

Encephalitis: diagnosis, management and recent advances in the field of encephalitides

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Abstract

Encephalitis describes inflammation of the brain parenchyma, typically caused by either an infectious agent or through an autoimmune process which may be postinfectious, paraneoplastic or idiopathic. Patients can present with a combination of fever, alterations in behaviour, personality, cognition and consciousness. They may also exhibit focal neurological deficits, seizures, movement disorders and/or autonomic instability. However, it can sometimes present non-specifically, and this combined with its many causes make it a difficult to manage neurological syndrome. Despite improved treatments in some forms of encephalitides, encephalitis remains a global concern due to its high mortality and morbidity. Prompt diagnosis and administration of specific and supportive management options can lead to better outcomes. Over the last decade, research in encephalitis has led to marked developments in the understanding, diagnosis and management of encephalitis. In parallel, the number of autoimmune encephalitis syndromes has rapidly expanded and clinically characteristic syndromes in association with pathogenic autoantibodies have been defined. By focusing on findings presented at the Encephalitis Society's conference in December 2021, this article reviews the causes, clinical manifestations and management of encephalitis and integrate recent advances and challenges of research into encephalitis.

Keywords: neuropathology, adult neurology, infectious disease/HIV

Introduction

Encephalitis describes inflammation of the brain parenchyma, typically caused by either an infectious agent or through an autoimmune process which may be postinfectious, paraneoplastic or idiopathic. Patients can present with a combination of fever, alterations in behaviour, personality, cognition and consciousness. They may also exhibit focal neurological deficits, seizures, movement disorders and/or autonomic instability. The estimated worldwide incidence of encephalitis ranges from 3.5 to 12.3 per 100 000 patients/year [1, 2]. Despite improved treatments in some forms of encephalitis, overall this syndrome remains a global concern due to its high mortality and morbidity [3, 4]. Regardless of the aetiology, prompt diagnosis and administration of specific and supportive management options can lead to better outcomes in the majority. This relies on correct and rapid identification of the cause of the encephalitis and access to effective treatments.

Brain infections are a global research priority [3] and over the last decade research in this area has led to marked developments in the understanding, diagnosis and management of encephalitis.

In parallel, the number of autoimmune encephalitis syndromes has rapidly expanded and clinically characteristic syndromes in association with pathogenic autoantibodies have been defined [5, 6].

The Encephalitis Society's annual conference [7] attracts physicians, researchers and healthcare professionals from across the world and is a forum where the latest developments in encephalitis are presented and discussed. By focusing on findings presented at the Encephalitis Society's conference in December 2021, this article will review the causes, clinical manifestations and management of encephalitis and integrate recent advances and challenges of research into encephalitis.

Definition

The diagnostic criteria for encephalitis capture any patient presenting with [8]:

- Altered mental status lasting over 24 hours, with no alternative cause identified.

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And at least two of the following:

- Documented fever above 38°C within the last 72 hours before or after presentation.
- Seizure activity not related to a pre-existing seizure disorder.
- New focal neurological signs.
- Cerebral spinal fluid (CSF) pleocytosis.
- New neuroimaging findings suggestive of encephalitis.
- Abnormal findings on electroencephalography that is consistent with encephalitis.

Due to the broad range of pathologies which present with alterations in mental status, a high index of suspicion is required. Moreover, most patients with encephalitis will not have a severely depressed Glasgow coma scale (GCS) score on admission and may even do well on basic cognitive testing, such as the mini-mental test, and many—especially those with autoimmune forms—often lack a fever or CSF pleocytosis. Arguably the most important investigation is therefore a collateral history from friends and family who state that the patient is ‘just not themselves’ [9]. Clinicians should directly ask this question and, if the answer is affirmative, this finding should be taken very seriously. In addition, any patient with altered mental status and fever with no obvious cause should be managed as a central nervous system (CNS) infection until proven otherwise [10]. Importantly, approximately a quarter of patients with proven encephalitis will have some symptoms suggestive of infection outside of the CNS, such as dysuria or coryzal features [11]. Therefore, minor features such as dysuria in a young person who is not septic, or cough in a patient who is not hypoxic, should not be considered sufficient to exclude infective encephalitis on clinical grounds; rather empirical treatment should be started and the source of infection investigated, including with a lumbar puncture (LP). Indeed, on average four to five patients are investigated for each case of a CNS infection identified [12].

Aetiology

Causes of encephalitis can be divided into infectious and autoimmune processes (Table 1).

Viruses such as herpes viruses, arboviruses, enteroviruses and adenoviruses are the most common causes of infective encephalitis globally [2] *Japanese encephalitis virus* is the main cause of viral encephalitis in many countries in Asia, whereas herpes simplex virus (HSV) is most common in high-resource settings [2]. Bacterial, fungal and parasitic infections are less common causes.

