Encephalitis

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Abstract

Brain inflammation secondary to encephalitis is an urgent global emergency and presents multiple opportunities to reduce current substantial morbidity and mortality. Aetiologies can be divided into infectious and autoimmune causes. We highlight pragmatic clinical approaches to recognize and distinguish the commonest pathogenic viruses and emerging range of autoantibodies encountered in routine practice. These pre-test impressions are judiciously shaped by valuable simple investigations, in particular serum and cerebrospinal fluid nucleic acid and autoantibody testing, to identify the precise aetiological agent. This clinically led approach ensures early recognition of encephalitis subtypes and facilitates the timely administration of antivirals and immunotherapies, proven to improve patient outcomes, and to minimize the frequent misdiagnosis of autoimmune encephalitis. Finally, we review emerging targeted therapeutic approaches, measurements of encephalitis survivor outcomes, urgent environmental and vaccine strategies and novel approaches to, overall, improve diagnosis and holistic care in encephalitis patients, cognisant of long-term patient, caregiver and economic burden.

Introduction

Encephalitis has long been one of medicine's most challenging and enigmatic syndromes: spanning the still-unexplained 20th century epidemic of encephalitis lethargica, the rapidly expanding spectrum of causative autoantibodies identified in the last two decades, and contemporary outbreaks driven by emerging viral pathogens. Encompassed within the umbrella of brain inflammation, encephalitis represents a heterogeneous group of disorders with increasingly recognized infectious and autoimmune aetiologies. Despite the potential for prevention and, in some cases, reversibility with early therapeutic interventions, encephalitis carries a high mortality with myriad sequelae, including life-changing disabilities.[1,2] Encephalitis is observed in people of all ages, sex and ethnicity worldwide, although epidemiological features vary by aetiology. Global incidence data estimates 500,000-1.5 million people develop encephalitis each year.[2-4] In 2021, encephalitis was the fourth leading cause of neurological health loss in children under five, and 13th across all age groups with an estimated 100,000 people dying annually from the condition.[1,3] Encephalitis imposes a substantial economic burden: hospitalisation estimates were ~$2 billion in USA[5] and >£23 million/year in England,[6] excluding costs associated with intensive care, rehabilitation and long-term dependence.

Moreover, the World Health Organization (WHO) describes encephalitis as an 'increasing global threat' with 'an urgent public health imperative'.[7-9] Recommended methods to avert this potential crisis include prevention, improved recognition and timely treatment. Several forms of infectious encephalitis (IE) are preventable, with improved vaccine confidence and vaccination programs key to reducing incidence rates and, thereby, associated death and disability.[10] Further, early diagnosis and timely treatments are interdependent, and equally pivotal in improving patient outcomes and mortality rates. In herpes simplex virus (HSV) encephalitis, timely acyclovir administration reduces mortality from ~70% to ~20%

(p=0.03).[11,12] By analogy, forms of autoimmune encephalitis (AE) show most impressive clinical improvements after early immunotherapy administration, with some studies observing poorer outcomes for each day of immunotherapy delay.[13-15] Prompt treatment administration in IE and AE is primarily facilitated by education of physicians to recognize the key presenting clinical features, a focal point of this review. Improving accurate recognition of encephalitis will avoid two well-recognised problems: missed opportunities for earlier therapies and over-diagnosis. The latter are principally secondary to the misattribution of AE in the context of clinically irrelevant autoantibody results and multiple varied encephalopathy syndromes (Fig.1-3).[16,17]

Over the last two decades, IE incidence has gradually declined, principally due to vaccinations and improved recognition. In contrast, AE diagnoses have risen dramatically, driven by the discovery of pathogenic autoantibodies which identify syndromes previously considered idiopathic.[18-20] Overall, all-cause AE is at least as common as IE in developed countries,[21,22] with similar observations emerging in low-to-middle-income countries (LMIC).[23,24] Hence, AE and IE, and their subtypes, should be considered side-by-side in the contemporary management of encephalitis.

In this *Seminar*, we leverage clinical observations to facilitate the accurate recognition of common IE and AE forms, and highlight established and promising emerging diagnostics. Next, pragmatic acute therapeutic strategies are outlined, alongside promising avenues for precision medicine, and we discuss how these shape patient outcomes after encephalitis. When distinctive, we provide brief perspectives on encephalitis in LMICs, children and immunocompromised hosts. Finally, we review recent developments and highlight outstanding research questions in encephalitis care, spanning prevention, climate change, clinical classifications and enhanced molecular diagnostics.

Search strategy and selection criteria

To capture key recent publications in the field, Embase and Medline databases from 2022-2025 (4th June 2025) were searched using the following terms: encephalitis; anti-N-methyl-D-aspartate receptor encephalitis; viral encephalitis; Japanese encephalitis; West Nile Fever; Varicella Zoster; limbic encephalitis (search strategy, Suppl.Methods WebAppendix p.1). Restrictions included English language, human studies, and clinical studies/trials, observational studies, guidelines, multicentre studies, and practice guidelines. 184 and 350 unique references were generated, respectively. We also searched these articles for further references which we judged relevant, in addition to landmark publications familiar to the authors. Review articles are cited as referenced summaries for topics outside the scope of this Seminar.

What is encephalitis?

