from other disorders that sometimes mimic HSE on MRI.

Sutter et al. (2015) look at the EEG characteristics of HSV encephalitis. They analyse clinical data and EEG recordings from the first week after admission to the intensive care units (ICU) of 76 patients with acute encephalitis. The patients were divided in two categories: HSV encephalitis and non-HSV encephalitis. Their findings revealed a higher proportion of periodic discharges (PDs) along with focal slowing in HSV encephalitis as compared to other aetiologies although clinical characteristics did not differ greatly. Furthermore, a normal EEG was significantly associated with survival, as a normal EEG was found in 18 survivors and in none who died.


Intracranial pressure (ICP) in herpes simplex encephalitis (HSE): what is the protocol?

Singhi et al. (2015) report a case of a seven-year-old boy with severe HSE and medically refractory intracranial hypertension who underwent decompressive craniectomy over the right temporal area on day five of hospitalisation. The authors emphasise the importance of recognising early signs of medically refractory intracranial hypertension, and timely medical and surgical intervention in children with HSE for improving outcomes and reducing fatalities.

Safain et al. (2015) present a 22-year-old woman with severe HSE requiring aggressive ICP management utilising all modalities (both medical and surgical) known to control ICP. At six-month follow-up the patient has made a good recovery: Performing a literature research, the authors note the limited data on the appropriate indications for IC monitoring and even less data on the appropriate medical as well as surgical management of intracranial hypertension in HSE. They argue that their case-report adds to the literature and provides evidence that aggressive combined medical and surgical therapy is necessary even in cases of severe HSE with transtentorial herniation, as there is evidence for the potential of good recovery.

Jouan et al. (2015) report three patients with a high ICP and brain herniation who eventually underwent decompressive craniectomy after a failure in administered medical treatments to decrease intracranial pressure. They noted that initial brain images were not predictive of the risk of brain herniation. No significant difference between the outcomes of these patients and the outcomes of the patients without ICP was noted.


Tick-Borne encephalitis (TBE) in children

“…in children presenting with a meningoencephalitis and bilateral thalamic involvement in the MRI, TBE should therefore be included in the differential diagnosis.”
(Von Stülpnagel et al., 2015)

Krbková et al. (2015) reviewed the clinical course and outcomes of TBE in 170 children. Tick bites were reported in 74% of the children within two months prior to the onset of illness. Multiple tick bites (up to 10) were reported by 34% of children. Three children (2%) had a history of drinking unpasteurized goat milk and the father of one of them was diagnosed with a TBE infection at the same time.
The illness had a biphasic clinical course in 58% of cases. The duration of the first phase of infection was between 2-14 days and manifested as an upper respiratory tract infection treated with antibiotics. Only three children were admitted to hospital and the cerebrospinal fluid (CSF) of two tested were negative for TBE virus (serum of both of them was positive in the second phase). The second phase was characterised by headache in 98%, high fever in 86%, vomiting in 64% and meningeal signs in 92% of the children. Neurological involvement was characterised as meningitis in 130 children (77%), encephalitis in 22 children (13%) and encephalitis in one child (1%). Children with meningoencephalitis were more often admitted to the intensive care unit (ICU).

Half of the children were left with temporary headache or fatigue. Cognitive problems were found in 11% of the children. At follow-up (6-12months) children presented with short-term memory difficulties (4%), speech impairment (1%), behavioural difficulties (2%) and visual abnormalities (1%); three children had more than one such disability. Substantial worsening of school grades was noted in 6% of the children.

Von Stülpnagel et al. (2016) reviewed the magnetic resonance imaging (MRI) findings and outcomes in 11 children and adolescents with TBE. MRI (within the first week after admission) showed symmetric or asymmetric T2-hyperintensities in both thalami in seven patients with additional bilateral lesions in putamen and/or caudate nucleus in three patients, and additional cortical lesions in two patients. One patient (the youngest) presented with T2-hyperintensities affecting the whole left cerebral hemisphere including white and grey matter and both cerebellar hemispheres. Four patients experienced complete recovery. Six children were left with neurological sequelae: hemiparesis (four), cognitive deficits (four) and intractable epilepsy (two patients). One patient died of a malignant brain oedema. Three patients had a normal MRI, which predicted favourable outcomes in two patients, but one developed pharmaco-resistant epilepsy. MRI showing bilateral thalamic involvement was associated with neurological sequelae or death in six patients, and only one, who had also received intravenous immunoglobulin, showed complete recovery. The authors conclude that TBE should be suspected in children with meningoencephalitis and bilateral thalamic involvement in the MRI.


Clinical relevance of anti-Japanese encephalitis virus (JEV) IgM and herpes virus (HV) deoxyribonucleic acid (DNA) in cerebrospinal fluid (CSF) of patients with encephalitis

Dubot-Péres et al. (2015) investigated if the presence of anti-JEV IgM antibody in CSF equals diagnosis of JE. One hundred and thirty-one patients with acute encephalitis syndromes or pure meningitis syndromes with biologically confirmed JEV were included in the study. Viral detection in CSF was observed in five patients and detection of anti-JEV IgM in CSF in 93 patients or just serum samples in 33. Of the 33 positive serum patients, 19 had also other pathogens detected which could alone be the cause of encephalitis. There was also the possibility that the clinical symptoms are caused by a duality of causes. These findings prompt the authors to suggest that the diagnosis of JEV infection by serology might be inaccurate in a substantial proportion of patients. They also argue that the incidence of acute neurological infections due to JEV might be overestimated and detection of anti-JEV IgM in patients with acute infections of the central nervous system (CNS) should not rule out other treatable diseases, particularly bacterial infections.


Human rabies

Rabies is a severe acute viral infection of the central nervous system (CNS) caused by all members of the Lyssavirus genus. Human rabies is a disease with almost 100% fatal outcome. The first human rabies survivor without benefit of prior vaccination was reported from Milwaukee in 2005. Caicedo et al. (2015) report a second unvaccinated patient who showed early recovery from rabies and then died accidentally during convalescence. The nine-year-old girl presented with rabies of vampire bat phylogeny transmitted by bat bite. The patient had initial clinical improvement on day 14 in hospital which was faster than the Milwaukee patient, but she died on day 76 of hospitalisation. Antibody response in serum and cerebrospinal fluid was robust and no rabies virus was cultured at autopsy. Rabies virus genome was present in neocortex but absent in brainstem. The authors conclude that the early recovery is linked to the detection of neutralising antibody and clearance of infectious (cultivable) rabies virus in the CNS by 76 days, but not clearance of detectable viral subcomponents such as nucleoprotein antigen or RNA in brain. Netravathi et al. (2015) describe a patient who is the first documented long-term rabies survivor with neurological sequelae and polymerase chain reaction (PCR) positivity even after four and half years of illness. The authors suggest that this finding may be an indication of an ongoing persistent or sub-acute infectious process.


Measles-induced encephalitis

Fisher et al. (2015) investigated the pathophysiology of measles infection and reviewed the presentation, diagnosis and treatment of the four types of measles-induced encephalitis: primary measles encephalitis, acute post-measles encephalitis, measles inclusion body encephalitis and subacute sclerosing panencephalitis (SSPE). The early symptoms of infection may be not specific and the diagnosis might be delayed. The 2012 guidelines on management of viral encephalitis may be able to assist with diagnosis and treatment. The incidence rates of measles-induced encephalitis vary between types from 1-3/1000 measles infections for primary measles encephalitis to 1/25,000 measles infections for SSPE.

In primary measles encephalitis the brain becomes infected during the rash phase of the infection. The measles virus RNA is detected in the cerebrospinal fluid (CSF). Acute post-measles encephalitis is caused by immune-mediated brain inflammation subsequent to measles infection. Sometimes an overlapping of the two types of encephalitis described above may occur. Measles inclusion body encephalitis mostly develops in immune-deficient children usually within one year of measles infection or vaccination. SSPE occurs mostly in children 6–15 years after measles infection. Clinical manifestations of SSPE include behavioural changes and cognitive decline, initially followed within weeks or months by motor dysfunction, seizures (often myoclonic in nature), ocular disturbances (necrotising retinitis in 50% of patients) and ultimately coma and death usually within three years after the onset.