A major set of aetiologies of non-infectious encephalitis are encompassed by the title ‘autoimmune encephalitis’. In some cases of autoimmune encephalitis, a specific autoantibody is identifiable in serum or CSF samples which is directed against a CNS antigen [13]. The most common aetiology in the young is associated with antibodies against the N-methyl D-aspartate receptor (NMDAR). In those above 50 years of age, leucine-rich glioma-inactivated 1 (LGI1) antibodies appear to be the most common known autoantibody [14, 15], but recent data suggest that this may hold true across all autoimmune encephalitis cases [16]. In addition to these two autoantibodies, many other pathogenic autoantibodies have been described in the last decade and the incidence of these are increasing [6, 13, 17]. This is likely due to increased recognition, testing and the appreciation that such syndromes have been misclassified for many years [18]. These autoimmune encephalitides can be paraneoplastic syndromes, a well-described being the link between NMDAR-antibody encephalitis and ovarian teratomas [19]. However,

Table 1. Selected causes of encephalitis [4, 8, 28]

Infectious causes	Immune-mediated causes
Virus	Autoantibody-mediated
Herpes simplex virus	NMDAR
<i>Japanese encephalitis virus</i>	AMPA
Enteroviruses	GABA A/B
<i>Cytomegalovirus</i>	LGI1
Varicella zoster virus	CASPR2
West Nile virus	IgLON5
Human herpesviruses 6 and 7	MOG including acute disseminated encephalomyelitis
Epstein-Barr virus	
Human immunodeficiency virus	
Rabies virus	
Bacteria	
<i>Neisseria meningitidis</i>	
<i>Streptococcus pneumoniae</i>	
<i>Mycoplasma pneumoniae</i>	
<i>Mycobacterium tuberculosis</i>	
<i>Listeria monocytogenes</i>	
<i>Treponema pallidum</i>	
Fungi	
<i>Histoplasma capsulatum</i>	
<i>Cryptococcus neoformans</i>	
<i>Candida</i> spp.	
<i>Aspergillus</i> spp.	
Parasites	
<i>Plasmodium</i> spp.	
<i>Toxoplasma gondii</i>	

AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2, contactin-associated protein-like 2; GABA, gamma-aminobutyric acid; IgLON5, immunoglobulin-like cell adhesion molecule 5; LGI1, leucine-rich glioma-inactivated 1; MOG, myelin oligodendrocyte glycoprotein; NMDAR, N-methyl D-aspartate receptor.

even in this syndrome, a tumour may be present in <30% of patients [20]. In addition, antibodies have also been identified in patients who have an apparent ‘relapse’ of viral encephalitis, particularly HSV encephalitis, where they appear to represent a secondary autoimmune process after viral clearance from the CNS [21]. However, these antibodies have also been identified in patients with HSV encephalitis who do not relapse and make a good recovery. Therefore, the clinical progression of the patient is critical in determining the significance of any antibodies identified in this context.

The other major cause of non-infectious encephalitis is acute demyelinating encephalomyelitis (ADEM). ADEM is defined as a demyelinating disorder caused by an autoimmune response. This immune response often occurs after an infection or vaccination and is primarily seen in paediatric populations [22]. ADEM appears to be commonly associated with antibodies to myelin oligodendrocyte glycoprotein [23].

Encephalitis 2021: emerging infectious encephalitides

Talks by Professor Kiran Thakur, Columbia University Irving Medical Center, USA and Dr Tina Damodar, Department of Neurovirology, NIMHANS, Bangalore, India

A growing concern discussed at Encephalitis 2021 are the increasing outbreaks of arthropodborne encephalitides [24]. Arthropods, such as ticks, mosquitos and mites, can act as vectors for viruses. Such viruses are called arboviruses and neurological involvement can be commonly seen in infections caused by arboviruses such

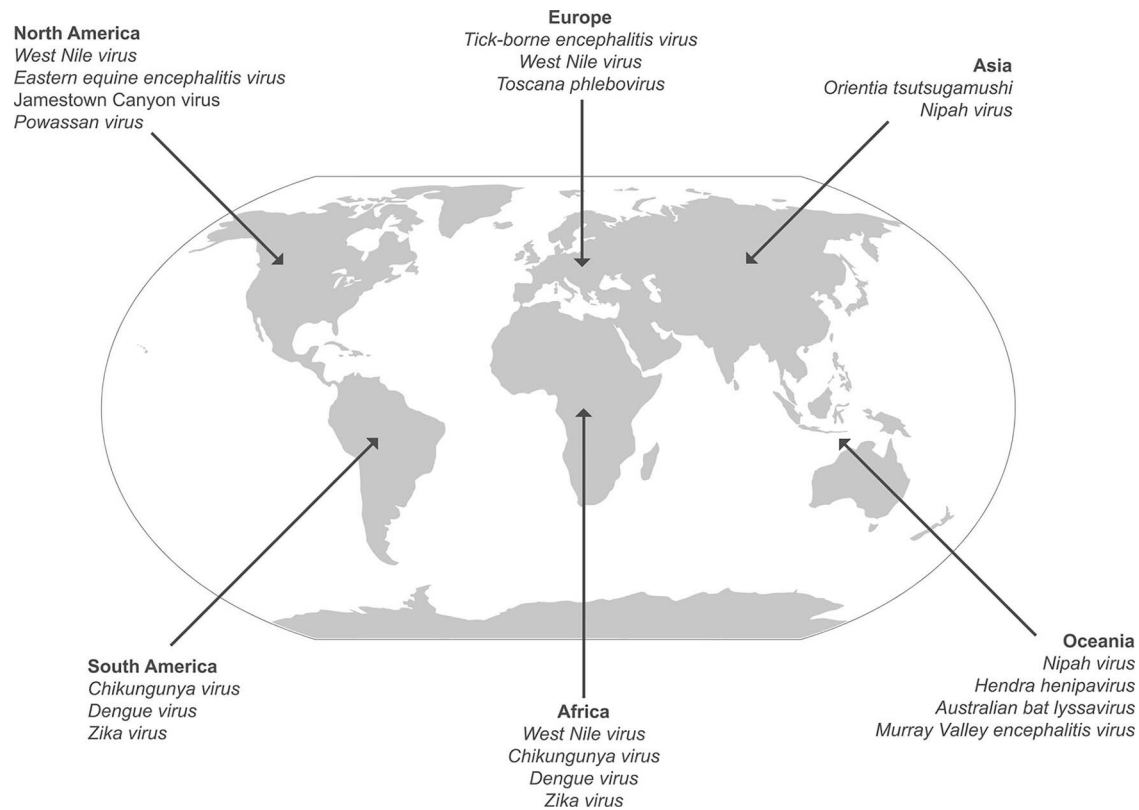


Figure 1. Emerging infectious encephalitides across the globe [28].

as Japanese encephalitis (JE), Zika virus, tickborne encephalitis and West Nile virus.

