Acute encephalitis in immunocompetent adults

Arun Venkatesan, Benedict D Michael, John C Probasco, Romergryko G Geocadin, Tom Solomon

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Johns Hopkins Encephalitis Center, Department of Neurology (A Venkatesan MD, Prof R G Geocadin MD, J C Probasco MD), **Department of Neurosurgery** (Prof R G Geocadin), **and Department of Anaesthesia/Critical Care** (Prof R G Geocadin), **Johns Hopkins University School of Medicine, Baltimore, MD, USA; Center for Immune and Inflammatory Disease, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA** (B D Michael, MRCP); **National Institute for Health Research Health Protection Research Unit in Emerging and Zoonotic Infections, Institute of Infection and Global Health, University of Liverpool, Liverpool, UK** (B D Michael MRCP, Prof T Solomon FRCP); **and Department of Neurology, the Walton Center NHS Foundation Trust, Liverpool, UK** (B D Michael, Prof T Solomon)

Correspondence to:
Dr Arun Venkatesan, MD
Johns Hopkins Encephalitis Center, Department of Neurology, Johns Hopkins School of Medicine, Baltimore, 21287 MD, USA
avenkat2@jhmi.edu

Encephalitis is a condition of inflammation of the brain parenchyma, occurs as a result of infectious or autoimmune causes, and can lead to encephalopathy, seizures, focal neurological deficits, neurological disability, and death. Viral causes account for the largest proportion, but in the last decade there has been growing recognition of anti-neuronal antibody syndromes. This Seminar focuses on the diagnosis and management of acute encephalitis in adults. Although viral and autoimmune causes are highlighted because of their prominent roles in encephalitis, other infectious pathogens are also considered. The role of cerebrospinal fluid studies, MRI, and novel diagnostic modalities (eg, next-generation sequencing) are discussed. Management approaches, including treatment of acute neurological complications and the use of immune suppressive and modulatory drugs for cases of suspected or confirmed autoimmune cause, are covered. Additionally, we discuss the remaining challenges in the diagnosis, management, and prognosis of encephalitis.

Introduction

Encephalitis is inflammation of the brain parenchyma with associated neurological dysfunction and can be due to a wide variety of infectious and autoimmune causes. Encephalitis most often manifests as encephalopathy, although for autoimmune encephalitides short-term memory loss or new onset psychiatric changes alone can occur (panel 1).[1,2] Patients with suspected encephalitis must be evaluated for alternative conditions[3,4] because encephalopathy can arise from a broad range of pathological processes. Additionally, clinical consensus criteria incorporate the requirement of acute to subacute clinical progression on the order of days to weeks to better differentiate acute encephalitis from other neurodegenerative causes of rapidly progressive dementia.[5] Other supportive elements for a diagnosis of encephalitis include fever, seizures not attributable to a pre-existing seizure disorder, new onset focal neurological findings, or investigative findings (eg, cerebrospinal fluid [CSF] pleocytosis and neuroimaging or electroencephalographic abnormalities). Confidence in the diagnosis of encephalitis rises with increasing numbers of supportive features.[1] Notably, the frequency of autoimmune encephalitis could be underestimated by the use of such definitions since the presence of supportive elements, in particular CSF pleocytosis and MRI abnormalities, might be less common than in infectious encephalitis. Autoimmune encephalitis can present with new onset seizures and status epilepticus in the absence of other cognitive or behavioural changes, and therefore accounts for a subset of patients with the clinical syndromes of new onset refractory status epilepticus or febrile infection-related epilepsy syndrome.[6,7] Although rare, autoimmune encephalitis can manifest with isolated psychiatric symptoms.[8]

Up to 12·6 per 100 000 individuals are affected by encephalitis annually, with the highest incidence in children.[9–12] The leading identified causes are viral, followed by the syndrome of acute disseminated encephalomyelitis (ADEM), which is typically a post-infectious or para-infectious condition. Of viral causes, Japanese encephalitis virus (JEV) is the most commonly identified epidemic cause and herpes simplex virus (HSV) the most commonly identified sporadic cause. In recent years the epidemiology has changed because of the emergence and spread of arthropod-borne viruses such as Zika and chikungunya, and the increasing use of vaccines (eg, against JEV and varicella zoster virus) in some countries. Overall, approximately 40–50% of all identified cases are caused by infectious agents.[9,13] Autoimmune conditions, increasingly recognised and tested for since the initial description of anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis over a decade ago, account for approximately 20–30% of cases,[13–15] and the remaining cases do not have a causal diagnosis despite extensive evaluation.