Recently, due to a decline in public confidence in the MMR vaccine, the decrease of vaccination rates in the UK and Europe was notable. In 2013, outbreaks were reported in the North West of England (376 cases) and Swansea (644 cases). The authors draw attention to the risk of an increase in these cases of potentially fatal encephalitis in the developed countries such as the UK if an inadequate number of individuals are vaccinated.

A raise in the number of measles infection may see the incidence of SSPE change in the future. The incidence of SSPE in countries with routine immunisation programmes was considered to be 0.06-1/1,000,000. Guler et al. (2015) investigated the demographic and prognostic factors of 64 consecutive SSPE patients diagnosed at a tertiary centre in Turkey between June 2007 and June 2013. In this country, the incidence of SSPE is considered to be 2.2/1,000,000. There were 41 males (64.1%) and 23 females (35.9%). There was a history of consanguineous marriage in 27 (42.2%) patients. The time between the initial diagnosis and death (lifespan) was an average of 3.8 years. The average age of patients at the time of first symptoms was 8.5 years. The average duration between the time of first symptoms and diagnosis was 101 days. The average incubation period was 7.6 years. Fifty-nine patients received SSPE treatment protocol with isoprinosine and/or interferon and the remaining five patients received antiepileptic drugs. Thirty patients received alternative therapies in addition to the SSPE treatment protocol. There was no significant difference in lifespan between patients with different types of treatment. Diagnosis age, incubation period, and duration between the diagnosis and first symptom of SSPE were the most important factors that affected prognosis and lifespan. The authors conclude that the only most important thing in preventing this disease is high immunisation rates.

Kuşkonmaz et al. (2015) describe the first clinical trial of mesenchymal stem cells (MSCs) for the treatment of SSPE. Five children with clinically worsening SSPE received autologous infusions of MSCs. The cells were administered recurrently via intravenous and intrathecal routes, and the children were monitored clinically, radiographically and by laboratory studies. No acute adverse effects, including fever, rash, itching or infection, occurred during or after MSC application. One child died from respiratory problems five weeks after MSC infusion and before any follow-up visit. At follow-up, two patients remained in the same stage, one patient died from disease progression and respiratory problems three weeks after the second MSC infusion and one patient progressed to a stage III. Unfortunately, the MSC treatment did not have any clear benefits. Moreover, two children showed new inflammatory lesions on magnetic resonance imaging (MRI).


Rare presentations of viral encephalitis

Fok et al. (2005) present a case of encephalitis with human metapneumovirus pneumonia (HMPV) in a 47-year-old adult highlighting that clinicians need to be aware of the possibility of HMPV causing encephalitis in adults with preceding respiratory infection.

Luciani et al. (2015) present a paediatic case of acute disseminated encephalomyelitis (ADEM) associated with Madariaga virus (MADV) infection in Panama. The authors argue that MADV should be included in the aetologic differential diagnosis of ADEM in endemic countries.

Sánchez-Fauquier et al. (2015) report a case of a two-year-old girl with encephalitis associated with norovirus infection. The viral genome was detected in the cerebrospinal fluid (CSF) and stool by reverse transcription polymerase chain reaction.

Cui et al. (2015) investigated encephalitis cases among the patients presenting with severe fever with thrombocytopenia syndrome (SFTS), an infectious disease caused by a novel bunyavirus. They discovered that 19.1% of those patients had encephalitis, of which 44.7% had a fatal outcome.

Dereymaeker et al. (2015) report a case of a neonate patient with clinical and biochemical findings of transient central hypothyroidism associated with human Parechovirus type 3 (HPeV-3) encephalitis. The authors suggest that in this case an assessment of thyroid function is required to conclude whether a transient hypothyroidism may be triggered by viral meningencephalitis and if treatment may influence neurodevelopmental outcome.

Brown et al. (2015) report an 18-month-old boy who developed encephalopathy for which extensive investigation did not found a cause six weeks after stem cell transplant. RNA sequencing on brain biopsy identified astrovirus [AstV] of the VA1 and humanmink-ovine–like (HMO)-C subgroup as the likely causative agent in this case. The authors emphasize the utility of deep sequencing in a clinical setting to determine unexpected or novel pathogens.
Anderson et al. (2015) report a case of a 62-year-old woman with seizures and encephalitis. The patient’s CSF was positive for both herpes simplex virus 1 and 2 (HSV-1 and HSV-2).


Autoimmune encephalitis

"The absence on identification of a known antibody should not exclude the diagnosis of autoimmune encephalopathy or preclude initiation of treatment." (Lim et al., 2015)

Autoimmune encephalopathies: an overview

Leyboldt et al. (2015) present an overview of autoimmune encephalopathies and key features of twelve autoimmune encephalitis disorders. They include a novel encephalopathy with IgLON5 antibodies whose clinical syndrome develops over years and manifests with abnormal sleep movements and behaviours. The common features that distinguish autoimmune encephalopathies from classical paraneoplastic syndromes are: affect all ages; present with or without a tumour; are associated with antibodies that target extracellular epitopes of cell-surface or synaptic proteins and alter the structure of function of the target antigen; often respond to immunotherapy resulting in good recovery. Prodromal symptoms of autoimmune encephalitis often mimic infectious or bacterial encephalitis. The development of further symptoms such as alteration of mood, behaviour and memory, decreased level of consciousness and seizures are common for most types of autoimmune encephalitis. These symptoms' characteristics together with other further manifestations (psychiatric and movement disorders), tumour screening and magnetic resonance imaging (MRI) findings suggest specific types of autoimmune encephalitis. These symptoms' characteristics together with other further manifestations (psychiatric and movement disorders), tumour screening and magnetic resonance imaging (MRI) findings suggest specific types of autoimmune encephalitis.

Lim et al. (2015) present an overview of autoimmune encephalopathies in children looking at clinical and paraclinical features, antibody detection methods, diagnosis and treatment strategies and specific antibody-mediated syndromes. The authors draw attention to the fact that some clinical manifestations overlap between children with different antibodies and children with the same antibodies can present differently. The authors argue that the specific and most appropriate antibody detection methods are currently the cell-based assays (CBAs) which permit optimal detection of antibodies binding extracellular epitopes of the neuronal surface antigens in a way that would occur when antigen is exposed to circulating antibodies. Clinicians should have a good understanding of the assays used and communicate with the clinical laboratory in order to interpret accurately these tests. The authors propose a clinical algorithm to help clinicians decide empirical immunotherapy initiation if an autoimmune cause is suspected. The absence of a known antibody alone should not exclude the diagnosis of an autoimmune encephalopathy or starting the treatment.

Dubey et al. (2015) undertook a study of 64 patients with autoimmune encephalopathy. Sixteen patients had antibodies against NMDA-receptor (mostly less than 40 years of age), nine against voltage-gated potassium channel complex antigens (VGKCc) (mostly between 40 and 60 years of age), six against Glutamic Acid Decarboxylase-65 (GAD-65), three against GABA_A receptor and one had anti-Hu antibody. Nine patients had thyroperoxidase (TPO) as the only serological marker. In 20 patients no encephalitis-related antibody was identified. Eight of the 12 paediatric patients had anti-NMDA receptor antibodies. The symptomatology was associated with the type of encephalitis related antibody. A tumour (breast, ovarian, prostate, lung, pancreas, testicular, thyroid, thymoma and lymphoma) was detected in 12 patients. Forty-four patients had seizures. The most common initial symptoms among NMDA-receptor antibody (43.7%) and VGKCc antibody (44.4%) groups were behavioural changes. The majority of patients in the anti-GAD antibody group developed movement disorder (66.7%) and speech changes (50%). Autonomic dysfunction was more common for patients with anti-NMDA receptor antibodies. Fifty-nine patients had immunomodulatory therapy. More than a half of patients showed clinical improvement at follow-up. Early diagnosis and immunotherapy were associated with clinical improvement.