Within general medicine, neurology, paediatrics, psychiatry and emergency medicine practices, regularly asked questions include: “is this encephalitis?” and, if so, “which form of encephalitis?” These reflect the importance of recognising syndromes that are potentially treatable or even reversible – and hence *“not to miss”*. Initially, answers can be guided by understanding core features which broadly distinguish encephalopathy from encephalitis (Suppl.Table 1 WebAppendix p.2-3).[25] Encephalopathy typically manifests over a few days with diffuse brain dysfunction, often coma and/or disorientation, but without focal neurological features consistent with structural disease, and commonly with an identified underlying cause including toxins, metabolic disturbances (e.g. liver or renal failure, Wernicke-Korsakoff syndrome), systemic infection, hypertension or cerebral hypoxia.[26-28] Typically, magnetic resonance imaging (MRI) and routine cerebrospinal fluid (CSF) studies are normal, whereas electroencephalography (EEG) shows diffuse slowing, consistent with

global, non-focal, brain disturbances. In contrast, many forms of encephalitis (Fig.1), particularly most known IE, present over a similar time course but with combinations of fever, new-onset seizures and focal deficits, such as aphasia, hemiparesis and brainstem signs, with CSF pleocytosis, and often MRI hyperintensities. In addition to the causes of encephalopathies,[26,28] other mimics of encephalitis include the myriad differential diagnoses within the rapidly progressive dementia category, including treatable conditions such as cerebral vasculitis, inflammatory cerebral amyloid angiopathy, non-convulsive seizures and new onset refractory status epilepticus (NORSE).[29,30] Distinguishing these represents an 'entry' point to specific causes of IE and AE and, hence, directed treatments.

A clinical approach to differentiating common encephalitis aetiologies

Once encephalitis is considered likely (also see Diagnostic Investigations and Fig.4), management options differ by the primary two aetiologically defined subtypes: IE versus AE. Broadly, these share core features of headache, seizures with multiple cognitive and psychiatric disturbances, hence the acute encephalitis work up should involve parallel testing of IE and AE aetiologies, to ensure timely diagnosis (Fig.1-3). Nevertheless, the relative prominence of these clinical features and their onset duration can provide simple features to potentially distinguish between IE and AE and, in many cases, their subtypes (Fig.1).

Most forms of IE present with neurological symptoms a few days after a prodrome of systemic symptoms with combinations of fever, headache, confusion, seizures, psychiatric changes and/or focal deficits. More detailed clinical observations and investigations can differentiate IE aetiologies to guide appropriate management (Fig.2B-C and Suppl.Table 2 WebAppendix p.4-18). Worldwide, the most common IE is mediated by HSV-1, with a bimodal age distribution mostly affecting those <30 and >60 years. In elderly patients or the

immunosuppressed, HSV-encephalitis may present more non-specifically, with altered consciousness and without headache or fever. The other common forms of IE are associated with varicella zoster virus (VZV), West Nile Virus (WNV), Japanese encephalitis virus (JEV), and enteroviruses, and can be differentiated based upon the local epidemiology and more distinctive individual phenotypes (Fig.2B). For example, VZV encephalitis characteristically presents with vasculopathy-mediated strokes; anterior spinal cord involvement with WNV can present with flaccid limb weakness; JEV causes heterogenous movement disorders, and enterovirus often causes additional brainstem features. Although outside of this review's scope, some forms of IE can present more chronically, often require a high index of suspicion, and typically reflect host vulnerability or delayed reactivation, rather than acute pathogen invasion.[31]

In general, most forms of AE present less abruptly than IE, with combinations of cognitive and psychiatric features, seizures, movement disorders, loss of awareness and other focal deficits such as aphasia and limb weakness.[15,19,32] Patient demographics and clinical profiles are often sufficient to distinguish between the common autoantigen-defined syndromes (Fig.1 and 3).[15,19,20,33,34] In turn, this autoantigen-based classification informs the expected immunotherapy response and the likelihood, and nature, of any underlying tumour ('paraneoplastic' syndromes; Fig.3B-C).[35,36] In broad terms, onset over 3-7 days with early and prominent psychiatric features rapidly evolving to seizures, cognitive dysfunction, and/or movement disorders, is most characteristic of N-methyl D-aspartate receptor (NMDAR)-antibodies, the commonest AE in those <40 years.[37] Myelin oligodendrocyte glycoprotein (MOG)-antibodies associate with a similarly acute presentation, representing an increasingly recognised, mostly childhood, AE.[38,39] NMDAR- and MOG-antibody encephalitis can mimic IE as they often show a viral prodrome of coryzal features, fever and mild headache for a few

days. In contrast, most other known AE syndromes present over weeks or even months without these more systemic features. Indeed, a few weeks of frequent focal seizures with amnesia and disorientation represent the hallmarks of leucine-rich glioma-inactivated 1 (LGI1)-antibody encephalitis, which typically affects those >40 years old. [13,40-42] Similar features present in contactin-associated protein like 2 (CASPR2)-antibody encephalitis, which dominantly affects males over 60 years (Fig.3).[40,43] By contrast, a few months of frequent focal seizures with subtle cognitive-affective deficits in a young female suggests glutamic acid decarboxylase 65 (GAD65)-antibody associated encephalitis. Hence, simple clinical observations create pre-test probabilities towards diagnosis of autoantigen-defined AE syndromes, which help direct and interpret first-line investigations in these and the rapidly growing range of AE subtypes (Fig.1, Fig.3-4 and Supplementary Table 3 WebAppendix p.19-32).

Clinical features in autoimmune encephalitis

The last two decades has witnessed a dramatic rise in the number of autoantibodies that strongly associate with forms of encephalitis, meaning the current 10/100,000 prevalence of AE is likely to grow as new autoantibodies continue to be discovered (Fig.3C).[15,21,34,41,42] Many AE-associated autoantibodies are directed against intracellular targets (Fig.3C and Supplementary Table 3 WebAppendix p.22-32): these lack access to their target in intact, live neurons and glia, and, hence, are considered non-pathogenic.[18,19] Rather, they represent valuable biomarkers of conditions likely mediated by T cells,[44] often indicating predictable clinical profiles and directing a search for specific remote tumours.[35,36] For example, severe isolated cerebellar ataxia often associates with Yo-antibodies and a uterine, fallopian or breast cancer, whereas limbic-hypothalamic encephalitis with narcolepsy associates with Ma2-antibodies and a testicular cancer.[36]

By contrast, autoantibodies directed against extracellular epitopes are likely directly pathogenic (Fig.3C).[15,18,20] The commonest of these autoantigens, LGI1, the NMDAR, CASPR2 and MOG, each show distinctive features (Fig.3B). As autoantibody results often take a few weeks to return, recognition of characteristic clinical features remains key to early diagnosis.