In this Seminar we chiefly focus on the diagnosis and management of acute encephalitis in immunocompetent adults.

Search strategy and selection criteria

We searched the Cochrane Library, MEDLINE, and Embase for literature published between January, 2012, and September, 2018, using the search terms "encephalitis" in combination with the terms "adult" and "immunocompetent". We mostly selected literature that has been published in the past 5 years but did not exclude older publications that are commonly referenced and highly regarded. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are cited to provide readers with more details and references beyond this Seminar.

Clinical presentation

The clinical evaluation begins with a careful medical history and examination, looking for features of encephalitis in general, the class of encephalitis (whether infectious or autoimmune), and specific causes and syndromes. The history should include recent illness, ill contacts, travel, exposures (eg, to animals), vaccinations, ingestions, cancer, and immunocompromise (eg, HIV or chemotherapy) to contextualise the acute encephalitis presentation and guide the differential diagnosis (tables 1 and 2).

Some common causes of encephalitis are associated with distinguishing clinical features. For example, olfactory hallucinations and feelings of déjà vu are common in the early stages of HSV encephalitis and reflect its predilection for the temporal lobe. Anti-NMDA receptor encephalitis is suggested by a prodromal influenza-like illness followed by subacute cognitive decline, behavioural changes, psychosis, movement disorders (eg, orofacial dyskinesia), seizures, and autonomic instability. Consideration of patient demographics is also helpful because the disease mainly affects children and young adults, with a 4:1 female to male predominance.[16,17] Patients with antibodies against the leucine-rich glioma inactivated 1 (LGI-1) protein often present with faciobrachial dystonic movements before development of frank seizures, cognitive deficits, and behavioural changes.[18,19]

Limbic encephalitis

Inflammation of the limbic system in the brain typically results in some combination of anterograde memory dysfunction, behavioural changes, and seizures. One of the most common causes of limbic encephalitis is HSV encephalitis, accompanied by fever, headache, and focal neurological deficits, with temporal lobe abnormalities visualised through neuroimaging. Other notable infections include, varicella zoster virus (VZV), syphilis, and rarely Mycobacterium tuberculosis.[20] Autoimmune limbic encephalitis emerges as the predominant consideration in patients who have had HSV encephalitis and other infectious organisms that affect the temporal lobes excluded as a possible diagnosis. Anti-NMDAR encephalitis typically presents with additional clinical manifestations and the presence of faciobrachial dystonic movements suggests anti-encephalitis. Peripheral nervous system involvement can occur in encephalitis associated with antibodies to contactin-associated protein 2 (CASPR-2),[21] and limbic encephalitis occurring in the setting of lung cancer is often associated with antibodies to the $GABA_B$ receptor.[22]

Brainstem encephalitis

By contrast with limbic encephalitis, patients with brainstem encephalitis can have preserved consciousness and behaviour and thus might not strictly fulfil proposed diagnostic criteria for encephalitis.[1,2] However, focal neurological deficits (most commonly ataxia, ocular dysfunction, bulbar dysfunction, and limb paresis) suggest areas of inflammation in the midbrain, pons, and medulla. Differential considerations include listeria, brucella, arthropod-borne viruses, and other infectious and autoimmune causes (appendix). Intractable vomiting and persistent hiccoughs can suggest involvement of the area postrema within the medulla as in neuromyelitis optica.[23] Brainstem encephalitis in enterovirus infection, particularly enterovirus 71, is associated with autonomic dysfunction, which results in fluctuating blood pressure and neurogenic pulmonary oedema with haemorrhage.[24]