Variations in global temperature have had a strong impact on the environmental suitability for the transmission of vectorborne diseases [25]. Arthropod populations are increasing, and their geographical ranges are expanding [26]. An example of this is how global temperature changes have resulted in the global area suitable for the *Aedes aegypti* mosquito increasing by 1.5% per decade between 1950 and 2000 [27]. This mosquito is a known vector of several arboviruses which cause encephalitis including JE, dengue and chikungunya viruses. This trend is predicted to accelerate in the coming decades and arbovirus outbreaks are becoming more common across the world (Figure 1) [28]. These areas' populations are potentially immunologically naïve to these emerging pathogens. This, combined with the paucity of treatment options for arboviral diseases, poses an emerging public health risk and is a reminder how global temperature change can alter the epidemiology of infectious encephalitis [24].

Changing ecology has caused new encephalitis-causing pathogens to come to prominence. An example discussed at Encephalitis 2021 was the increasing prevalence of scrub typhus in India [29]. Scrub typhus is caused by the rickettsial bacterium *Orientia tsutsugamushi* and is transmitted by the bite of the larvae (chiggers) of *Leptotrombidium* mites. After first emerging in 1940s in north-eastern region of India, the region experienced no cases for decades until it re-emerged in 2010 [28]. Deforestation, increased land use in agriculture and greater rainfall during monsoon seasons increase chigger numbers [30]. These changes, along with the successful JE vaccination programme in India, have led to scrub typhus replacing JE to become the leading cause of acute encephalitis in certain regions of India [29]. If this pattern continues, we can expect an increase in arthropodborne encephalitis globally, and more research into the epidemiology

and management of these diseases is vital in the face of a changing global climate.

Encephalitis 2021: autoimmune encephalitis **Talks by Professor Jerome Honnorat, Hospices Civils de Lyon, France; Professor Virginie Desestret, Hospices Civils de Lyon, France and Ms Selina Yogeshwar, Charité- Universitätsmedizin Berlin, Germany**

Autoimmune encephalitis remains an area of great research interest. It is a syndrome of growing prevalence, with autoimmune encephalitis being the leading cause of encephalitis in patients under 30 years of age [31]. This increase may be due to the growing awareness of these disorders [6] with over a dozen new-type autoantibodies being identified in the last 15 years [19]. Many of these have features which we traditionally do not associate with encephalitides, such as a lack of MRI changes or focal neurological deficits. Moreover, the expanding availability of commercial testing has likely led to more patients being tested, with a corresponding decline in the proportion of tested patients found to be positive [32]. Importantly, it has become clear that antibodies with the most diagnostic utility, and greatest pathogenic potential, are typically directed against the extracellular domains of neuronal proteins. It is this characteristic which has helped dismiss some antibodies as not clinically relevant, and bring others to the fore [33, 34].

An example discussed at Encephalitis 2021 was encephalitis caused by antibodies against the immunoglobulin-like cell adhesion molecule 5 (IgLON5). IgLON5-antibody disease has been characterised as an autoimmune encephalitis with a neurodegenerative-like presentation, rather than the rapid onset we see in NMDAR-antibody encephalitis, for example [35]. It has been <10 years since it was first described and case numbers

Table 2. A selection of intermediate (30%–70% association with cancer) and high-risk (above 70% association with cancer) autoantibody-mediated encephalitis [39, 40]

Autoantibody-mediated encephalitis	Related tumour
Intermediate-risk antibodies	Ovarian or extraovarian teratomas
NMDAR	Small cell lung cancer, malignant thymoma
AMPA	Small cell lung cancer
GABA A/B	Malignant thymoma
CASPR2	Hodgkin's lymphoma
mGluR5	Small and non-small cell lung cancer,
High-risk antibodies	neuroendocrine tumours and neuroblastoma
Hu	Small cell lung cancer and thymoma
CRMP5	Small and non-small cell lung cancer, breast cancer
Yo	Testicular cancer, non-small cell lung cancer
Ma2	

AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2, contactin-associated protein-like 2; CRMP5, anticollapsing response-mediator protein-5; GABA, gamma-aminobutyric acid; mGluR5, metabotropic glutamate receptor 5; NMDAR, N-methyl-D-aspartate receptor; PCA2, Purkinje cell antigen 2.

in literature amount to <100 [36]. Early studies have shown that patients with IgLON5-antibody encephalitis present prominently with unusual, and characteristic, sleep disturbances and, at Encephalitis 2021, it was suggested that temporal atrophy may be a common finding in these patients, perhaps correlating with the sleep-based symptomology [35, 37, 38]. Further studies of these newly discovered autoantibodies are required, but the paucity of cases means multicentre and multicountry collaborations are vital.