LGI1-antibody encephalitis is the commonest form of adult onset AE, with an incidence of ~2/million/year, a ~2:1 male:female ratio, and median age of onset 64 years.[13,40,42] Typically, LGI1-antibody encephalitis presents over a few weeks with increasingly frequent focal seizures, often occurring several times per hour at disease nadir (Fig.4G). LGI1-antibodes associate with a pathognomonic seizure appearance, termed faciobrachial dystonic seizures (FBDS), consisting of short-lived posturing episodes predominantly affecting the ipsilateral face and arm (Fig.3B; Suppl.Videos 1-2).[13,45] FBDS are described by patients as jolts, jerks, or spasms, lasting 1-3 seconds, and may be dramatic and associated with dropping items and falls. Typically, after a few weeks of increasing frequencies of FBDS, or other focal seizures, patients develop dense anterograde and retrograde amnesia with disorientation and behavioural changes. This can be mistaken for neurodegenerative conditions, such as Alzheimer's disease, particularly in the ~50% without medial temporal lobe swelling on MRI,[46] although most dementias present over years with few seizures.[16] Under 5% of LGI1-antibody encephalitis patients have a tumour, and 50% have serum hyponatraemia, a potential early, albeit non-specific, diagnostic clue.[13]

CASPR2-antibody encephalitis shows several similarities with LGI1-antibody encephalitis (Fig.3B), as a late-onset male dominant disease (8:1 ratio), and both share strong yet distinct

HLA-DRB1 allele associations.[47] However, CASPR2-antibody encephalitis patients display fewer seizures with more sleep disturbances, dysautonomia and cerebellar involvement, and 50% show peripheral nerve involvement with hyperexcitability or neuropathic pain and, particularly in these cases (often termed Morvan's syndrome), a thymoma should be excluded.[36,40,43]

NMDAR-antibodies cause the commonest form of AE in children and young adults,[14,37,48] and show an overall ~30% association with ovarian teratomas, partly accounting for the observed 3:1 female bias. The teratoma contains germinal centre-like structures and B cells which can secrete NMDAR-antibodies, likely explaining clinical benefits observed after early tumour removal.[37,49] More rarely, NMDAR-antibody encephalitis affects those >50 years with a low rate of teratomas but high rate of myriad malignancies, and a poor overall prognosis.[37,50]Adults typically present over a few days with florid multi-domain psychiatric manifestations spanning affective, psychotic, behavioural and sleep features, often resulting in early encounters with mental health services.[14,37,48] However, typically within just a few days, almost all patients develop cognitive disturbances, seizures and/or a complex movement disorder characterised by dystonia, chorea, stereotypies and catatonia (Suppl.Videos 3-5). This rapid onset and progression to neurological deficits typically distinguishes NMDAR-antibody encephalitis from primary psychiatric diagnoses.[51-54] Childhood presentations usually show less florid psychiatry and, rather, a rapidly evolving encephalopathy with more prominent seizures and movement disorders.[55,56] Thereafter, within just a few more days, both adults and children frequently require intensive care for depressed consciousness and/or central hypoventilation, and ~30% develop a multi-organ dysautonomia associated with potentially lethal cardiac dysrhythmias.[14,37,48] Early screening for these typical sequelae, with appropriate monitoring measures, aims to help reduce the consistently reported

mortality rate of 5-10%.[14,37,48,57] Despite the marked severity of this encephalitis, routine MRI is typically unremarkable.[58] Indeed, biomarkers of recovery in this, and other forms of AE, are still required to help titrate immunotherapy regimes.

In MOG-antibody encephalitis, the next most common paediatric AE which can also affect adults, patients show a short history of delirium, focal deficits and seizures, often with a meningoencephalitis causing headache and neck stiffness.[39,59] MRI is usually abnormal and can be highly characteristic, revealing cortical and subcortical swelling, with both parenchymal and meningeal enhancement (Fig.4D).[39] Patients may also manifest synchronous or old optic neuritis and transverse myelitis, other well-recognised associations of MOG-antibody associated disease (MOGAD). CSF typically contains leucocytes, often with a high opening pressure, and tumours are rare.[38]

GAD65-antibody associated AE predominantly affects young adult females with accompanying autoimmune comorbidities, who have a few months of progressive frequent focal seizures, with mild memory and affective disturbances but without prominent disorientation.[41,60] This dominant phenotype of temporal lobe seizures and neuropsychiatric involvement without delirium is typically accompanied by normal routine CSF and MRI findings. Serologically, very high levels of GAD65-antibodies are required to confirm neurological relevance, compared to the far lower levels found in type 1 diabetes and a substantial proportion of healthy subjects.[60,61]

Other less common forms of AE are associated with antibodies against multiple neuronal and glial proteins, including the gamma-aminobutyric acid (GABA) A and B, glycine and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors (Fig.3C and

Suppl.Table 3 WebAppendix p.19-32).[15] Also, ~10-20% of patients lack a known autoantibody target, termed 'seronegative' AE:[62] to avoid over-diagnosis of a syndrome with – by definition – absence of serological biomarkers, coherence should be carefully sought between typical clinical, imaging and CSF findings.[16] The increasing numbers of oncology patients that are administered immune checkpoint inhibitors and CAR-T cells can develop AE, as one immune-related adverse effect.[63,64] In these cases, management focuses on balancing the pressing need to treat the underlying cancer against risks of inducing neurological worsening or relapse.