***Panel 1:* Clinical diagnosis of encephalitis**

- Acute or subacute onset of altered level of consciousness, lethargy, and personality change; short-term memory deficits or psychiatric symptoms also support clinical diagnosis of encephalitis, particularly for autoimmune encephalitides although they can also be seen in infectious encephalitis
- Supportive elements:
  - New focal CNS findings
  - Seizures not explained by previous seizure disorder
  - Cerebral spinal fluid white blood cell pleocytosis
  - Imaging features of encephalitis (eg, new MRI T2/fluid-attenuated inversion recovery and gadolinium enhancing lesions compatible with inflammation or demyelination; fluorodeoxyglucose-PET hyperavidity in mesial temporal lobes noted in some cases of autoimmune limbic encephalitis)
  - Focal or diffuse abnormality on EEG consistent with encephalitis and not attributable to another cause
  - Febrile illness within the 72 h before or after presentation, particularly for infectious encephalitides although can also be seen in autoimmune encephalitis
- Reasonable exclusion of alternative causes

Other syndromes

Tremors and other movement disorders can be seen in autoantibody-mediated encephalitides but their occurrence in patients who rapidly lose consciousness is characteristic for encephalitis caused by arthropod-borne viruses, including flaviviruses (eg, JEV) and alphaviruses (eg, eastern equine encephalitis virus). Neuroimaging often shows marked inflammation of the thalamus and basal ganglia in these patients.[25] These same viruses and enteroviruses can also attack the anterior horn cells of the spinal cord and cause acute flaccid paralysis, which could be part of an encephalitis syndrome.[24,26] Several additional syndromes beyond the scope of this Seminar deserve mention: encephalopathy in the setting of antithyroid antibodies could represent Hashimoto encephalopathy, an autoimmune condition also known as steroid responsive encephalopathy associated with autoimmune thyroiditis; and acute cerebellitis with or without additional brainstem or supratentorial dysfunction can result from various infectious and autoimmune conditions.[2,27–31]

Multifocal encephalitis

Although arthropod-borne viruses and enteroviruses can present with multifocal involvement of the CNS, especially the deep grey matter, acute disseminated encephalomyelitis (ADEM) is a demyelinating syndrome of the nervous system that typically presents with clinical features suggestive of multiple areas of inflammation in the white matter of the cerebral hemispheres, cerebellum, brainstem, and spinal cord, with additional cranial nerve involvement. Patients often develop encephalopathy accompanied by optic neuropathy, abnormal gait, and paresis.[32] Antecedent vaccination or infection within