Cancers are one of recognised triggers of autoimmune encephalitis and numerous presentations at Encephalitis 2021 touched on these paraneoplastic syndromes. In these cases, the remote effects of a cancer cause an immune-mediated response directed at CNS antigens, predominantly due to molecular mimicry. Specific autoantibodies, which associate with particular tumours (Table 2), are typically directed at intracellular targets. These paraneoplastic neurological syndromes are classically subacute in onset with often inexorable progression due to accelerated neuronal death [39]; hence, these patients have poor outcomes. Many patients will develop neurological symptoms and signs prior to features of an underlying cancer. As such, autoimmune encephalitides are now classed as either an intermediate or high-risk phenotype for underlying malignancies, depending on presence of antibodies known to be associated with established paraneoplastic processes [40]. These new proposed criteria can enhance the clinical care of this cohort of patients who can deteriorate very quickly and remind us about the importance of screening for underlying malignancies in patients with autoimmune encephalitis both acutely and at follow-up.

Mechanism of disease

The clinical features of infectious encephalitis occur primarily due to inflammation of the brain, but the exact range of mechanisms by which this develops is not yet fully understood.

The likely mechanism of disease may be neurotropic infections causing a release of cytokines leading to cytotoxicity, inflammation and damage [41]. This leads to increased permeability

of the blood-brain barrier (BBB) and perivascular lymphocytic infiltration which can lead to further breakdown in the BBB [42] (Figure 2).

In encephalitis secondary to autoantibodies targeting neuronal surface/synaptic antigens, the mechanisms may be more diverse [43]. These antigen targets are often found in the limbic system of the brain, and several in vitro and in vivo models demonstrate the direct pathogenicity of these antibodies [44–47]. However, the molecular interactions of antibodies with antigens can lead to complement deposition, antigen internalisation and direct modulation of the antigenic target's function. Hence, depending on the target antigen, the precise potential therapeutic intervention will differ significantly. The origins and sources of these autoantibodies may be secondary to infections, cancer or—most commonly—unknown mechanisms [48]. However, increasingly clear immunogenetic associations and B cell studies are shedding light on this field [43, 49, 50].

Encephalitis 2021: immunology Talks by Dr Bo Sun, University of Oxford, UK and Dr Adam Al-Diwani, University of Oxford, UK

Understanding the immunology underpinning autoimmune encephalitis is an ongoing research mission and, at Encephalitis 2021, the immunology of autoantibody-mediated encephalitides were discussed.

Contactin-associated protein-2 (CASPR2) is a cellular adhesion molecule and CASPR2-antibodies can lead to an autoimmune encephalitis characterised by a diversity of manifestations [14, 51]. Interestingly, 30% of patients with CASPR2-antibody encephalitis suffer relapses following treatment [52]. At Encephalitis 2021, it was shown that both B cell cultures from both patients with CASPR2-antibody and healthy donors harbour CASPR2-reactive B cells in their naïve repertoires, suggesting that even in healthy patients CASPR2 reactivity is present. However, only patients with CASPR2-antibody showed memory B cells directed against CASPR2. Therefore, a failure in peripheral B cell tolerance is proposed to play a key role in disease pathogenesis [53].

A further talk discussed the anatomical localisations of these autoantigen-specific B cells, which has particular importance in highlighting the dynamics of CNS-peripheral interactions with relevance to both health and CNS diseases. The authors found that both cervical lymph nodes (the first peripheral port of drainage of CNS lymphatics) and ovarian teratomas harboured NMDAR-reactive B cells [54]. These findings built on previous work showing tertiary lymphoid structures within ovarian teratomas [50, 55] and led to the suggestion that the autoimmunisation in patients with NMDAR-antibody encephalitis could be captured and studied directly from patients [56]. The authors emphasised gratitude to their altruistic patients who volunteered for lymph node aspirations and inspired this project.

These studies are important in illustrating how immunological tolerance may play a significant role in understanding the mechanism of disease of autoimmune encephalitis, which might ultimately lead to targeted immune-modulatory therapies.

Encephalitis 2021: COVID-19-related neurological disease

Talks by Dr Emily Happy Miller, Irving Medical Center, and New York Presbyterian Hospital, USA and Dr Oliver Harschnitz, Sloan-Kettering Institute for Cancer Research, USA

Another emerging, or rather emerged, disease discussed at length at Encephalitis 2021 was COVID-19. Up to one-third of patients

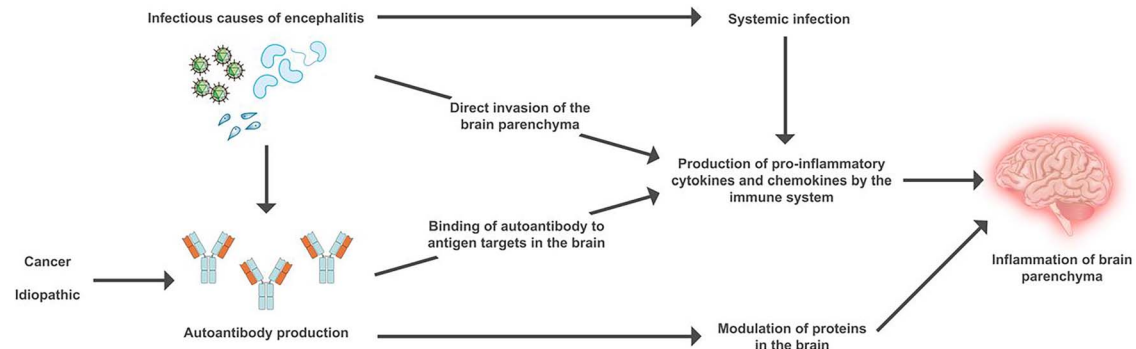


Figure 2. Overview of pathophysiology causing encephalitis.

with COVID-19 experience at least one neurological manifestation [57, 58]. Although encephalitis is a rare complication of COVID-19 [59], ADEM incidences in the first wave appeared increased compared with prepandemic and caused significant mortality and morbidity in patients with COVID-19 [60, 61]. To date, there is little evidence that primary SARS-Cov-2 infection of the brain is a significant contributing factor in these cases. Low levels of viral RNA are reported in brain tissue of patients with COVID-19 at autopsy [62].