Recent observations have temporally linked aetiologically distinct forms of AE and IE with the recognition that acyclovir-treated HSV-1 encephalitis can precede, typically by 6-12 weeks, a form of AE most closely resembling NMDAR-antibody encephalitis and without detectable CSF HSV-1 DNA.[65,66] This example of post-infectious autoimmunity occurs in ~25% of children and adolescents with HSV-1 encephalitis, with lower rates in adults, and is successfully treated with immunotherapy without further antimicrobials.

Clinical features in infectious encephalitis

IE remains a significant global neurological burden is highly heterogeneous, varying by geography, season, and year.[3] Five pathogens contribute a substantial proportion of cases globally, namely, HSV, VZV, WNV, JEV and enteroviruses, and their clinical (Fig.2) and radiological features (Suppl.Fig.1 WebAppendix p.39) will be our focus herein. Prior reviews have comprehensively summarised more extensive ranges of IE.[67,68]

JEV remains the leading cause of epidemic encephalitis in Asia, accounting for ~25,000 deaths annually.[69] Although most human JEV infections are asymptomatic, particularly among vaccinated individuals, a minority develop clinically apparent disease, classically with

an acute encephalitis.[70] Historically, this severe disease occurred predominantly in children; however, in regions with sustained paediatric vaccination programs, the epidemiology is shifting to increasingly affect adults.[71] The incubation period of JEV ranges from 5-15 days following an infective mosquito bite. Onset is typically with a non-specific febrile prodrome of fever, headache, and vomiting, which may progress within several days to delirium and seizures.[70,72-74] JEV exhibits marked neurotropism for deep grey matter structures, with the thalamus and basal ganglia frequently demonstrating lesions by both neuroimaging and neuropathology (Fig.4B). Consistent with this, affected individuals often develop movement disorders including parkinsonism through hyperkinesis, such as chorea and athetosis.[74,75] These can resemble abnormal movements in NMDAR-antibody encephalitis (Suppl.Videos 3-5), which can occur occasionally after JEV.[24,76] Vaccination remains the most effective preventive measure for JEV, recommended by WHO for those living in or traveling to endemic areas, and can provide long-lasting protection.[77]

HSV-1 is the predominant cause of sporadic encephalitis in Western countries.[3] Unlike JEV, there is no effective HSV-1 vaccine and long-term morbidity persists in ~90% of patients.[78,79] However, prompt intravenous acyclovir dramatically decreases mortality, making its empirical administration standard of care with continued acyclovir recommended until a true negative CSF HSV-1 PCR result.[79-81] Multiplex testing platforms can shorten the time to HSV detection, thereby reducing unnecessary empiric acyclovir use, improving cost-effectiveness and decreasing length of hospital stay.[82,83]

WNV is the most common mosquito-borne cause of encephalitis in North America, with outbreaks reported in parts of Europe, the Middle East, North Africa and Africa.[84] In the USA, neuroinvasive disease occurs with a 5% case-fatality and 59% hospitalization rate,[85] while Europe reported 1,340 locally acquired cases and 104 deaths in 2022.[86] Similar to JEV,

~80% of infections are asymptomatic. While the majority of symptomatic cases are self-limited febrile illnesses,[84] neuroinvasive disease occurs in <1%, typically primarily older adults and immunocompromised patients who present with fever, headache, vomiting, rash, altered mental status and systemic laboratory abnormalities, including hyponatremia, acute renal failure, and lymphopenia.[84,87] Also, acute flaccid paralysis can be a characteristic feature causing weakness and wasting of arms or legs. EEG, MRI and CSF frequently demonstrate abnormalities, the latter often markedly so, with >50 cells/μL.[87,88] Neuroinvasive disease is established by detection of CSF WNV-IgM. Currently, no vaccine or targeted antiviral therapy exists with supportive care representing standard of care, and mosquito and avian host public health measures essential for transmission prevention.

Enteroviruses are a major global cause of paediatric encephalitis, particularly in Asia and South Asia, especially enterovirus-A71.[89-91] Outbreaks are seasonal in temperate climates but may occur year-round in tropical regions, with the geographic distribution varying by strain.[92] Clinically, enterovirus encephalitis usually presents with fever, headache, altered mental status, and, in severe cases, coma. Certain strains are associated with distinct clinical phenotypes. For example, enterovirus-A71 has been linked to severe and sometimes fatal brainstem inflammation, whereas enterovirus-D68 has been implicated in associated acute flaccid paralysis.[93,94] Diagnosis relies on the detection of CSF enteroviral RNA by PCR; whereas serologic testing is generally less sensitive. Given no specific therapies exist for enteroviruses, current management is primarily supportive, with ongoing research exploring antiviral and immunomodulatory strategies for severe cases.

VZV can cause both meningitis and encephalitis, with encephalitis occurring more frequently in older adults and immunocompromised individuals and is associated with worse outcomes.[95-97] A vesicular rash may only infrequently accompany VZV encephalitis.[79,96] VZV

encephalitis commonly results in a vasculopathy, affecting large or small vessels, which leads to ischemic or haemorrhagic strokes.[98] Neuroimaging may reveal frontal and temporal lobe oedema, which can mimic HSV-1 encephalitis (Fig.4A),[99] and vascular imaging vessel wall irregularities or stenosis, consistent with a vasculopathy.[100] CSF VZV PCR has limited diagnostic sensitivity, whereas CSF VZV IgG detection is more sensitive although sometimes negative early in the disease course.[101,102]

Diagnostic Investigations

The four most important first-line investigations, blood tests, CSF studies, brain imaging and electroencephalography (EEG), show false positive and negative results in IE and AE subtypes, mandating their interpretation alongside well-formed clinical impressions.