	Incidence, region, and risk factors	Clinical features
Viral		
Global sporadic		
Herpesviridae		
Herpes simplex virus type 1	2–4 per 1 000 000 per year	Encephalitis>meningitis; seizures, language, memory disturbance, and rarely brainstem involvement; SIADH
Herpes simplex virus type 2	0·2–0·4 per 1 000 000 per year	Meningitis>encephalitis and radiculitis; meningitis could be recurrent
Varicella zoster virus	1·02 per 1 000 000 per year	Meningoencephalitis, cerebellitis, stroke, myelopathy, retinitis; can occur before, during, or after zoster rash or in absence of rash
Epstein-Barr virus	0·5–3% of encephalitis cases; more in immunocompromised	Brainstem or cerebellar signs, transverse myelitis; also associated with CNS lymphoma
Human herpes virus type 6	>80% seroprevalence; encephalitis more likely if immunocompromised (particularly haemapoietic stem-cell transplant)	Meningitis, encephalitis, myelitis, and exanthema
Human herpes virus type 7	Rare; 98% seroprevalence	Encephalitis and flaccid paralysis
Picornaviridae		
Enterovirus type 70 and 71	2% of encephalitis cases; large sporadic outbreaks in southeast Asia (EV71)	Meningitis>encephalitis, rhombencephalitis, myelitis, and flaccid paralysis; hand, foot, and mouth disease; cardiac complications
Coxsackie virus	0·5% of encephalitis cases that have a peak in summer and a smaller peak in winter	Meningitis>encephalitis, hepatitis, and flaccid paralysis; hand, foot, and mouth disease
Poliovirus	Outbreaks in unvaccinated	Encephalitis, seizures, and flaccid paralysis
Paramyxoviridae		
Measles virus	Infections occur in unvaccinated; acute encephalitis occurs in 1 per 1000 cases of measles	Acute encephalitis is ADEM-like; inclusion body encephalitis and subacute sclerosing panencephalitis are subacute or chronic forms of encephalitis following measles infection
Mumps virus	Unvaccinated	Headache and sensorineural hearing loss; previous parotitis
Orthomyxoviridae		
Influenza virus	1·2 per 100 000 symptomatic infections	Non-specific or radiologically classified (eg, acute necrotising encephalopathy and acute haemorrhagic leukoencephalopathy)
Geographically-restricted		
Flaviviridae		
Japanese encephalitis virus	Approximately 70 000 encephalitis cases per year, which mostly occur in Asia and northern Australia	Encephalitis, extra-pyramidal features, and flaccid paralysis; case-fatality 20–30%
Dengue virus	50–100 million infections per year of which 0·5–6% encephalopathy or encephalitis; South and Southeast Asia, South and Central America, and Africa	Meningoencephalitis, GBS, myositis, and neuralgical amyotrophy; prominent headache, myalgia, fever, thrombocytopenia, and shock
West Nile virus	1 in 150 develop neuroinvasive disease; re-emerged in southern Europe	More severe in elderly patients; encephalitis, extra-pyramidal features, flaccid paralysis, and myoclonus; more rarely, brainstem, radiculopathy, GBS, retinitis, or optic neuritis; morbilliform maculopapular rash sparing palms and soles
Zika virus	Africa, India, east Asia; has emerged in South and Central America, Florida, and Texas	Prominent conjunctivitis and maculopapular rash; GBS>encephalitis
St Louis encephalitis virus	Up to 20 per year in southern and western states of USA; Central and South America	Neurological involvement and severity greatest in the older age group, seizures, urinary features, and SIADH; case fatality 3–30%
Murray Valley encephalitis virus	1 per 150–1000 infections symptomatic; Australia, New Guinea, and Irian Jaya	1–4 week incubation; high fever, diarrhoea, macular rash, cough, and flaccid paralysis or brainstem involvement can occur; case fatality 15–30%
Tick-borne encephalitis virus	8–15 per 100 000 per year in endemic areas (particularly eastern Europe and Russia)	Cranial nerve involvement, flaccid paralysis, and tremor
Powassan virus	Canada and Asia; emerging in northeast and midwest USA; tick bite	Febrile prodrome; case fatality 10%
Bunyaviridae		
La Crosse virus	50 to 100 per year in southeastern and Midwestern states of USA; late spring through fall	More commonly children, encephalitis, meningitis, and fatality rare
Toscana virus	Predominantly southern Europe: Italy, Cypress, Greece, Turkey, France, Spain, and Germany; Summer	2 days to 2 weeks incubation, meningitis, encephalitis, myalgia, rarely stroke, or hydrocephalus
Togaviridae		
Chikungunya virus	Africa and South Asia; has emerged in Central and South America	Meningoencephalitis, myelopathy, and myeloneuropathy; prominent arthralgia, lymphopenia, and hepatomegaly
Eastern and Western equine encephalitis viruses	5 to 15 per year in USA for Eastern (Massachusetts, Florida, Georgia, and North Carolina); Western occurs in western portions of USA and Canada	Encephalitis and meningitis; case fatality 50–70% for Eastern and <10% for Western

(Table 1 continues on next page)