Microglial (antigen-presenting cells which are activated following exposure to pathogens) were found to be activated in these specimens, often accompanied by neuronophagia [58]. One hypothesis, therefore, is that the COVID-19 neurological changes may be caused by neuronophagia [63]. However, these areas did not correspond to those with detectable viral RNA and therefore it is unlikely that direct viral neuro-invasion is responsible for the observed neuropathological changes [57, 58]. Other presented data suggested COVID-19 induces senescence in human dopaminergic inducible pluripotent stem cells in vitro. This is an early suggestion that dopamine neuron involvement may be a factor in the neuropathology seen in COVID-19 [64]. There remain significant gaps in our understanding in the effect of COVID-19 on the neurological system, and long-term monitoring of neurological problems in patients with COVID-19 is underway (www.covid-cns.org).

Clinical manifestations

A vital aspect of assessing a patient with suspected encephalitis is to look for clues as to the cause of the encephalitis. This can enable targeted therapy which has a significant effect on mortality and morbidity.

Although presenting symptoms can be varied, particular symptoms are more associated with specific causes (Table 3). Therefore, the clinician should try and hone in on these details in the history. Identification of the timeline of symptoms is important. Encephalitis is typically subacute in onset, although this can vary: we are discovering new autoimmune causes such as LGI1-antibody and CASPR2-antibody encephalitis which may follow a chronic course of disease [6, 37].

Evidence of personality or behavioural change, hallucinations and other neuropsychiatric symptoms should be investigated. This is a common presentation of some autoimmune encephalitides [65] and may have very particular features which highlight it as especially distinctive [66].

A travel history is vital with particular emphasis on contacts with animals, mosquitoes or other insects. In areas with vector-borne causes of encephalitis, the location and season in which patients present can also give clues as to what a causative infective agent may be.

Table 3. Overview of symptoms at presentation which may suggest aetiology

Symptoms suggestive of infectious cause	Symptoms suggestive of immune-mediated cause
Acute or subacute onset	Subacute or chronic onset
Prodromal flu-like illness	Altered personality, behaviour, psychosis, catatonia
Alterations in personality, behaviour, cognition or consciousness	Sleep disorder-disruption
Vomiting or gastrointestinal upset	Memory issues
Travel history or exposure to known vectors of encephalitis causing infections	Recent viral illness
Immunocompromise	Seizures (eg, brachiofacial dystonic)
Skin rashes	Status epilepticus
	Autonomic instability
	Movement disorders (eg, orofacial dyskinesia)
	Underlying symptoms concerning for malignancy

A medical history should seek to identify any background of immunocompromise.

Encephalitis 2021: neuropsychiatric presentations of encephalitis

Talk by Dr Helena Ariño, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK

An area of growing interest is the overlap between autoimmune encephalitis and neuropsychiatric diseases [67], with NMDAR-antibody encephalitis often presenting with predominantly psychiatric features. At Encephalitis 2021, it was discussed how harnessing digital medical records may provide a valid method to phenotype NMDAR-antibody encephalitis in patients presenting with neuropsychiatric symptoms [68]. Psychiatric symptoms at the onset of NMDAR-antibody encephalitis and can occur weeks before other clinical signs suggestive of the disease. However, indiscriminate screening of psychiatric patients is not cost-effective and poses a major risk by leading to patient misidentification. Analysing clinical text through natural language processing was shown to have promise in phenotyping NMDAR-antibody encephalitis versus other patients with psychosis. Terms such as 'paediatric', 'bladder' and 'shaking' in medical records were suggested to reflect NMDAR-antibody encephalitis, and machine learning algorithms to analyse clinical texts containing the mental state examination or quotes from patients may help predict encephalitis [68].

These novel methods are showing potential promise in our clinical repertoire in diagnosing conditions, but require large datasets which may be challenging to generate in conditions such as autoimmune encephalitis and may not surpass everyday clinical acumen.

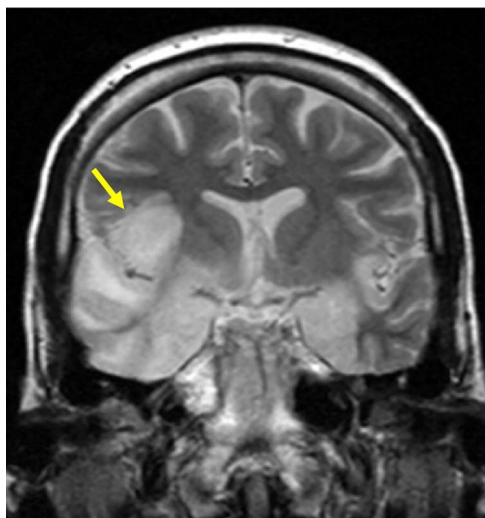


Figure 3. Coronal T2-weighted MRI of a patient with herpes simplex virus encephalitis illustrating high signal changes in the temporal lobes (source: Dr Laughlin Dawes, 2008).

Diagnosis

The key to establishing evidence of CNS inflammation is to obtain and analyse CSF through a LP. Neuroimaging is not a prerequisite for LP and is only indicated prior to LP in cases when focal neurological signs, papilloedema, seizures or a GCS <13 is present, as these features suggest obstructive raised intracranial pressure [17].