Routine blood testing is typically normal in AE and IE, principally providing reassurance to exclude systemic causes of encephalopathy, such as metabolic disturbances or sepsis (Suppl.Table 1 WebAppendix p.2-3). An important exception is AE-associated autoantibodies which, wherever possible, should be tested in both blood and CSF.[41]

CSF provides a window into the brain and is indicated in *all* suspected cases of encephalitis not exhibiting the very few absolute contraindications to sampling CSF (Fig.2A). Spinal taps are usually well tolerated, only require local anaesthetic, last ~15 minutes with an experienced operator, necessitate minimal post-procedure bedrest and low-diameter blunt needles induce post-procedure headaches in <5%.[103,104] Yet, CSF is too often obtained late, principally due to concerns around headache and the very rare complication of cerebral herniation. However, simple recommendations to stratify associated risks are proven to reduce mortality and time to antimicrobials, and improve patient outcomes.[105,106] In practice,

clinicians suspecting acute encephalitis should exclude the few features strongly suggestive of markedly raised intracranial pressure,[107,108] and urgently obtain CSF and immediately thereafter administer intravenous acyclovir, plus consider empiric antibiotics to cover a possible bacterial meningoencephalitis (Fig.2A). In cases where a CSF collection must be delayed until CT can be performed, or in very agitated patients who may need sedation, acyclovir can be administered empirically, with the intention of rapidly excluding contraindications, achieving a short lag to CSF sampling.

In the appropriate clinical context, an elevated CSF leucocyte count (>5 cells/μL) often confirms the syndromic diagnosis of encephalitis. A normal CSF leucocyte count is a useful 'rule out' for IE, although imperfect as ~20% of patients may lack leucocytes particularly those sampled early in their illness, the immunocompromised or elderly.[109] Next, to define the specific IE cause, rapid multiplex PCRs from CSF can detect several pre-specified viruses, bacteria, and fungi. When unsuccessful, metagenomic next-generation sequencing may theoretically detect any CSF DNA or RNA, including from novel organisms,[68] although false negatives can occur with low CSF nucleic acid burden, and some chronic or latent infections. Adjunctive serological, respiratory or stool evaluations may still be required to identify some infectious pathogens, for example WNV, JEV and Eastern Equine Encephalitis.

Elevated CSF leucocyte counts by routine microscopy are only detected in some AE subtypes, notably with NMDAR- and MOG-antibodies (Fig.1). Flow cytometry is more sensitive and detects abundant immune cells in many acute AE patients, yet not widely available outside of research laboratories.[110,111] CSF autoantibodies are a highly specific result in AE,[112] although in some AE, most notably with LGI1-antibodies, serum autoantibody testing is more sensitive.[41] CSF protein and glucose levels are typically unremarkable or non-specifically elevated in most forms of IE and AE.

While CT head can facilitate select spinal taps, it is rarely diagnostic in AE, and in only few subtypes of IE, notably the HSV-1 encephalitis associated frontotemporal intracranial haemorrhage and cerebral oedema (Fig.4A). Brain MRI is more useful than CT, given a normal MRI represents a sensitive 'rule out' for IE, and abnormal MRI patterns can often substantially narrow down the specific pathogen (Supplementary Fig.1 WebAppendix p.39). In several forms of AE, swelling predominantly affects the limbic regions ('limbic' encephalitis; Fig.4C), particularly the medial temporal lobes on T2-weighted/FLAIR sequences. When this swelling extends outside the hippocampal-amygdala regions, or is accompanied by diffusion restriction or contrast enhancement, IE is favoured over AE.[46] MRI can also show multifocal white matter lesions affecting subcortical regions and deep nuclei, for example in association with MOG- and $GABA_AR$-antibodies (Fig.4D-E). However, MRI is unremarkable in >50% of common forms of AE, including LGI1-, CASPR2- and NMDAR-antibody encephalitis (Fig.1), a finding which commonly prompts under-diagnosis.[16] Upon suspicion of a paraneoplastic condition, CT or PET body imaging directs the search for a tumour (Fig.4F).

EEG is another valuable early investigation to rule out treatable subclinical seizures and, in AE cases with normal MRI, to observe focal or diffuse slowing which support the diagnosis.[32,113] EEG is normal in 20-60% of AE cases but abnormal in 50-90% of IE cases, exhibiting few specific features such as temporal lobe periodic lateralized epileptiform discharges in HSV-1 encephalitis.[113,114]

Management

A common, critical theme in both AE and IE is the time-dependent potential for recovery and need to prioritise prompt administration of immunotherapies and antimicrobials, respectively. Additionally, supportive care includes strategic use of anti-psychotics, mood stabilizers, benzodiazepines and anti-seizure medications, to control the varied psychiatric, behavioural, sleep, movement disorder and seizure manifestations.[115] In AE, the risk of an enduring tendency to seizures, hence autoantibody-associated epilepsy, is generally <10%, typically mitigating need for lifelong anti-seizure medications.[116,117] Whereas post-IE, epilepsy is more common and often benefits from anti-seizure medications.[118] Additionally, differential frequencies of tumours associated with AE subtypes offer stratified approaches to prompt tumour identification and removal (Fig.3).[36]

Acyclovir (10 mg/kg three times daily for at least 14 days) remains the cornerstone of HSV-1 encephalitis treatment,[12] with greatest benefit proven to occur when administered within 24–48 hours of symptom onset.[119] Acyclovir can safely be administered concurrently with dexamethasone (10 mg/kg four times daily for 4 days), albeit without apparent clinical benefits.[120] Other antiviral therapies indicated for further specific pathogens, include ganciclovir for cytomegalovirus encephalitis, and acyclovir or valacyclovir for VZV.[5] For certain RNA viruses, including enteroviruses or flaviviruses, agents under evaluation include ribavirin and favipiravir.[121]

Immunotherapies are the mainstay of AE treatment and their early administration consistently associates with improved outcomes across AE subtypes.[13,14,122,123] Yet, the only one completed randomized controlled trial (RCT) confirmed a small, statistically significant benefit of IVIG over placebo in both achieving seizure control and cognitive improvements in LGI1-/CASPR2-antibody encephalitis ($p=0.044$, odds ratio = 10.5, 95% CI = 1.1–98.9).[124] Therefore, while several trials are actively recruiting (Suppl.Table 4 WebAppendix p.33-