	Incidence, region, and risk factors	Clinical features
(Continued from previous page)		
Paramyxoviridae		
Nipah virus	Exposure to pigs and bats; previously Malaysia and Singapore; emergence in Bangladesh and India	4–45 day incubation, dystonia, myoclonus, and lower motor neurone signs
Rhabdoviridae		
Rabies virus	50–100 000 per year; exposure to bats and dogs; Asia, Africa, and Central and South America	Encephalitis with bizarre behaviour, hydrophobia, or ascending flaccid paralysis before encephalopathy and death
Bacterial		
Bartonella spp	*Bartonella henselae*: exposure to cats	Encephalopathy>encephalitis; seizures
Borrelia spp	Exposure to ticks; USA and Europe	Cranial nerve palsy>radiculitis>meningitis>encephalitis
Brucella spp	Middle East, Mongolia, and Southern Europe; raw milk exposure	Heterogeneous neurological manifestations
Listeria monocytogenes	High prevalence of neurolisteriosis in France; limited data from Africa, Latin America, and Asia	Listeria rhomboencephalitis: typically biphasic presentation, with initial prodrome of fever, headache, and malaise followed days to weeks by dysphagia, dysarthria, and facial weakness
Mycobacterium tuberculosis	Worldwide distribution, up to a third of the current world's population might be infected	Subacute meningitis>encephalitis; more common in children and immunocompromised; hydrocephalus
Mycoplasma pneumoniae	Children>adults	About 50% will have respiratory symptoms, either concomitantly or preceding the neurological syndrome by 1–4 weeks
Rickettsia, Ehrlichia, and Anaplasma	Tick-borne	Profound headache; photophobia, conjunctivitis, and acute hearing impairment; transaminitis
Treponema pallidum	Re-emerging in USA and elsewhere in HIV settings	Protean manifestations; acute encephalitis is a rare occurrence
Fungal		
Blastomyces dermatides	Africa, Central America, USA	Rare CNS involvement includes mass lesions, abscess, and meningitis
Coccidiodes immitis	Mexico, South America, Southwestern USA; inhalation of soil	Meningitis>>encephalitis
Cryptococcus spp	Global distribution; *Cryptococcus gattii* emerging in northwest USA	Meningitis>>encephalitis
Histoplasma capsulatum	USA, Latin America, Africa, and Asia	CNS manifestations can occur years after initial pulmonary infection; hydrocephalus
Parasitic		
Acanthamoeba spp	Broad worldwide distribution	Variable neurological presentation; often subacute rather than acute; accompanying keratitis
Balamuthia mandrillaris	Mainly USA, Mexico, South America, and Africa; contact with soil	Cutaneous lesions; hydrocephalus is common
Baylisascaris procyonis	Exposure to raccoon faeces	Severity of disease related to burden of egg ingestion; incubation 2–4 weeks; eye involvement
Naegleria fowleri	Worldwide distribution, summer (exposure to fresh water), neti pot usage	Incubation 5–7 days; prominent headache, fever, nuchal rigidity, and personality changes

GBS=Guillain-Barré Syndrome. SIADH=syndrome of inappropriate antidiuretic hormone secretion. CSF=cerebral spinal fluid. EEG=electroencephalogram. FDG-PET=fluorodeoxyglucose positron emission tomography.

Table 1: **Selected infectious causes of encephalitis in immunocompetent individuals and associated epidemiologic and clinical features**

4 weeks of presentation is commonly reported, up to 65% in one large series,[33] and in some cases antibodies against the myelin oligodendrocyte glycoprotein (MOG) are found (appendix).

Investigations

The key tests to establish the diagnosis and find out the specific cause are assessment of the CSF, MRI, ancillary investigations of blood and other samples, and electroencephalography (EEG). Because of the plethora of pathogens, autoimmune, post-infectious, para-infectious, and paraneoplastic causes of acute encephalitis, we have sought to provide a pragmatic investigation strategy with emphasis on the more common causes and those responsive to treatment. In practice a limited range of causes account for most cases of acute encephalitis in which a cause is identified. Therefore, assessment for these is recommended for all patients, with further testing tailored to reflect demographics, exposure, immune status, CSF, and imaging findings.

See Online for appendix

CSF analysis

In all cases of suspected encephalitis, obtaining CSF is pivotal to confirm the diagnosis and direct treatment. Guidelines from countries such as the UK, USA, and Australia recommend that a lumbar puncture is done urgently and that this should not be delayed to obtain neuroimaging, except for some specific circumstances (panel 2).[4,34,35] Important studies include opening pressure, cell count and differential, glucose (with corresponding serum glucose), protein, oligoclonal bands, IgG index, gram stain, bacterial cultures, PCR for bacteria, HSV1, HSV2, VZV, enterovirus, IgG and IgM testing for some pathogens, cryptococcal antigen or India ink staining, and