In viral encephalitis, the CSF typically shows a predominantly lymphocytic pleocytosis. Protein levels may be moderately elevated or normal and the CSF: blood glucose ratio is typically normal in these samples. Sending CSF samples for viral PCR in a timely manner is vital. Delaying the LP, and therefore CSF viral PCR, can lead to diagnostic uncertainty as the viral load declines, particularly after aciclovir has been started in cases due to HSV and varicella zoster. Repeat LPs to collect CSF and serum for antiviral antibody testing may be useful in achieving a diagnosis at these delayed timepoints.

Autoantibody testing should be considered in all cases, particularly those with a recognisable phenotype of autoimmune encephalitis [17]. The diagnostic assays used in diagnosing autoimmune encephalitis includes cell-based assays and immunohistochemistry for neuronal surface antibodies, with increasing evidence suggesting live cell-based assays perform optimally in these diseases, and in-house fixed cell-based assays better than commercially available equivalents [69, 70].

Brain imaging is recommended to assess for changes suggestive of encephalitis and to exclude other diagnoses such as space-occupying lesions. MRI, particularly with diffusion-weighted imaging (DWI) sequences, is the modality of choice to assess changes associated with encephalitis. Some pathogens have specific changes seen on neuroimaging, the most well-known being HSV encephalitis causing bilateral but asymmetrical inflammation of the temporal and frontal lobes [71] (Figure 3). Autoimmune encephalitis can give variable changes on MRI, but the most common feature is bilateral and symmetrical inflammation of the limbic system [48]. In cases of suspected ADEM, MRI typically shows bilateral white matter lesions which can be both supra- and infratentorial and involve the brainstem and spinal cord [72].

In the case of autoimmune encephalitis, body imaging to rule out underlying malignancies must also be considered, such as positron emission tomography and whole-body CT imaging.

Electroencephalogram can be useful in investigating encephalitis as it can provide evidence of encephalopathy, which would be unusual in primary psychiatric diagnoses, or subclinical seizures. Indeed, autoimmune encephalitis may be an important cause of non-convulsive status epilepticus in high-income settings [73]. Certain characteristic patterns have been described in autoimmune encephalitis, in particular the pathognomic extreme delta brush appearance in NMDAR-antibody encephalitis [74].

The above investigations should be undertaken alongside more common investigations to rule out differentials. A HIV test should be offered to all patients with suspected brain infections.

Encephalitis 2021: new diagnostic tools

Talk by Dr Álvaro Bonelli, Rey Juan Carlos University Hospital, Móstoles, Spain

It is still difficult to identify the causative agent in many cases with presumed encephalitis where, even in developed settings, approximately a third of patients do not have a pathogen or autoantibody identified [11, 72]. Novel laboratory techniques which may help to stratify unknown patients into aetiological groups were discussed at Encephalitis 2021. New qualitative multiplexed techniques such as *FilmArray Meningitis and Encephalitis Panel* allow the study of up to 14 pathogens in 1 hour with a high sensitivity and specificity [75]. Studies have shown that the percentage of CNS aetiological diagnosis were higher in the group that had multiplex PCR testing, and this approach reduced the number of molecular biology techniques required to reach a diagnosis [76]. This technique may allow more causative agents to be identified in a single step and therefore should allow clinicians to better direct therapeutic interventions. This concept is analogous to the use of immunohistochemistry and live neuron binding as methods to detect as of yet unknown autoantibodies in patients with autoimmune encephalitis [5, 48].

Management

Patients with encephalitis can become acutely unwell and supportive management is important. This includes managing airway, breathing and circulation.

Airway management is particularly important in patients presenting in a comatose state or with uncontrollable seizures. Seizures are a common sequela of encephalitis [77], and access to anticonvulsant drugs and intensive care units (especially in the case of status epilepticus) is vital. Almost 70% of patients with autoimmune encephalitis have seizures during their illness [78]. Suboptimally controlled seizures can be linked with raised intracranial pressure and greater morbidity and mortality. Recent studies into seizure management were discussed at Encephalitis 2021. A novel therapy discussed was the use of a neurosteroid. Neurosteroids are steroids produced by glial cells and principal neurons. The use of a neurosteroid has been shown to rescue epileptiform activity in murine anti-NMDA encephalitis models. These in vitro models show how NMDAR modulation can prevent anti-NMDA encephalitis' pathogenic antibody effects such as seizures and treat them once established [79]. Further work on identifying patients at risks of seizures, and potential novel treatment options are important as we move forward in managing encephalitis.

The role of steroids in viral encephalitis to reduce the inflammation associated with infection is an ongoing area of study. Results from a multicentre randomised controlled trial in HSV encephalitis are currently awaited (<https://www.dexenceph.org.uk/>) and aim to be presented at Encephalitis 2022 [80].

Although many viruses have been reported to cause encephalitis, targeted antiviral therapy is limited to HSV and VZV encephalitis [72]. Aciclovir should be initiated empirically in all patients with suspected encephalitis (pending other diagnostic investigations) as it reduces HSV mortality from approximately 70% to 10%–20%, and has minimal side effects [71, 72, 81]. Should another infection be identified as causative pathogen in a patient with encephalitis, appropriate antimicrobial therapy should be initiated.