38),[125] current evidence comes largely from retrospective observational data and expert consensus.[115,122] Broadly speaking, each antigen-defined syndrome has relatively distinct immunotherapy requirements. For example, most patients with LGI1-antibody disease show seizure cessation and improvements in both cognition and quality of life within a few weeks of first-line therapies, corticosteroids, plasma exchange and/or IVIG.[13,40,126] Whereas, in NMDAR-antibody encephalitis ~50% of patients show limited responses to these agents, and benefit from addition of second-line therapies, in particular rituximab, cyclophosphamide and ofatumumab, which reduce disability, mortality, relapse rates, and corticosteroid-induced side effects.[14,37,57,127,128] Across AE syndromes, optimal times to escalate and withdraw these immunotherapies are not yet understood.[115] On the contrary, benefits of immunotherapy in GAD65-antibody encephalitis appear limited, if any.[60]

Multiple alternative immunotherapies are emerging and are either in or approaching clinical trials in AE (Fig.5; Suppl.Table 4 Web Appendix p. 33-38). Examples monoclonal antibodies (e.g. inebilizumab) or chimeric antigen receptor (CAR) T cells which target CD19, and likely delete broader B cell lineages than anti-CD20 agents, drugs which target both many B and plasma cells (e.g. CD38-directed daratumumab), proteosome inhibition which more selectively targets plasma cells (e.g. bortezomib), blockade of the pleotropic IL-6-IL-6R pathway with tocilizumab or satralizumab, and accelerated IgG degradation via FcRn blockade.[129,130] More precision experimental therapies include monovalent nonfunctional recombinant NMDAR-antibodies which block endogenous pathogenic autoantibody binding, direct modulators of autoantigen function,[131,132] and chimeric autoantibody receptor T cell therapies which express the autoantigen therefore aiming to selectively deplete autoantigen-reactive B cells.[133]

Outcomes

After acute, and in some cases prolonged, immunotherapies the overall function of AE patients continues to improve for several years.[13,14,43,134] In IE, there are more limited improvements after acute anti-viral agents, likely due to the less reversible nature of the original lesion. Overall, most patients with AE and IE develop persistent, often substantial, stereotypical sequelae across cognitive, physical, psycho-social and functional domains (Fig.6A).[135-137] Major residual neurocognitive problems involve memory, mood, personality changes, emotional regulation, attention, sleep and fatigue, with varied relative preponderances across specific AE and IE syndromes.[134-140] Such deficits are likely underrecognized due to limited patient follow-up, encephalitis-induced communication and cognitive difficulties, and limited research exposure, falsely truncating the comprehensive encephalitis survivor experience.

Relapses are also a concern in AE, with rates of 10-50%, varying with AE subtype. Relapses can be challenging to identify, particularly in patients re-presenting with *formes frustes* of the sentinel syndrome, such as seizures or psychiatric features alone. In this setting, clinically-anchored decision making alongside repeat investigations should distinguish between a genuine relapse rather than post-encephalitis manifestations, to prompt immunotherapy and prevent deterioration.

In both adults and children, long-term functional consequences of encephalitis include failure to return to work, delayed education, and limited social reintegration, and often become apparent only after formal detailed neuropsychological testing, occupational health assessments or carer interviews.[136,138,141] Resultant delays in engaging with multiple relevant services can significantly burden both patients and caregivers. Additional challenges include poor public awareness of encephalitis, under-recognised post-traumatic stress disorder after

prolonged ICU admissions, and, for AE patients, pervasive anxiety around potential relapses.[142] Despite these observations, comprehensive patient journeys remain poorly described in IE and AE, yet may identify features not captured by clinicians (Supplementary videos 6-7).

In AE, this issue is confounded by having imported scores from other disciplines.[136] The modified Rankin score (mRS), extensively reported in AE, was originally a clinician-assessed stroke outcome tool, primarily capturing physical and functional activities of daily living. The clinical assessment scale in AE (CASE) represents a more specific clinician-reporting tool including AE-relevant domains such as seizures, conscious level, psychiatric features and movement disorders, making it particularly well suited to NMDAR-antibody encephalitis.[143] Only one dedicated patient reported outcome measure (PROM) has been reported in AE, in LGI1-antibody encephalitis:[135] termed LANTERN, and correlates more closely with patient-rated quality-of-life than either clinician-rated or imported patient rated scales (Fig.6B). Similar to AE, global disability scales including the mRS, Glasgow Outcome Scale, Barthel Index and generic health-related quality-of-life measures (e.g. Euro-Qol-5D) are commonly used in IE, though not validated in this setting.[137] To better incorporate cognitive and psychosocial sequelae, the Liverpool Outcome Score was developed specifically for paediatric encephalitis, and demonstrates sensitivity to early recovery.[144] IE-specific PROMs are awaited to significantly enhance patient-centeredness and clinical relevance in both research and practice.

Controversies and Outstanding Research Questions

Recent years have witnessed major strides towards delineating causes of previously idiopathic forms of AE and IE, establishing large cohorts to retrospectively analyse their management, and evaluate outcomes. Yet, multiple unresolved questions demand focused

attention to guide future clinical and scientific directions and decrease the still significant morbidity and mortality.

First, the aetiology of a substantial proportion of cases remains undetermined even with current molecular and serologic techniques, highlighting the need for more sensitive and multiplex platforms, including low cost point-of-care testing to better serve LMICs.[145,146] Second, there is limited understanding of potentially-modifiable host factors, including genetic and immunologic susceptibilities in IE and AE.[47,147] Yet, these are paramount to understanding pathogenesis and hence root cause directed treatments. Third, epidemiologic data remain incomplete, particularly in many LMICs, where under-diagnosis is prevalent given limited contemporary diagnostic facilities and reporting systems.[148] Finally, rehabilitation and supportive interventions are under-explored, yet would likely benefit encephalitis patients.