	Incidence and risk factors	Clinical features
Extracellular antigen (eg, synaptic receptor, ion channel)		
NMDA receptor	4% of all encephalitis cases; incidence about 2 per million; 70-90% female; young (often aged 40 years or younger)	Behavioural change as initial symptom, autonomic instability, choreoathetosis, orofacial dyskinesia, and progressing to central hypoventilation; malignancy more likely in females; ovarian teratoma
LGI-1 (previously VGKC-complex)	Approximately 1 per million and 2–3% of all encephalitis cases	LE preceded by faciobrachial dystonic seizures thought to be pathognomic, hyponatraemia; if paraneoplastic (<10% of cases) then breast, lymphoma, thymoma, and thyroid cancer are possible
CASPR2 (previously VGKC-complex)	90% male	Neuromyotonia, insomnia, dysautonomia, LE, and neuropathic pain syndromes; thymoma 20–50%
GABA-B receptor	5% of autoimmune encephalitis cases	LE>>>ataxia and orolingual movements; 50% SCLC, and neuroendocrine neoplasia
GABA-A receptor	Likely rare, but diagnosed with increasing frequency as clinical features become better defined and diagnostic testing is more readily available	LE prominent seizures, status epilepticus, and EPC; some catatonia and frontal signs; multiple cortical and subcortical changes; Hodgkin's lymphoma and <5% thymoma
Glycine receptor	>60 cases	Progressive encephalopathy with rigidity and myoclonus, occasionally stiff person syndrome, and optic neuritis; thymoma <10%; often found in asymptomatic patients
AMPA receptor	More frequently female	GluR1 and 2 subunits; 50–65% cancer (eg, breast, SCLC, thymoma, ovarian teratoma); aggressive LE often requires second-line therapy
mGluR5	Rare	LE plus prominent psychiatric features; 70% Hodgkin's lymphoma
DPPX	Likely rare, but diagnosed with increasing frequency as clinical features become better defined and diagnostic testing is more readily available	Encephalitis with hyperekplexia and preceding severe diarrhoea <10% lymphoma; typically an indolent course
Neurexin 3 alpha	Likely rare, but diagnosed with increasing frequency as clinical features become better defined and diagnostic testing is more readily available	Prodromal fever, headache, or gastrointestinal symptoms; orofacial dyskinesias and need for respiratory support
Dopamine 2	Very rare and limited cases reported; predominantly children	Basal ganglia encephalitis or some Sydenham's chorea
Intracellular antigen		
ANNA1 (anti-Hu)	High-titre serum antibodies are associated with neurological disease and found in 3% of patients with SCLC	LE alone or with brainstem, cerebellar and sensory neuronopathy >95%; over 80% associated with cancer, SCLC>thymoma
ANNA 2 (anti-Ri)	Rare	Encephalitis, cerebellar degeneration, brainstem, myelopathy, peripheral neuropathy, and opsoclonus-myoclonus; SCLC or breast adenocarcinoma
ANNA3	Rare	No singular phenotype specificity; LE; peripheral neuropathy, cerebellar, brainstem, and myelopathy; SCLC and oesophageal adenocarcinoma
AGNA (SOX1)	Rare	No singular phenotype specificity; LE; cerebellar and LEMS; SCLC
CRMP-5	Rare	Cognitive, cerebellar, optic neuritis, and chorea; myelopathy, radiculopathy, neuropathy, and LEMS; SCLC, thymoma
GAD65	Antibodies present in most individuals with type 1 diabetes, but rare cause of encephalitis	Isolated LE or with movement disorder, seizures and cerebellar signs; stiff person syndrome and myelopathy; new type 1 diabetes; possibly as common as LGI-1; usually not paraneoplastic but if so SCLC>thymic cancer>breast, renal cancer
GFAP	Recently described; 3-fold less common than anti-NMDA receptor encephalitis	Headache, subacute encephalopathy, optic papillitis, myelitis, tremor, ataxia; various tumours
Ma	Rare	LE alone or with upper brainstem diencephalic dysfunction; non-Hodgkin's lymphoma, breast cancer, gastrointestinal cancer, lung cancer, or testicular seminoma
PCA-2	Rare	No singular phenotype specificity; LE; brainstem, cerebellar, LEMS, and peripheral or autonomic; SCLC