Antibodies against the potassium channel-related protein complex: diagnosis and treatment algorithm

Montijo et al. (2015) review the syndromes associated with antibodies against voltage-gated potassium channels (VGKC) related protein complex and the main antigens, the protein LGI1 and Caspr2. Anti-LGI1 antibodies occur in classic limbic encephalitis (LE) with short-term memory loss and epileptic seizures. It is more common in men over 60 years of age. Cerebrospinal fluid (CSF) is usually normal, but some patients present with moderate lymphocytosis and increased protein levels. In 84% of the patients, magnetic resonance imaging (MRI) shows unilateral or bilateral increase in signal intensity in the medial temporal region. Tumours are very rarely found, and are often thymomas. Most of the patients (70%-80%) respond to treatment with steroids, intravenous immunoglobulins (IVG) or plasma exchange. Patients are often left with memory deficits. Relapses are rare. Patients with anti-Caspr2 antibodies present with encephalitis,
Electroencephalographic (EEG) changes in anti-NMDA receptor encephalitis

Veciana et al. (2015) investigated the EEG activity in 15 anti-NMDA receptor encephalitis patients. Nine patients experienced seizures and five patients had status epilepticus (SE). EEG was abnormal in the acute phase in 14 patients (93.3%). Extreme delta brush (EDB) was noted in five (33.3%) patients, all with SE. None of the patients without SE exhibited EDB pattern. The other nine patients presented with rhythmic delta activity (five) and excessive beta activity (four). Wang et al. (2015) report two cases of anti-NMDA receptor encephalitis who were first misdiagnosed as having herpes simplex encephalitis (HSE) and psychosis and in which the EDB pattern of beta bursting on the peaks and/or the troughs of delta waves led to subsequent NMDA receptor antibody testing and the confirmative diagnosis. They argue that EDB correlated to other clinical signs of anti-NMDA receptor encephalitis could be indicators for prompt immunotherapy prior to antibody testing.

Nosadini et al. (2015) report the EEG activity in five paediatric cases with anti-NMDA receptor encephalitis. They identified four stages of the disease course related to EEG activity: early phase characterised by the presence of intermixed slow waves predominant on the anterior regions of the scalp; florid stage when electric cerebral activity markedly deteriorates giving way to a peculiar rhythmic theta-delta activity unreactive to stimuli and unrelated to clinical changes; recovery phase when the rhythmic activity gradually disappears in the electroencephalographic along with the gradual reappearance of a physiologic posterior activity, even before a clinical turning point is obvious; and finally, normalisation of electric cerebral activity. The authors recognise the importance of identifying these characteristic longitudinal electroencephalographic patterns in order to provide an early diagnosis and treatment.

Nilsson and Blaabjerg (2015) draw attention to a neurocardiac prodrome in anti-LGI1 encephalitis by reporting a case of anti-LGI1 encephalitis. The authors argue that anti-LGI1 encephalitis should be considered in a patient with severe episodic bradycardia followed by personality or cognitive change, especially in combination with hypotenremia.


New antibody targets: Ma2, AMPAR, GABAα, and GABAβ

Mrabet et al. (2015) report a case of anti-Ma2-encephalitis in a two-year-old child (the youngest case reported in the literature) who presented with refractory focal seizures associated with fever, followed by behavioural changes, speech disturbances and confusional episodes. Magnetic resonance imaging (MRI) showed left temporo-parietal brain involvement. Serum and CSF analysis showed a highly sensitive anti-Ma2 antibodies levels in both serum and CSF (with a higher CSF level) which led to the diagnosis of anti-Ma2 encephalitis. No tumour was found, but given the high risk for malignancy in these patients, a further tumour screening programme was initiated. The authors report a review of published cases of anti-Ma2 encephalitis and argue that their case is unique as this rare condition has mainly been reported in adult men with testicular germ cell tumour, non-small cell lung cancer or breast cancer.

Höftberger et al. (2015) report a case series of 22 newly identified patients with antibodies to the D-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) focusing on clinical features, comorbidities and outcome. Tumours were found in 14 patients (six lung, four thymoma, two breast, two ovarian teratoma). Twelve patients presented with neurological symptoms before tumour diagnosis. In two patients a tumour was identified before the development of encephalitis. Twelve patients displayed symptoms of limbic encephalitis (LE). Eight patients presented with limbic dysfunction along with multifocal/diffuse encephalopathy. The other two patients presented one with LE preceded by motor deficits, and one with psychosis with bipolar features. Seven patients had other neuronal antibodies, six of them with an associated tumour or cancer. They presented with symptoms or tumours that reflected the concurrent autoimmunity.
did not show subunit specificity. Clinical features of 15 representative patients (six with α1, five with γ2 and four with undefined subunit specificity) included seizures (7), memory impairment (7) with confusion or disorientation (4), or psychiatric features (5) with hallucinations (2) or anxiety (4). History of a tumour was present in one patient. One patient with severe catatonia improved greatly after treatment with plasma exchange. Most patients did not receive immunotherapies. The authors argue that this study suggests an association of a potentially pathogenic antibody with clinical characteristics less typical for autoimmune encephalitis.


**Treatment of anti-NMDA receptor encephalitis - evaluation of therapeutic plasma exchange (TPE), symptomatic treatment and intrathecal treatment**

American Society for Apheresis (ASFA) considers that there is not enough data to support TPE for routine use in anti-NMDA receptor antibody encephalitis. DeSena et al. (2015) investigated the use of TPE versus intravenous methylprednisolone in the treatment of anti-NMDA receptor encephalitis. Fourteen patients were included in the study: three adults and eleven children. Ten patients received both steroids and TPE during the same hospitalisation: seven reported an improvement after TPE with the modified Rankin score and three patients after steroids. The conclusion is TPE after steroids might be more effective than corticosteroids alone in the early stages of anti-NMDA receptor antibody encephalitis. The authors acknowledge that the results are preliminary and further studies are needed.


**Clinical relevance of the presence of antibodies**

Rossi et al. (2015) undertook an investigation into neuronal antibodies in patients with suspected prion disease and found that patients with confirmed sporadic Creutzfeldt-Jakob disease (sCJD) develop serum neuronal antibodies very rarely and only at low titres. The role of these antibodies is not yet clear. In their study, three patients with suspected sCJD had a clinical picture of autoimmune encephalitis and very high VGKC-complex/LGI1 antibodies. The authors argue that it is important to consider autoimmune encephalitis in the differential diagnosis of CJD and to test for the relevant antibodies especially VGKC-complex antibody.

Huda et al. (2015) investigated the clinical relevance of the presence of VGKC-complex antibodies. Fifty-seven out of 1,298 [4%] patients tested for VGKC antibodies were positive for these antibodies with titres >100pM. Patients with titres >400 pM were considered to have a classic VGKC-complex channelopathy. LG1 or Caspr2 antibodies subtypes were only found in patients with classic VGKC complex channelopathy. Patients with titres <400
pM were diagnosed with peripheral nerve hyperexcitability (PNH) and other central and/or peripheral nervous system disorders. The rate of malignancy in patients with antibody anti-VGKC (irrespective of titre) was significantly higher than the national incidence. The authors conclude that clinical phenotyping and antibody titres >400 pM can help determine VGKC-complex antibody relevance.

Hacohen et al. (2015) also investigated the clinical relevance of VGKC–complex antibodies in children. Three hundred and sixty-three children were classified as having an inflammatory condition (159) or non-inflammatory condition (204). Out of all children, 39 sera were found positive >100pM. Thirty children had inflammatory conditions and nine children non-inflammatory. Twelve titres >400pM were found among the inflammatory group. In four patients, antibodies were binding to the surface of the neurons [three were positive for specific antigens]. The findings of the study suggest that VGKC- abs can be a non-specific biomarker for neuronal inflammation but cannot indicate a specific clinical syndrome in children. Some of the antibodies may bind to intracellular epitopes on the VGKC subunits, or to the intracellular interacting proteins, but in many the targets remain undefined.