In IE, emerging and re-emerging aetiologies represent a significant global health challenge, driven by viral evolution, environmental changes and globalization. Climate change has expanded the geographic range and activity of mosquito and tick vectors, with increased WNV and JEV, and examples including Zika, Chikungunya and Powassan viruses as causes of IE in previously unaffected regions.[149,150] Deforestation has increased human contact with wildlife reservoirs, facilitating spillover events such as high-mortality sporadic outbreaks secondary to Nipah virus, with high pandemic potential.[151] Availability and uptake of vaccinations remains challenging, with vaccination programs for pathogens such as JEV and tick-borne encephalitis markedly reducing disease burden. Whereas declines in vaccine coverage correspond to cases of measles encephalitis and subacute sclerosing panencephalitis, illustrating severe consequences of vaccine hesitancy.[152] Continued investment in vaccine deployment and vector control strategies are essential to mitigate these

emerging threats and, reassuringly, vaccines have not been associated with new cases of neurological autoimmune diseases.[153,154]

In AE, there remains frequent diagnostic conflation with several other clinical entities, including seronegative AE, Hashimoto's encephalopathy, Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS), and subacute neurodevelopmental or regression syndromes.[16,112,155-158] Additionally, isolated psychiatric features, brain fog and subjective disorientation are highly unusual presentations of AE.[15,53] Collectively, reports associating these syndromes and presentations with AE usually suffer from limited or low-quality autoantibody testing, including employment of non-native autoantigens, testing of CSF or serum in isolation and high rates of low-specificity autoantibodies in healthy or disease controls, a lack of objective inflammatory findings on CSF or MRI testing, and diagnostic constructs which are largely consensus-based and remain in evolution.[16,53,112,159] Hence, these disorders show ongoing uncertainties regarding robust biomarkers, pathobiology, and disease boundaries: key areas for future study. Within this, robustly-standardized autoantibody detection methods are also a fundamental future aim which should strive to retain conformationally native formats of autoantigens, hence mimicking those which patient IgG recognise *in vivo*.[16,20,34] In parallel, characterising the B and T cell biology which fundamentally underlies autoantibody production is showing clear avenues to improve biological disease understanding while guiding novel diagnostics and therapeutics, towards patient-centric care pathways.[111,133,160,161]

Conclusions

The last few years have reclassified many once enigmatic and idiopathic forms of encephalitis with molecularly precise aetiology-based definitions. Yet, improved physician education regarding clinical presentations, targeted research agendas and funding to improve

diagnostic capacities, and global public health initiatives are essential to meet the outstanding urgent patient needs aimed at reducing the overall encephalitis survivor and carer burden to improve outcomes in this, WHO-designated, urgent public health imperative.

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Conflict of interests

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Encephalitis International: she personally receives no honoraria or grant support, Encephalitis International does receive grants, honoraria, speaker fees and expenses from various sources including pharmaceutical and diagnostic companies. KT has received consulting fees from Delvie Bio, the Pan American Health Organization, and the World Health Organization. KT is a member of Encephalitis International Scientific Advisory Panel. SRI has received honoraria/research support from UCB, Immunovant, MedImmun, Roche, Janssen, Cerebral therapeutics, ADC therapeutics, Brain, CSL Behring, and ONO Pharma; licensed royalties on patent application WO/2010/046716 entitled “Neurological Autoimmune Disorders”; and has filed two other patents entitled “Diagnostic method and therapy” (WO2019211633 and US-2021-0071249-A1; PCT application WO202189788A1) and “Biomarkers” (PCT/GB2022/050614 and WO202189788A1).

Author contributions

SB - Conceptualization, Data curation, Formal Analysis, Methodology, Visualization, Writing-original draft, Writing-review & editing. DS - Conceptualization, Data curation, Formal Analysis, Methodology, Visualization, Writing-original draft, Writing-review & editing. AE - Conceptualization, Data curation, Formal Analysis, Methodology, Resources, Visualization, Writing-original draft, Writing-review & editing. KT - Conceptualization, Data curation, Formal Analysis, Methodology, Visualization, Writing-original draft, Writing-review & editing. SRI - Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Resources, Supervision, Visualization, Writing-original draft, Writing-review & editing. The authors confirm that the paper has not been submitted to another journal, and has not been published in whole or part elsewhere.

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Figure legends

Figure 1. Pragmatic approach to distinguish common forms of encephalitis. Encephalopathy, infectious encephalitis and forms of autoimmune encephalitis can be largely differentiated based on tempo of symptom onset, the dominant clinical features and, thereafter, by incorporating MRI, presence of CSF cells and PCR results. This clinical 'rule of thumb' is intended to provide a simple, digestible approach to capture common encephalitis syndromes, without being definitive, and should be refined with data from Supplementary Table 1, Figure 2 and 3. ROC = reduction of consciousness.

Figure 2. Acute and Infectious encephalitis: features and approach. A. Approach to diagnostic work up in acute encephalitis including safe expedition of cerebrospinal fluid sampling,[107,108] and timely, parallel testing of both infectious and autoimmune aetiologies from blood and CSF. **B.** Pathogen discovery timeline, describing vaccine preventable (blue, above line) and currently non-preventable aetiologies (pink, below line). Black dots represent when the virus was isolated, blude dots when the virus was discovered and syringes when the vaccine was discovered. *Mouse-brain derived; **Cell-culture derived. Created with BioRender.com. **C.** Key clinical features of the five commonest IE viruses, with rates of each feature displayed in each cell, extracted from the five largest studies of each virus. Median age of onset shown, Sx = symptoms, MRI = temporal lobe changes, CSF = leucocytosis, EEG = electroencephalogram abnormalities. Zeros are entered for unreported data.