The first-line treatment of autoimmune cases includes immunotherapy such as high-dose steroid therapy with or without intravenous immunoglobulin (IVIg) and/or plasmapheresis, while second-line treatment options include rituximab and/or cyclophosphamide [82]. The benefit of adjunctive IVIg in patients receiving high-dose steroids is currently under investigation in a trial (EncephIg). Also, in LGI1-antibody encephalitis, there is a clinical trial which aims to study the value of reducing IgG levels with blockade of the FcRn molecule which typically recycles IgG. Furthermore, a CD19 monoclonal antibody is being trialled in patients with NMDAR-antibody encephalitis as a way to improve outcomes.

A key aspect of encephalitis treatment is the management of its long-term sequelae resulting from damage and injury to the brain. Many patients suffer from long-term effects such as emotional, behavioural, physical and cognitive deficits. Social effects are often forgotten, including ability to drive and loss of work or education due to disability, yet are common impairments in some of these conditions [83]. Access to neuropsychology, neuropsychiatry and occupational therapy services along with ensuring adequate postdischarge follow-up is important in addressing the long-term effects of this condition. In addition, there is also the impact on the family to consider, such as the development of mental health problems, carer burden and family breakdown. Patients and families affected may benefit from using the information and support services provided by patient organisations such as The Encephalitis Society (www.encephalitis.info).

Encephalitis 2021: the need for greater access to encephalitis management

Talks by Professor Deanna Saylor, The Johns Hopkins University School of Medicine, USA; Dr Jamil Kahwagi, Centre Hospitalier National Universitaire de Fann, Senegal and Dr Adawa Manuela, COVID-19 ORCA Patient Management Center, Cameroon

Managing encephalitis in low-resource settings is challenging. This can be due to a combination of access to diagnostic tools, medications and scope for management in specialist settings, along with cultural challenges associated with accessing healthcare. These difficulties were discussed at Encephalitis 2021.

The aetiology of infectious encephalitis remains poorly described in African settings. In resource-limited settings such as Senegal, it was reported that encephalitis cases rarely have an aetiological diagnosis and treatment can often be inconsistent [84, 85]. A large challenge faced in sub-Saharan Africa is the lack of access to injectable aciclovir [84]. A potential compromise is oral valaciclovir which may be a more readily accessible alternative to intravenous aciclovir in settings with limited resources, although more robust studies are required to assess whether its efficacy

is comparable [86–88]. Tackling disparity in access to important medications globally is huge challenge, and one which will need to be solved to help improve encephalitis management in low-income to middle-income/resource settings.

Encephalitis management requires the involvement of neurological specialists, but they are not always available in low-income to middle-income/resource settings. The median number of adult neurologists per 100 000 population globally is 0.43—in comparison, high-income countries average almost five neurologists per 100 000 people [89]. In Encephalitis 2021, it was reported that sub-Saharan Africa has very few countries with neurology training programmes, and the ratio of neurologist to population is unlikely to improve. The recent development of a specialist neurological training programme at University Teaching Hospital Lusaka, Zambia illustrates how robust systems of neurological care in resource-limited settings can be developed. This programme emphasises the importance of in-country neurology teaching and is on track to train 13 adult and 2 paediatric neurologists in its first 5 years [90]. The importance of ensuring good training will be vital in improving outcomes in diseases such as encephalitis in low-resource settings.

What next?

Encephalitis remains a difficult to manage neurological syndrome due to its many causes, sometimes non-specific presentations and a lack of recognition and awareness. An integral aspect of management is to first identify the causative pathogen or autoantibody to enable directed therapy. Recent advances in the field can lead to improved outcomes and reduced disability in encephalitis. However, challenges we recognise in 2022 include emerging pathogens, access to therapy in low-income to middle-income settings and characterising autoantibody-mediated encephalitides, as well as a better understanding of the long-term consequences for patients and their families (box 1).

Box 1 Oral presentations at Encephalitis 2021 [7]

- Analysing clinical text from electronic health records to diagnose anti-N-methyl D-aspartate receptor (NMDAR) encephalitis, a feasibility study (Dr Helena Ariño, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK).
- Defining the neuroinvasive potential of SARS CoV-2 in brain autopsies of patients with COVID-19 (Dr Emily Happy Miller, Columbia University Irving Medical Center, and New York Presbyterian Hospital, New York, USA).
- Immune and genetic signature of breast carcinomas triggering Yo paraneoplastic cerebellar degeneration (Professor Virginie Desestret, Hospices Civils de Lyon, Université Claude Bernard Lyon, France).
- Paraneoplastic encephalitis (Professor Jerome Honnorat, Hospices Civils de Lyon, France).
- Dissecting contactin-associated protein-like 2 (CASPR2)-antibody encephalitis with patient-derived CASPR2-specific monoclonal antibodies (Dr Bo Sun, University of Oxford/John Radcliffe Hospital, Oxford, UK).
- Clinical and laboratory findings of acute encephalitis syndrome associated with scrub typhus infection in children admitted to tertiary care hospitals in South India (Dr Tina Damodar, Department of Neurovirology, NIMHANS, Bangalore, India).