Zandi et al. (2015) investigated the clinical relevance of the NMDAR–abs positive test by looking at a case series of 56 positive or low positive patients. According to their clinical data and response to immunotherapies, the patients were divided in four categories: definite paraneoplastic (9), definite non-paraneoplastic (16), possible (18) and unlikely autoimmune (13). The authors also looked and recorded the number of their core features (encephalopathy, psychiatric, cognitive, epileptic, extrapyramidal and inflammatory cerebrospinal fluid). Positive NMDAR-abs were found mostly in definite types (72%), but also in 28% of possible and 15% of unlikely cases. Low positive was also found in definite cases. In a few cases of definite and possible the antibody level rose to positive levels during the disease course. The authors did not find any specific characteristics to distinguish low positive or positive patients who may respond to immunotherapies. But based on their findings, the authors suggest that immunotherapies could be considered for those with three or more of the core clinical features, including an abnormal cerebrospinal fluid (CSF). They conclude that clinical assessment is essential in management of NMDAR–abs mediated disorders irrespective of the antibody detection.

Gresa-Arribas et al. (2015) enquired why some patients with GAD-abs develop one neurological syndrome versus another and if these patients have distinct underlying immune responses. They examined the serum and CSF of 106 patients with anti-GAD related syndromes. 100% of serum samples had GAD65-ab and 88% of serum samples had GAD67-ab. All CSF samples were positive for both GAD65-ab and GAD67-ab. Nine paired serum-CSF samples had serum negative and CSF positive for GAD67-ab. This data shows that the immune response against GAD is different in CSF and serum, being more widespread in CSF. The authors did not find any association between clinical phenotype and the presence of antibodies against other proteins in the inhibitory synopsis. The study also revealed that GAD-ab are not internalised in live neurons, so their direct pathogenicity is questioned.

Venkatesan et al. (2015) review the emerging concepts in brain immunity especially the link between infection and autoimmune encephalitis. Looking at the pathogenesis of anti-NMDA receptor encephalitis non-tumour cases, the authors discuss the arguments for the infectious link theories: prodromal symptoms, cerebrospinal fluid [CSF] findings (pleocytosis early in the disease course rather than later, and the presence of oligoclonal bands later in the course of the disease rather than the onset of the disease) and coincidence of several infectious aetiologies reported in some cases. The authors note that NMDA receptor antibodies generated following herpes simplex encephalitis [HSE] may differ from antibodies in classic anti-NMDA receptor encephalitis. HSE may trigger central nervous system [CNS] autoimmunity and subsequently anti-NMDA receptor encephalitis, but in order to better understand and define this association and perhaps identify new infection-associated autoimmune encephalitides, careful clinical phenotyping together with broad screening for antibody and cell-mediated autoimmunity are necessary.

Armanie et al. (2015) report 14 patients with immune-mediated relapsing symptoms post-HSE. All patients had repeat CSF polymerase chain reaction [PCR] for HSV which was negative. Patients were divided in two groups: children group (6) and adult/teenagers group (8). The clinical manifestations of the children group included a classical syndrome of choreoathetosis post-HSE in association with IgG antibodies against the GluN1 subunit of the NMDA receptor and one of them also had antibodies against the GABA_A receptor.

In the teenage and adult group, clinical manifestations mimicked a viral relapse in three patients [managed with acyclovir in the first instance] and a recrudescence of residual viral-related deficits in the other [managed with antipsychotics and antidepressants]. None of these patients developed choreoathetosis. Seven patients presented with acute or subacute change of behaviour, agitation, aggression, suicidal ideation, confusion, or delusional thoughts, and one patient with refractory seizures and status epilepticus requiring mechanical ventilation and barbiturate coma. Five patients had IgG antibodies against the GluN1 subunit of the NMDA (all 5 in CSF, 2 also in serum) and three patients had antibodies against unknown neuronal antigens. Comparing these two groups, the main clinical manifestations are different in adults/teenagers from those in young children. The authors argue that careful consideration should be given to patients with HSE followed by any symptom relapse, worsening of deficits, or development of behavioural-psychiatric alterations with or without choreoathetosis or abnormal movements. Determination of CSF and serum neuronal cell surface antibodies should...
be considered. While waiting for results and if the CSF PCR for HSV is negative, empirical immunotherapy should be initiated.

Ellul et al. (2016) report an unusual association between HSV encephalitis and anti-NMDA receptor antibodies. Their patient, a three-year-old boy with anti-NMDA receptor encephalitis, did not have typical features of severe HSV encephalitis during his initial illness, four weeks before the autoimmune presentation. Lumbar puncture (LP) was not performed on initial illness and CSF PCS was negative for HSV virus during his autoimmune illness. PCR of the parenchyma of the temporal lobe lesion was positive for HSV type 1, 25 days from the onset of the illness and there was histological evidence within some of the neurons. The authors argue that this case brings evidence for a preceding subtle HSV type 1 infection in some patients with anti-NMDA receptor encephalitis which may be the trigger for the immune response.

Bamford et al. (2015) describe a paediatric case of post HSE NMDA-receptor-antibody-associated relapse presented with severe encephalopathy and movement disorder. Early recognition of clinical features of this entity allowed for rapid autantibody testing and swift immunotherapy initiation. This resulted in an amelioration of the severe neurological symptoms creating potential for neurorehabilitation. The authors suggest a therapeutic strategy for patients presenting possible NMDA receptor encephalitis after HSE which include: excluding HSV replication using CSF plus or minus blood HSV PCR; postponing therapies with an established risk of HSV reactivation after treatment with immunoglobulin (IVIG) or plasmapheresis; administering antiviral therapy in patients undergoing immunotherapy; regular surveillance for HSV reactivation using blood/CSF PCR.

Bradshaw et al. (2015) present a case of HSE associated with VGKC antibody. After a prodromal phase with an upper respiratory tract infection, a 33-year-old woman developed fever, headache, meningismus, word finding difficulty, and confusion followed by a tonic-clonic seizure. After an initial improvement she developed right superior temporal quadrant anopia with right lateral rectus palsy. IV dexamethasone was initiated without any improvement. N-type VGKC autoantibody were found in serum. IVIG was initiated and the patient improved significantly. The authors conclude that an autoimmune aetiology should be considered early in the differential diagnosis of encephalitis if the patient does not respond to anti-viral therapy or his condition aggravates.


Acute disseminated encephalomyelitis (ADEM): an overview and open questions

Steiner and Kennedy (2015) present an outline of the current understanding of acute disseminated encephalomyelitis. ADEM usually affects children and young adults, but can also occur in older age. ADEM has diagnosis guidelines for the children group, but none for the adult group. These guidelines highlight that ADEM is a diagnosis of exclusion. Clinical syndrome is broad and includes multiple symptoms. Initially, patients present with malaise, headache, nausea, vomiting, and fever. These symptoms are followed rapidly by neurological manifestations: depressed consciousness, long tract signs, ataxia, signs of meningeal irritation, spinal cord abnormalities, visual defects, speech impairment, cerebellar disturbances, and seizures. Behavioural abnormalities, dystonia, and other movement disorders are also reported. The authors note that a subtle disease with a nonspecific irritability and headache can also be possible. Magnetic resonance imaging (MRI) is an important tool in the diagnosis of ADEM. T2-weighted and fluid-attenuated inversion recovery can best reveal the specific lesions. White matter lesions are typically multiple and asymmetrical and grey matter lesions tend to be symmetrical and often involve the thalamus and the basal ganglia. Spinal cord abnormalities on MRI: swollen and enhancing intramedullary lesions are also reported. The authors emphasise that although the lesions’ characteristics are very important in the differential diagnosis of ADEM, they do not correlate with the prognosis. ADEM is usually a monophasic illness, but recurrences have been reported. These can take two clinical courses: multiphasic, when the clinical presentations represent different brain loci involvement in each relapse and when recurrences have a tendency for the same site to be affected.