Figure 3. Autoimmune encephalitis features and discovery timeline. A. Fundamental clinical features across demographics, symptoms and simple investigations direct the detection of autoantigen-reactive antibodies. Examples shown with LGI1 and NMDAR

antibodies which are somewhat skewed towards white and non-white populations, respectively. Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved. **B.** Demographics, clinical features and investigations in autoimmune encephalitis extracting the rates of each feature from the five largest studies of each of the five commonest autoantibodies. Median age of onset shown, FBDS = Faciobrachial dystonic seizures, MD = movement disorder, ↓Na+ = serum hyponatraemia, MRI = temporal lobe changes, CSF cells = leucocytes; EEG = electroencephalogram abnormalities. Zeros are entered for unreported data. **C.** Timeline of discovery for autoantibodies which target extracellular (above line) and intracellular (below line) epitopes. Created with BioRender.com.

Figure 4. Brain imaging and patient diary in infectious and autoimmune encephalitis. A. CT head showing haemorrhage (arrows) and oedema (hypodense) in right temporal lobe secondary to HSV-1 encephalitis. **B.** Left and right basal ganglia involvement with Japanese encephalitis virus. **C.** Limbic encephalitis associated with autoantibodies against the $GABA_B$ receptor associated with hippocampal-amygdala high signal on T2 imaging (arrows). **D.** FLAIR imaging showing multifocal bilateral subcortical and right thalamic hyperintensities associated with MOG antibodies. **E.** Multifocal fluffy cortical and juxta/subcortical FLAIR hyperintensities seen with $GABA_A$-receptor antibody encephalitis. **F.** Left hilar lymph nodes associated with small cell lung cancer and $GABA_B$ receptor antibodies. **G.** Patient diary recording one day of focal seizures per column, daily totals are circled.

Figure 5. Established and emerging immunotherapies for treating autoimmune encephalitis. After first line therapies, second line immunotherapies should be considered, including B cell depletion with CD19 or CD20 targeting medications, and also CAR-T cells, IL-6R blockade with tocilizumab or satralizumab (an example of cytokine modulation) and drugs which delete plasma cells, including daratumumab (targeting CD38, which is also expressed on some B cells) and the proteosome inhibitor bortezomib. Emerging options include inhibition of leucocyte entry to the CNS (e.g. natalizumab), blockade of FcRN IgG uptake to prolong the half-life of IgG (e.g. with efgartigimod), blockade of the endogenous antibody binding (e.g. with single decoy arm therapeutics), direct pharmacological autoantigen binding to overcome the autoantibody effects (e.g. allosteric modulators), CAART cells which express the autoantigen to induce selective deletion of autoantigen-reactive B cells and a variety of T cell tolerisation or modulation approaches, to deny help to

B cells. Depicted key neuroimmune compartments involved in the generation of pathogenic autoantibodies include bone marrow (the source of B cells and early T cells) and lymph nodes (a key site of B-T cell crosstalk).
CAR-T = Chimeric Antigen Receptor T cells. CAART = Chimeric AutoAntibody Receptor T cells. CNS = Central Nervous System. FcRN = Fc receptor neonatal. IL-6R = interleukin-6 receptor. Created with BioRender.com.

Figure 6. Patient outcomes after encephalitis. A. Multiple functional domains are affected by infectious and autoimmune encephalitis. **B.** In LGI1-antibody encephalitis the patient rated quality of life (EQ5D-VAS) correlates most closely with the patient reported outcome measure, rather than clinician assessed modified Rankin score (mRS) or clinical assessment scale in AE (CASE).[135]

Supplementary Figure 1. MRI findings in infectious encephalitis. Suggestive neuroradiographic patterns categorized by immunocompromised state (broadly, AIDS, post-transplant, medication-related).

Supplementary videos

Supplementary videos 1-2. Faciobrachial dystonic seizures. Video 1 from [45] (with permissions) showing the highly distinctive frequent dystonic spasms affecting the face and ipsilateral arm, with some also involving the leg and precipitating a fall in Video 2.

Supplementary videos 3-5. NMDAR-antibody encephalitis movement disorders. From[162] (with permissions). Complex leg and arm movements with choreiform, dystonic and stereotypy components (Video 3), complex limb movements in an agitated child (Video 4) and orofacial and limb involvement (Video 5).

Supplementary video 6. A lived experience of infectious encephalitis. https://youtu.be/me6qqoqF0t8?si=s-hJIpBIPqa0x1N8.

Supplementary video 7. A lived experience of autoimmune encephalitis. https://youtu.be/Wh3jb7s1x48?si=HOyEVVG2A6O9TOSg

Supplementary video 8. Approach to Encephalitis by Setting. In this video, Dr. Deanna Saylor (University of North Carolina, USA) discusses with Dr. Kathryn Holroyd (Columbia University, USA) and Dr. Mashina Chomba (University of Zambia) their diagnostic and therapeutic approaches for patients presenting with possible encephalitis. They focus on how resource constraints and availability necessitate thoughtful adaptations to recommended approaches. Drs. Holroyd and Chomba also discuss how local epidemiology affects their pre-test probability of infectious versus autoimmune encephalitis and how this impacts their diagnostic and empiric therapeutic approaches as well.

Web appendix

Supplementary Methods – full search strategy

Supplementary Table 1. Clinical and investigation features which help differentiate forms of encephalopathy and encephalitis.

Supplementary Table 2. Infectious causes of encephalitis.

Supplementary Table 3. Autoantibodies which target extracellular and intracellular epitopes, the latter divided into non-tumor and tumour associated (paraneoplastic).

Supplementary Table 4. Trials in autoimmune encephalitis and related disorders.

Supplementary Figure 1. MRI findings in infectious encephalitis.