- Infectious encephalitis during the second wave of COVID-19: an observational study among hospitalised patients in Dakar, Senegal (Dr Jamil Kahwagi, Centre Hospitalier National Universitaire de Fann, Dakar, Senegal).
- Direct evaluation of cervical lymph node and ovarian teratoma as sites of autoimmunisation in NMDAR-antibody encephalitis (Dr Adam Al-Diwani, Department of Psychiatry, University of Oxford, Oxford, UK).
- Developing neurological care and training in resource-limited settings (Assistant Professor Deanna Saylor, The Johns Hopkins University School of Medicine, USA).
- Inborn errors of TLR3-dependent or MDA5-dependent type I interferon immunity in children with enterovirus rhombencephalitis (Dr Jie Chen, The Rockefeller University, New York, USA).
- Spatial and temporal brain atrophy in anti-immunoglobulin-like cell adhesion molecule 5 disease (Ms Selina Yogeshwar, Charité- Universitätsmedizin Berlin, Berlin, Germany).
- Encephalitis and autoimmune encephalitis in paediatric patients from Brazil (Dr Renata Barbosa Paolilo, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), São Paulo, Brazil).
- Novel treatment of an NMDAR-antibody-mediated seizure model (Dr Sukhvir Wright, Institute of Health and Neurodevelopment, Aston University, Birmingham, UK).
- Aetiological diagnosis in central nervous system infections: multiplex PCR (Dr Álvaro Bonelli, Rey Juan Carlos University Hospital, Móstoles, Madrid, Spain).
- SARS-CoV-2 infection causes dopaminergic neuron senescence (Dr Oliver Harschnitz, Sloan-Kettering Institute for Cancer Research, New York, USA).
- Aetiologies of encephalitis in non-HIV-infected patients in Cameroon (Dr Adawa Manuela, COVID-19 ORCA Patient Management Center, Yaoundé, Cameroon).
- Investigating long-term neuropsychological outcomes in paediatric autoimmune encephalitis using magnetoencephalography (Charly Billaud, School of Health and Life Sciences, Aston University, Birmingham, UK).
- Arthropod-borne encephalitides (Winifred Mercer Pitkin Assistant Professor Kiran Thakur, Columbia University Irving Medical Center, USA).

Further funding and work are needed to aid our understanding of this disease, and Encephalitis 2021 ended with a call to action to be part of World Encephalitis Day on 22 February 2022 and Encephalitis research month in June 2022. Encephalitis 2022 will be held on 30 November and 1 December 2022 at the Royal College of Physicians, London and you can receive invitations for abstract and conference sign up by taking advantage of free professional membership (www.encephalitis.info/professional-membership).

Main messages

- Encephalitis describes a syndrome of brain parenchyma inflammation, typically caused by either an infectious agent or through an autoimmune process.

- Patients can present with a combination of fevers, decreased consciousness and other neurological deficits; however, it can sometimes present non-specifically, and this combined with its many causes and lack of recognition make it a difficult to manage neurological syndrome.
- By focusing on findings presented at the Encephalitis Society's conference in December 2021, this article reviews the causes, clinical manifestations and management of encephalitis and integrate recent advances and challenges of research into encephalitis.

Current research questions

- Challenges we recognise in combating encephalitis in 2022 include emerging pathogens, access to therapy in low-income to middle-income settings and characterising autoantibody-mediated encephalitides, as well as a better understanding of the long-term consequences for patients and their families.
- Further funding and work are needed to aid our understanding of this disease, and Encephalitis 2021 ended with a call to action to be part of World Encephalitis Day on 22 February 2023 and Encephalitis Research Month in June 2022.
- Encephalitis 2022 will be held on 30 November and 1 December 2022 at the Royal College of Physicians, London and you can receive invitations for abstract and conference sign up by taking advantage of free professional membership (www.encephalitis.info/professional-membership).

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Self-assessment questions

1. To diagnose encephalitis, patients must have a fever and neurological signs. True/False

2. NMDAR-antibody encephalitis is often linked to underlying ovarian teratomas. True/False
3. IgLON5-antibody encephalitis presents with neurodegenerative presentation with characteristic sleep disturbances. True/False
4. A CT scan is always required prior to conducting a LP in a patient with encephalitis. True/False
5. Aciclovir should be initiated empirically in all patients with suspected encephalitis. True/False

Answers

1. False
2. True
3. True
4. False
5. True

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Contributors

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Competing interests

SRI is an inventor on 'Diagnostic strategy to improve specificity of CASPR2 antibody detection' (PCT/G82019/051257) and receives royalties on a licensed patent application for LGI1/CASPR2 testing as coapplicant (PCT/GB2009/051441) entitled 'Neurological Autoimmune Disorders'. SRI is supported by a senior clinical fellowship from the Medical Research Council (MR/V007173/1), Wellcome Trust Fellowship (104079/Z/14/Z) and the BMA Research Grants—Vera Down grant (2013) and Margaret Temple (2017), Epilepsy Research UK (P1201), the Fulbright UK-US commission (MS-Society research award) and by the NIHR Oxford Biomedical Research Centre. For the purpose of Open Access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission. SRI has received honoraria from UCB, Immunovant, MedImmune, Roche, Cerebral Therapeutics, ADC Therapeutics, Brain, Medlink Neurology and research support from CSL Behring, UCB and ONO Pharma. TS was Chair/Co-Chair of the UKRI/NIHR COVID-19 Rapid Response and Rolling Funding Initiatives (from March 2020), an Advisor to the UK COVID-19 Therapeutics Advisory Panel (UK-TAP, from August 2020) and a member of the MHRA COVID-19 Vaccines Benefit Risk Expert Working Group (from August 2020). He is also a trustee of the UK Academy of 19Medical Sciences (December 2021). TS is President of the Encephalitis Society. TS was an advisor to the GSK Ebola Vaccine programme and chaired a Siemens Diagnostics Clinical Advisory Board. TS was on the Data Safety Monitoring Committee of the GSK Study to Evaluate the Safety and Immunogenicity of a Candidate Ebola Vaccine in Children GSK3390107A (ChAd3 EBO-Z) vaccine. TS chaired the Siemens Healthineers Clinical Advisory Board. Data safety monitoring board: Study of Ebola vaccine and ChAd3-EBO-Z—commercial entity.

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