Although the distinction between ADEM, multiple sclerosis (MS) and neuromyelitis optica (NMO) is difficult to make and sometimes impossible, this is essential as these conditions have different therapies and prognosis. The long-term prognosis is usually good with full recovery happening in 1 - 6 months post-disease. Nevertheless, some patients are left with sequelae such as motor difficulties, visual problems, seizures, attention deficits, executive functions difficulties and behavioural abnormalities. The authors conclude by emphasising the need for a more appropriate understanding of this condition to enable a consensus regarding all of its aspects from epidemiology, pathology, diagnosis, treatment and prognosis. Further research is needed and the authors finalise their paper with some key questions that need to be answered.

Encephalitis in pregnancy and postpartum

“Young women with an acute onset of severe atypical psychiatric symptoms should be tested for anti-NMDA receptor encephalitis, particularly when they exhibit neurological symptoms.” (Bergink et al., 2015)

Herpes simplex virus (HSV) encephalitis in pregnancy

Dodd et al. (2015) report a 37-year-old woman, 33 weeks pregnant, who presented with seizures due to proven HSV-1 encephalitis. The patient in this case study had a history of probable viral encephalitis when she was 14. The patient had a healthy baby after an elective caesarean section at 39 weeks. At six months follow-up both mother and baby were doing well. A literature research on HSVE in pregnancy (17 patients) revealed that the majority of cases occurred in the later stages of pregnancy, with 11 in the third trimester, six in the second trimester and only one in the first trimester. The authors compared the clinical presentations and outcomes of the group of pregnant women with HSVE with a group of non-pregnant patients with HSV encephalitis and discovered that the two groups are very similar. The authors argue that although there are no specific guidelines for management of viral encephalitis in pregnancy, there is evidence that acyclovir is safe in pregnancy and not related to an increase in birth defects. If seizures are present, the lowest effective dose of anti-epileptic drugs is preferable, while avoiding polytherapy and particularly potentially teratogenic drugs.


Anti-NMDA receptor encephalitis in pregnancy and postpartum

Mathis et al. (2015) present a typical case of anti-NMDA receptor encephalitis in a 21-year-old woman who was ten weeks pregnant. The baby was delivered healthy and did not have any neurological presentations at six months follow-up. They conclude that behavioural changes in pregnant women should be a question mark for clinicians. Children whose mothers had anti-NMDA-receptor antibodies while pregnant should be followed up on long-term to shed some more light on the question of a transplantal transfer of NMDA receptor antibodies from mother to child. The same conclusion about the need to assess long-term neuropsychiatric outcomes of children exposed to NMDA receptor antibodies in utero results from Lamale-Smith et al. (2015) study of a case of anti-NMDA receptor encephalitis in a pregnant woman who did not respond to immunomodulatory therapy, but recovered well after delivery and oophorectomy. Antibody titers were positive in cord blood, but the baby was doing well at one year follow-up.

Koksal et al. (2015) report a 29-year-old woman who developed anti-NMDA receptor encephalitis three months after a normal delivery. She presented with insomnia, agitation, irritability and fear of death and went on to develop delusions, hallucinations and psychomotor excitement. Suspected of having postpartum psychosis and then neuroleptic malignant syndrome (NMS), she was treated both in psychiatric and neurological clinics. After having had a generalised seizures and continue hallucinations and delusions, she was further investigated. Anti-NMDA receptor antibody was negative in serum, but it was positive in CSF and she was diagnosed with anti-NMDA receptor encephalitis. Abdominal ultrasound examination and MRI revealed a right ovarian cystic teratoma. Treatment with intravenous immunoglobulin (IVIG) and methylprednisolone showed no improvement. After a successful laparoscopic ovarian tumour removal her condition improved and at six months follow-up she only presented behavioural difficulties. The authors conclude that anti-NMDA receptor encephalitis should be considered in the differential diagnosis of postpartum psychosis. Commenting on the results of this study, Caroff and Campbell (2015) bring into attention the increased risk of patients with encephalitis developing NMS as a complication of treatment with neuroleptics for delirium, agitation or psychosis, rather than this being a misdiagnosis or a diagnosis to exclude.

In order to raise awareness about the differential diagnosis of postpartum psychosis, Bergink et al. (2015) undertook a three step immunohistochemistry-based screening for central nervous system (CNS) autoantibodies in a cohort of patients with postpartum psychosis and matched postpartum comparison subjects. Of 96 patients with postpartum psychosis, two were found to have anti-NMDA-receptor encephalitis antibodies in serum and two unknown neuronal surface antibodies. They conclude that young women with an acute onset of severe atypical psychiatric symptoms should be tested for anti-NMDA receptor encephalitis, particularly when they exhibit neurological symptoms, including extrapyramidal side effects of low-dose antipsychotic treatment.


Seizures and encephalitis

"Children with encephalitis have a high rate of post-encephalitic epilepsy and children who present with seizures in the acute phase have a risk of developing refractory status epilepticus." [Lin et al., 2015]

Antiepileptic drugs (AEDs) in paediatric patients with encephalitis

Lin et al. [2015] investigated the effect of AEDs in paediatric patients with acute seizures due to encephalitis and epilepsy. The study included 1,038 patients diagnosed with acute encephalitis. Four hundred and sixty-three patients had seizures in the acute phase. The frequency of seizures was classified into single seizure (83), repetitive seizures (227), status epilepticus (100) and refractory status epilepticus (53).

Fifty-three out of 83 patients with single seizure did not receive any AEDs and the rest were controlled with diazepam or lorazepam. Out of 147 patients with repetitive seizures who received AEDs, 17 were controlled with diazepam or lorazepam and 130 with the second-line AEDs. Phenytoin was administered to 61 patients and phenobarbital was administered in 51 patients, which resulted in the cessation of clinical seizures in 75.4% and 94.1% of patients, respectively. The patients with status epilepticus and refractory status epilepticus were treated firstly with diazepam or lorazepam, followed by intravenous antiepileptic drugs. Phenytoin was administered to 104 patients and phenobarbital in 49 patients, which resulted in the cessation of clinical seizures in 47.1% and 51% of the patients, respectively.

Thirty-three children died. Mortality was related to poor control of status epilepticus. Of all those discharged (867 patients), 26% developed post-encephalitic epilepsy. At one year follow-up, 18.3% of them were seizure-free and 78.7% were receiving AEDs. The authors argue that phenobarbital appears to be a suitable second-line antiepileptic drug for seizures in paediatric encephalitis. Also, high-dose topiramate combined with intravenous high-dose phenobarbital or high-dose lidocaine may be considered as an alternative third-line treatment for refractory status epilepticus. The authors emphasize that children with encephalitis have a high rate of post-encephalitic epilepsy and children who present with seizures in the acute phase have a risk of developing refractory status epilepticus.


Risk factors in developing post-encephalitis epilepsy after childhood encephalitis

Rismanchi et al. [2015] reviewed 99 paediatric patients with suspected encephalitis enrolled in California Encephalitis Project aiming to determine the factors associated with the development of epilepsy after resolution of presumed childhood encephalitis. Twenty-four patients developed epilepsy. Post-encephalitis epilepsy was associated with seizures at presentation, an abnormal electroencephalography (EEG) and a longer hospital stay. Each additional antiepileptic drug used to control seizures increased the risk of developing epilepsy. A medically induced coma was a marker of post-encephalitis epilepsy. Seizures in those patients were particularly refractory, often requiring longer than 24 hours to obtain seizure control. After discharge, epilepsy development was more likely in patients discharged on antiepileptic drugs or readmitted after their acute illness.

Pillai et al. [2016] investigated the risk factors for developing post-encephalitic epilepsy (PE) and drug-resistant epilepsy (DRE) in childhood following infectious and autoimmune encephalitis. The study included 164 children with acute encephalitis. They defined PE as the use of antiepileptic drugs (AEDs) for 24 months and more, and DRE as the persistence of seizures despite two or more appropriate AEDs at final follow-up.