ADEM=acute disseminated encephalomyelitis. AGNA=anti-glial nuclear antibody. AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid. ANNA=antineuronal nuclear antibody. DPPX=dipeptidyl aminopeptidase. EPC=epilepsia partialis continua. GABA=gamma-aminobutyric acid. GAD=glutamic acid decarboxylase. GBS=Guillain-Barré syndrome. GFAP=glial fibrillary acidic protein. LEMS=Lambert-Eaton myaesthenic syndrome. LE=limbic encephalitis. LGI-1=leucine-rich glioma-inactivated. NMDA=N-methyl-D-aspartate. SCLC=small-cell lung cancer. VGKC=voltage-gated potassium channel antibody.

***Table 2*: Selected autoimmune causes of encephalitis and associated epidemiological and clinical features, by antibody**

testing for syphilis. Further causes can be investigated on the basis of clinical suspicion and are often done in concert with local, regional, or national public health services (table 3).

CSF analysis reveals moderate elevation in the white cell count in most viral cases, commonly 10–200 cells per µL³, although up to 800 cells per µL³ has been reported in HSV encephalitis.[36] Additionally, protein is modestly elevated and glucose is typically normal. When the CSF white cell count is >1000 cells per µL³, protein is >1 g/L, or CSF glucose level is less than two-thirds of serum levels, a non-viral infectious aetiology (ie, bacterial, mycobacterial, or fungal) should be strongly considered. Although, a lymphocytic pleocytosis is characteristic of viral encephalitis, neutrophils might predominate early in viral infection, and 3–26% with HSV encephalitis have no pleocytosis in early CSF samples.[36,37] Consequently, it is reasonable to obtain repeat CSF 24–72 h after the first lumbar puncture if clinical suspicion of encephalitis remains.[4,35,38] Eosinophils can be present in the setting of helminthic infections such as *Baylisascaris pryocyonis*, but can also be seen at lower frequency in fungal and mycobacterial encephalitis.[39]

In HSV encephalitis, even in the absence of a lymphocytic pleocytosis, there could be abnormalities in opening pressure or a modestly elevated CSF protein (typically 0·5–1 g/L), although >4 g/L has been reported.[36,40] Because of the haemorrhagic nature of HSV encephalitis, red blood cells and xanthochromia can also be identified as a late manifestation, and can also be found with VZV.[35,40] PCR has a high specificity (99%) and sensitivity (96%) for HSV.[4,35] However, in clinical practice the diagnosis can be missed if PCR is done on CSF taken early in the disease or if a sample is obtained late after aciclovir administration.[36] In these cases with a late lumbar puncture the diagnosis can be established by showing intrathecal synthesis of HSV antibody while presumptive treatment is given (table 3).[13]

Although flavivirus RNA can be detectable in serum by RT-PCR during the viraemic phase or the first few days of neurological symptoms, most patients are diagnosed by the detection of specific IgM antibodies, demonstration of a four-fold rise in titre by other assays, or by intrathecal synthesis.[41] Notably, optimisation of antibody testing for populations with multiple flavivirus exposure is challenging because of cross reactivity between the viruses. For Zika virus and West Nile virus, PCR of urine is helpful because it can remain positive after blood is cleared of the virus.[42]

In *Listeria monocytogenes* encephalitis there is typically a mild lymphocytic predominant pleocytosis with a normal to minimally elevated protein, similar to viral encephalitis; however, the CSF to serum glucose ratio is typically lower in listeria than in viral infections. Because the CSF bacterial culture for *L monocytogenes* is an insensitive test, multiple cultures from blood and CSF might be required to confirm the diagnosis.[43]

The diagnosis of CNS tuberculosis poses distinct challenges because the sensitivity of CSF smear is less than 25% and that of culture is less than 50%.[44,45] Identification is increased by extended examination of at least 5 mLs of CSF.[46] Numerous nucleic acid amplification tests have been developed with varying sensitivities and specificities, and in 2017 the WHO issued recommendations for use of the Xpert MTB/RIF assay as the initial test for diagnosis of tuberculous meningitis, supported by a small prospective study of adults infected with HIV in Uganda where the sensitivity was reported as 95%.[47]