The most popular causes of encephalitis included acute disseminated encephalomyelitis (ADEM) in 35 children, enterovirus (EV) in 20 children, M. pneumoniae in 11 children, anti-NMDA receptor encephalitis in ten and herpes simplex virus (HSV) in nine. There were 46 patients (28%) without an identified aetiology. Fifty-four percent of children had seizures during the acute encephalitis illness, and 85% of these patients received AEDs during hospitalisation. Status epilepticus occurred in 17% of the total cohort, and admission to the intensive care unit (ICU) in 40%.

Only 147 patients were available at follow-up. Thirty-one patients presented with PE, 21 of these patients still required AEDs at final follow-up (median 7.3 years) and two patients died: one of recurrent refractory status epilepticus, and the other of possible sudden unexplained death in epilepsy (SUDEP). Fifteen patients were diagnosed with DRE with 12 presenting with seizures during the acute illness and three patients developing epilepsy 3–6 years after encephalitis. The authors identified that status epilepticus, visual disturbance, focal seizures, magnetic resonance imaging (MRI) hippocampal/amygdala involvement, intensive care unit (ICU) admission, use of more than three AEDs, MRI gadolinium enhancement, seizures and EEG epileptiform discharges were associated with development of DRE. The clinical and radiologic predictors for PE closely resembled those for DRE. DRE was common in HSV (33%) and unknown encephalitis (20%), but absent in ADEM.
EV and anti-NMDA receptor encephalitis.


**Post-encephalitis epilepsy (PE) in adult patients**

Singh et al. (2015) studied a large cohort of adult patients with acute encephalitis presenting at the Mayo Clinic between January 2000 and December 2012 aiming to evaluate aetiologies, clinical presentations, outcomes and risk factors for PE. One hundred and ninety-eight patients were enrolled in the study. Median age was 58 years. 48% of patients had a viral cause, 22% autoimmune and 30% unknown/other. During the acute illness 54.5% patients with autoimmune encephalitis, 24.2% of the viral and 33.9% of unknown/other developed seizures. In total, 33.8% of all the patients developed seizures during the acute illness.

EEG showed interictal epileptiform discharges in 54% of the patients with seizures, periodic lateralized epileptiform discharges (PLEDs) in 41.2% and generalized periodic discharges (GPDs) in 5.9% patients. On MRI, 70.8% patients with seizures had fluid-attenuated inversion recovery (FLAIR)/T2 abnormalities, 31.3% diffusion abnormalities and 66.2% cortical involvement.

At discharge, 34.8% of viral encephalitis seizures patients had a good outcome, compared with 45.5% autoimmune encephalitis seizures patients and 60% unknown/other encephalitis seizures patients. Forty-three of all the patients developed PE. At follow-up 28 patients were on one antiepileptic drugs (AEDs), eight on two and three on three AEDs. Four patients stopped taking AEDs after a median time of 37 months. PE did not have a negative impact on the rate of good outcome at one year (70.7% of patients without PE vs. 87.7 % of patients with PE). The risk factors for developing PE were generalised seizures during hospitalisation, focal seizures and the presence of FLAIR/T2 abnormalities on MRI.

Diagnosis, treatment and outcomes of encephalitis

“There is now growing recognition that patients with idiopathic encephalitis may have treatable conditions if rapidly and accurately diagnosed” (Schubert and Wilson, 2015)

The future of diagnosing encephalitis: next-generation sequencing (NGS)

Schubert and Wilson (2015) reviewed the metagenomics and proteomics-based approaches applied to the diagnosis in idiopathic encephalitis. Next-generation sequencing (NGS) has enabled the application of metagenomics to the discovery of pathogens in infectious encephalitis cases which could have an enormous impact on the diagnostic and treatment management and public health monitoring. The traditional diagnostic methods are based on a candidate-based approach in which each individual diagnostic test is tailored to a particular infection suspected by the clinician after an appraisal of a patient’s medical history, risk factors and physical examination. The NGS has the advantage of identifying a new microbe for which a traditional candidate based test does not exist, a known microbe that is not known to cause a particular patient’s disease phenotype and a microbe known to cause a patient’s disease phenotype that is nevertheless rarely tested because of his low probability of being the aetiologic agent. These techniques are also low-cost and can process data in a very short time frame. The disadvantage of an NGS-based approach is the ability to amplify up all the genetic information in the sample such as skin contaminants and contaminants from lab reagents, will be also amplified. Proteomics is the study of proteins recovered directly from the environment. Proteomics-based techniques are extremely useful in autoimmune encephalitis in the process of identification and study of new autoantigens. Greninger et al. (2015) report the use of metagenomics NGS to investigate a case of meningocencephalitis in a 15-year-old girl.


New therapeutic interventions in viral encephalitis: intravenous immunoglobulin (IVIG) for Japanese encephalitis (JE) and valacyclovir in herpes simplex encephalitis (HSE)

Rayamajhi et al. (2015) conducted a pilot feasibility randomised double-blind placebo-controlled trial of IVIG containing anti-JEV neutralising antibody (ImmunoRel, 400mg/kg/day for five days) in children with suspected JE in Nepal and investigated the effect on serum neutralizing antibody titre and cytokine profiles. Twenty-two children were included in this study. None of the children were vaccinated against JE. Thirteen children had confirmed JE. Eleven children were in the IVIG group and eleven in the placebo group. One child from the IVIG group died of aspiration pneumonia and two children from placebo group died before follow-up. The proportion of patients experiencing full recovery without any sequelae was similar at discharge for both groups and slightly higher for the IVIG group at follow-up (3-6 months). There was a greater increase in neutralising antibody titres among patients treated with IVIG compared to those treated with placebo. Interleukin 6 (IL-6) and interleukin 4 (IL-4) responses were elevated in the IVIG group, providing an evidence to the hypothesis that administration of IVIG modulates the immune response. The authors concluded that a multi-centre RCT of IVIG for children with suspected JE is feasible in these settings with no protocol violations.

Gnann et al. (2015) present the results of a study designed to test the hypothesis that extended antiviral therapy would result in reduced neuropsychological morbidity and improved outcomes. Following completion of a standard course of intravenous acyclovir, 87 adult patients with HSE (confirmed by positive polymerase chain reaction (PCR) for HSV DNA in cerebrospinal fluid) were randomised to receive either valacyclovir (VACV) 2 g three times daily (n = 42) or placebo tablets (n = 47) for 90 days (12 tablets of study medication daily). At 12 months, there was no great difference in the neuropsychological impairment in VACV-treated vs placebo recipients, with 85.7% and 90.2%, respectively, of patients demonstrating no or mild neuropsychological impairment. The authors conclude that an additional three-month course of oral VACV therapy did not provide added benefit.


Acute encephalitis in the immunocompromised individuals

Saylor et al. (2015) summarise the current knowledge of acute encephalitis in immunocompromised individuals. The challenges associated with management of encephalitis in this group of patients include: atypical presentation (e.g. fewer prodromal symptoms, no cerebral spinal fluid (CSF) pleocytosis), greater risk of uncommon and novel agents (e.g. Balamuthia Mandrillaris) and increased...
morbidly and mortality [some cases due to acyclovir resistance]. The authors reviewed recent studies on acute encephalitis in immunocompromised patients and found that the risk of herpes simplex encephalitis (HSE) and herpes zoster varicella (HZV) encephalitis is increased in immunocompromised individuals who receive immune suppressive and immunomodulatory treatments (e.g. natalizimab, fingolimod) and in patients with cancer receiving cranial irradiation therapy. There is also a likelihood of encephalitis caused by pathogens transmitted through donated organs in immunocompromised patients, especially when donors are asymptomatic carriers of infections or remain undiagnosed prior to their death despite manifesting symptoms. Reactivation of BK virus in the settings of immunosuppression (transplant recipients and AIDS patients) is also discussed, these patients having a very poor prognosis with a high mortality rate. Given these particularities of acute encephalitis in the immunocompromised individuals, the authors argue that it is essential to rapidly identify the causes of encephalitis in these patients. Unbiased techniques for pathogen discovery such as next generation sequencing (NGS) will enhance the diagnosis management in these situations.


Consensus guidelines for the investigation and management of encephalitis in adults and children in Australia and New Zealand

Britton et al. (2015) report the development of consensus guidelines for the investigation and management of encephalitis in adults and children in Australia and New Zealand. Key considerations in the investigation and management of patients with encephalitis addressed in this guideline include:

- Which first-line investigations should be performed?
- Which aetiologies should be considered possible based on clinical features, risk factors and radiological features?
- What tests should be arranged in order to diagnose the common causes of encephalitis?
- When to consider empiric antimicrobials and immune modulatory therapies?
- What is the role of brain biopsy?

Two diagnostic algorithms are proposed to help clinicians with diagnosis and management of encephalitis. The first one supports clinicians to identify possible meningoencephalitis cases, exclude other conditions that mimic meningoencephalitis, initiate empiric acyclovir and antibiotic therapy, and discriminate between patients in whom encephalitis can be excluded from those where a more careful assessment is required. The second algorithm refers to patients where the diagnosis of encephalitis is likely and advocates for a staged and multidisciplinary approach to investigation and management. The authors highlight the importance of following these guidelines for the patient benefit.


The gap between national guidelines and existent practice in management of viral encephalitis in the UK

Backman et al. (2015) try to address this gap by aiming to develop an intervention to promote adherence to national guidelines for suspected viral encephalitis. The author developed a semi-structured interview around two key clinical behaviours in the management of patients with suspected encephalitis: performing a lumbar puncture and recognising the clinical features of suspected encephalitis. One-to-one interviews were conducted. The results showed that health care professionals may fail to diagnose encephalitis especially within the context of busy emergency departments because of its relative rarity and non-specific clinical features of suspected encephalitis. Furthermore, doctors are not sure when it is safe to perform diagnostic lumbar punctures, lack confidence in performing the procedure and experience difficulties in assembling the required kit and tests. There are a few difficulties around starting treatment, but more problems are posed by the failure to confirm the diagnosis and the decision to stop the treatment. The authors identified memory, attention and decision processes as a key determinant of clinical behaviour when managing encephalitis.

Following these findings, the authors developed a multifaceted intervention package including core and flexible components with embedded behaviour change techniques selected on the basis of identified needs and barriers to change. The package was presented to a one-day meeting of senior doctors and nurses from intervention hospitals, emphasising their roles in directly delivering the various intervention components locally and recommended that they each convene an action planning meeting on return to their hospitals. Presently a cluster randomised trial to evaluate the cost-effectiveness of this intervention package, compared to passive guideline dissemination takes place [Backman et al., 2015].


Managing encephalitis: challenges for nursing staff and families

Matata et al. (2015) present key facts about presentation, causes, diagnosis, treatment and outcomes of encephalitis aiming to improve the knowledge of encephalitis among nurses who play an important part in the acute management of patients with encephalitis. The authors focus on various topics of interest for nurses such as capacity and consent, nursing care of a patient undergoing lumbar puncture, challenges in caring for a patient with acute confusion or seizures, administering life-saving first aid, recognising signs of clinical deterioration and supporting distressed relatives. The paper also emphasizes the importance of accessing rehabilitation services, especially neuropsychology. Other sources of support are represented by various charities who can help patients and their families coming to terms with what happened to them and support them through recovery and rehabilitation. Easton et al. (2015) emphasizes the role of various professionals in the recovery and rehabilitation of paediatric patients with encephalitis. Family doctor, paediatric neurologist, community paediatrician, child/adolescent psychiatrist, educational psychologist, neuropsychologist, a range of nursing personnel (health visitor, school nurse, epilepsy nurse specialist) and various therapists (physiotherapist, speech and language therapists, occupational therapists) are likely to be involved and address various issues which may result from this illness in children. Encephalitis can also impact on family relationships; roles within the family may change, parents becoming carers, advocates, service coordinators and educators of others. Emotional support for the whole
family may be needed.


Easton A. Encephalitis a brief overview. Journal of Family Health 2015; 25(2)

Encephalitis in children: can the outcome be predicted?

Pillai et al. (2015) investigated clinical and radiologic features, serum and long-term outcomes in 164 Australian children with encephalitis. Infectious encephalitis was diagnosed in 30%, infectious-associated encephalopathy in 8%, immune mediated/antibody associated encephalitis in 34% and in 28% of the patients the cause was unknown. Potential dual or multiple aetiology was present in 7% of the patients. Forty percent of patients were admitted to intensive care unit (ICU). An abnormal outcome was noted in 71 patients: death in five patients, severe outcomes in 11, moderate in 29, and mild in 26. These outcomes included learning difficulties in 39 patients, behavioural problems in 33, epilepsy in 25 and speech problems in 24. Clinical relapses occurred in nine patients: one with herpes simplex encephalitis (HSE), one with acute disseminated encephalomyelitis (ADEM), three with anti-NMDA receptor antibody encephalitis, two with D2R antibody encephalitis and two with unknown encephalitis. One patient with HSV encephalitis who relapsed presented with chorea and anti-NMDA receptor and D2R antibodies. Poor outcome was associated with status epilepticus, ICU admission, diffusion restriction on magnetic resonance imaging (MRI) and movement disorder. Patients with an infectious prodrome were less likely to have a poor outcome.

Rismanchi et al. (2015) investigated the prognostic factors of long-term neurological sequelae in children with acute presumed encephalitis. Mean duration of follow-up was 29 months. Of the 99 patients in this study, 48 had neurological sequelae which included learning difficulties, developmental delay (e.g. gross motor, fine motor, social, language delays), behavioural problems (e.g. emotional lability, difficulty with impulse control, hyperactivity, anger outbursts) or focal neurological deficits. Factors associated with development of these neurological sequelae were younger age at onset, seizure at presentation and longer duration of hospital stay. Also children who were discharged on antiepileptic medication or who were readmitted after the acute illness had a higher likelihood of developing neurological sequelae. The authors emphasize that nearly half of the children are left with consequences after encephalitis.

Zekeridou et al. (2015) reviewed the treatment and outcomes of 36 children and adolescents with anti-NMDA receptor encephalitis. All of the patients received first-line immunotherapy (corticosteroids, intravenous immunoglobulins or plasma exchange) and 81% received second-line immunotherapy (rituximab or cyclophosphamide). The median time between emergence of clinical manifestations and first-line treatment was 19 days and between first-line and second-line treatment was 26 days. The modified Rankin scale was used to assess the outcomes. During the first 24 months, 30 patients achieved a good outcome (mRS≤2) and 20 patients had a complete recovery (mRS=0). One patient died and three patients relapsed. Good outcome was correlated with age: older children recovered better and more quickly than younger children even though the authors did not find any great differences in their treatment management. An initial mRS≤3 suggested a complete recovery.

Chou et al. (2015) investigated the relationship between attention deficit hyperactivity disorder (ADHD) and enteroviral encephalitis (EV) in children. This large study included 2646 children with ADHD who were matched according to sex, age, urbanisation level of residence, parental occupation and baseline year to people without ADHD at a ratio of 1:10. The mean of the duration from the initial EV infection to ADHD diagnosis was 6.1 years. Nearly half of the children with ADHD had EV infection. Children with mild EV infection had a 1.16-fold increased risk of ADHD and children with severe EV infection had a 2.82-fold increased risk of ADHD. The authors conclude that patients with EV encephalitis have an increased risk of developing ADHD. Children recovering from EV encephalitis should have a neuropsychologist assessment.

Chou I-C., Lin C-C., Kao C-H. Enterovirus encephalitis increases the risk of attention deficit hyperactivity disorder: A Taiwanese population-based case–control Study. Medicine 2015; 94(16):e707


Herpetic meningoencephalitis (HME): delay in treatment as a marker of unfavourable outcomes

Erdem et al. (2015) conducted a multicentre study in order to investigate predictors of HME outcomes. Four hundred and thirty-eight adult patients with a definite virological diagnosis from 35 referral centres in ten countries were included in the study. Almost half of the patients (44.5%) received antiviral treatment during the first two days after the onset of symptoms. Poor outcomes were reported in 232 (52.9%) patients: death in 44 and sequelae in 188. These included memory disorder (62), behavioural disorders (55), speech impairment (59), motor symptoms (48), cognitive impairment (29), headache (13), psychiatric disorders (10), balance disorder (6), and visual disturbances (5). Older age, male gender, lower Glasgow Coma Scale (GCS) scores, and convulsion were associated with the poor outcomes. But more importantly, a delay in establishing an effective antiviral treatment significantly increased the risk of unfavourable outcome.

Recovery and rehabilitation after encephalitis

“The unique and multiple needs of each patient mean that no one pathway fits everybody and a multidisciplinary approach is required”. (Bradley, 2015)

Proper name anomia after herpes simplex encephalitis (HSE)

Busigny et al. (2015) present a case of proper name anomia following HSE. Post-HSE, the patient complained about persistent word production and comprehension difficulties for names of persons, places, acronyms and some infrequent common nouns. Re-visiting Semenza’s four varieties of proper name anomia, the authors are asking if other types of proper name anomia can be identified. They undertook 20 experiments aiming to define the patient’s cognitive profile and the nature of his proper name anomia. The results of these experiments showed that the patient had production and comprehension deficit for unique and abstract verbal labels. His semantic access to individual knowledge was preserved for faces but compromised for names. The authors conclude that their patient does not fit any of the Semenza’s types of proper name anomia, instead he would present a fifth variety of proper name anomia that could be defined as a two-way lexico-semantic disconnection. This type would be characterized by a partial disconnection between semantic knowledge and the lexicon of proper name labels.


Specific functions of the left anterior temporal lobe

Patterson et al. (2015) analysed the cognitive outcomes of two patients: one patient recovering from a stroke with damage of the left temporal lobe ventral to the superior temporal sulcus and one patient with herpes simplex encephalitis (HSE) with damage of the left temporal lobe extending to the left inferior frontal gyrus. They compared these patients with reported cases of semantic dementia (SD). Their aim was to explore if the left temporal lesions of two non-SD patients are associated with a semantic impairment and, if this impairment would resemble SD. Following a range of cognitive tests, which assessed the patients’ general cognitive status and semantic memory, the authors determined that they had a moderate semantic impairment which resembled semantic dementia broadly, but differed in more detailed characteristics. Similar to SD patients they experienced severe anomaly that was not resolved by phonological cues and impairment on non-verbal as well as verbal semantic tasks. On the contrary, important features of the semantic dementia such as sensitivity to the familiarity and typicality of the stimulus material occurred only in tasks requiring verbal output. Although the extent of damage to the left hemisphere was greater in the patient with HSE, his performance on the tests [with only a few exceptions] was better than for the patient with stroke. The authors argue that their findings provide evidence of the specific functions of the left anterior temporal lobe.


Rehabilitation after anti-NMDA receptor encephalitis

In the context of very little information available on the rehabilitation of people with anti-NMDA receptor encephalitis, Bradley (2015) presents a case of a 52-year-old woman diagnosed with anti-NMDA receptor encephalitis who was treated with immunosuppression with steroids and intravenous immunoglobulin and transferred to an inpatient neurorehabilitation unit. Her difficulties were related to behavioural disturbance, communication, continence, mobility and cognition. The intervention plan was aimed at each one of these problems and involved cooperation from family and friends. Immunosuppressive medical management was continued. Occupational therapists and physiotherapists were involved. Distractions were minimalised and a routine was introduced. Behaviour improved following a short course of low dose olanzapine. Overall, she improved substantially and after five months in the rehabilitation unit she was discharged home with community follow-up required. The author highlights the challenges in the rehabilitation of these patients when there are no set guidelines for this type of rehabilitation. In addition, the unique and multiple needs of each patient mean that no one pathway fits everybody and a multidisciplinary approach is required.

The Encephalitis Society
Support, Awareness & Research for Inflammation of the Brain

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LIFE AFTER ENCEPHALITIS:
A NARRATIVE APPROACH BY DR AVA EASTON

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Life After Encephalitis
A Narrative Approach by Ava Easton

Life After Encephalitis provides a unique insight into the experiences of those affected by encephalitis, sharing the rich, perceptive, and often powerful, narratives of survivors and family members. It shows how listening to patient and family narratives can help us to understand how they make sense of what has happened to them, and also help professionals better understand and engage with them in practice. The book will also be useful for considering narratives associated with brain injuries from other causes, for example traumatic brain injury. Life After Encephalitis will appeal to a wide range of people: professionals working in neurology and rehabilitation, and also to and survivors of encephalitis, their families, and carers.

“This book is equally relevant to survivors, family members, carers, neurologists, psychiatrists, nurses, relatives and even disinterested readers. Ava Easton has brought the same demotic wisdom to this book that she exercises as the inspirational CEO of The Encephalitis Society. Over the years she has taken what was a deadly but obscure illness out to the world, and explained it simply and cogently to people who had no reason to have thought about it before, and to experts who had almost certainly never thought about it in those terms before. There is a useful explanation of the different forms of encephalitis, prevention measures, experts have their say, but at the heart of the book is a series of beautifully written, desperately moving first-hand accounts from those who have lived with the illness”. Simon Hattenstone, The Guardian

“Encephalitis is undoubtedly a thief, and Easton does an excellent job at explaining why”. Jules Morgan, The Lancet Neurology

Identity Unknown: How acute brain disease can destroy knowledge of oneself and others by Barbara Wilson, Claire Robertson and Joe Mole

Identity Unknown gives an exceptional, poignant and in-depth understanding of what it is like to live with the severe after-effects of brain damage caused by a viral infection of the brain. It tells the story of Claire, a nurse, wife, and mother of four, who having survived encephalitis, was left with an inability to recognise faces – a condition also known as prosopagnosia together with a loss of knowledge of people and more general loss of semantic memory.

Part One describes the current knowledge of encephalitis, of perception and memory, and the theoretical aspects of prosopagnosia and semantic memory. Part Two, told in Claire’s own words, is an account of her life before her illness, her memories of the early days in hospital, an account of the treatment she received at The Oliver Zangwill Centre, and her description of the long-term consequences of encephalitis. Claire’s profound insights, clear writing style, and powerful portrayal of her feelings provide us with a moving insider’s view of her condition. These chapters also contain additional commentary from Barbara Wilson, providing further detail about the condition, treatment possibilities, potential outcomes, and follow-up options.

Identity Unknown provides a unique personal insight into a condition which many of us have, for too long, known too little about. It will be of great interest to a broad audience including professionals working in rehabilitation settings, and all those who have sustained a brain injury, their families and carers.
About 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. Our work involves:

- Supporting adults, children, families and carers of those affected by encephalitis
- Producing high quality, evidence-based, peer-reviewed 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.

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. CPD points awarded.

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 mail@encephalitis.info or +44 (0)1653 692583.

We are now happy to reveal our ambitions for World Encephalitis Day (WED) on February 22, 2017.

We are asking our members – and you, our professional members – to help us “illuminate encephalitis” by lighting up landmarks, homes and buildings in your local communities.

Although it is still early days, we can reveal that the fountains at Trafalgar Square, Peace Bridge and Blackpool Tower have confirmed they will be turning red on February 22. We are hopeful other iconic landmarks across the globe will also show their support.

Our appeal to you is simple – do you know a landmark near you which can be illuminated in the colour red on World Encephalitis Day? It could be a hospital you work at? Your office? A sports club? A Church? Even a bridge! The more landmarks we turn red, the more we can “shine a light on encephalitis.” I hope you can support us in our ambitions. Thank you!
The Encephalitis Society
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Registered Charity Number: 1087843, Charitable Company registered in England and Wales Number: 4189027