Various antigen-based assays have been developed to diagnose fungal infections of the CNS, the most widely used being the cryptococcal antigen lateral flow assay. Cerebrospinal fluid testing for the (1–3)-β-D-glucan glycoprotein, a component of the cell wall of many fungi, has shown promise though limitations include false positives and the need for further validation.[48]

In autoimmune encephalitis the CSF abnormalities can be more subtle with a low to moderate lymphocytic pleocytosis and a mildly elevated protein; routine CSF studies can be normal in a third of patients overall.[15] Anti-NMDA receptor antibodies can be detected in both serum and CSF and, although titres are usually higher than in serum, adjustment for the CSF:serum IgG ratio often shows intrathecal production is greater and correlates more closely with clinical progression and immune-therapy response.[49–51] Most immunotherapy-responsive conditions associated with antibodies directed against the voltage-gated potassium channel (VGKC)-complex reflect those targeting two specific antigens tightly associated with this complex, LGI-1 and contactin-associated protein-2 (CASPR2). These targets comprise predominantly central and peripheral phenotypes of limbic encephalitis and neuromyotonia respectively, with the overlap of Morvan's syndrome, therefore antibody testing against these two targets is advised.[52–54] VGKC positivity in the absence of antibodies to LGI-1 and CASPR2 is not a clear marker of autoimmune inflammation.[55,56]

In practice, autoantibody testing should always be sent from the CSF and serum.[2] In some conditions (eg, anti-NMDA receptor) CSF antibody testing has been shown to be more sensitive than serum testing,[16,57] and in others (eg, anti-LGI-1), serum testing appears to be more sensitive.[18,58] Antibodies detected in the CSF are more likely to be causal; by contrast multiple antibodies are sometimes detected in the serum, of uncertain importance.[2,59]

***Panel 2:* Neuroimaging needed before lumbar puncture to exclude brain shift, swelling, or space occupying lesion**

- Acute change in level of consciousness, with moderate to severe impairment
- Focal neurological signs (including unequal, dilated, or poorly responsive pupils)
- Papilloedema
- Abnormal oculocephalic (doll's eye) movements
- Abnormal posture or posturing
- Relative bradycardia with hypertension
- Known immunocompromise

Neuroimaging

Neuroimaging can provide evidence of brain parenchymal inflammation, confirming the diagnosis and sometimes suggesting a specific aetiology; it can also aid in identifying conditions that mimic encephalitis. In all cases MRI is the preferred modality over CT because of both greater sensitivity and specificity. CT, which is more readily available, could be useful in confirming brain shift in those with suggestive clinical features.[4]

Although brain MRI alone cannot establish the cause of encephalitis, the location, pattern, and characteristics of the MRI abnormalities can be of tremendous help in supporting a specific diagnosis or in directing further testing (table 3), with the caveat that factors such as

	Laboratory testing*	Characteristic brain MRI findings
Virus		
HSV-1	CSF PCR (false negative can occur in first 72 hours); intrathecal antibody if >1 week of symptoms	Asymmetric abnormalities in mesiotemporal lobes, orbitofrontal lobes, and insular cortex with oedema, possible restricted diffusion or haemorrhage (late stage)
VZV	CSF PCR (potentially low sensitivity); intrathecal antibody may have better test characteristics than PCR, but needs to be further evaluated; PCR or DFA of skin lesions	Could affect temporal lobes, similar to HSV-1; lesions can occur in cerebellum and brainstem; ischaemic or haemorrhagic lesions in white matter or grey-white matter junction suggest vasculopathy
Enteroviruses	CSF PCR; respiratory or stool PCR; and stool culture	Frequently normal MRI, athough characteristic lesions of EV 71 occur in dorsal brainstem, dentate nuclei of cerebellum, and anterior horns of spinal cord
Measles	Serum IgG and IgM; CSF PCR (high sensitivity); PCR of nasopharyngeal, throat, or urine samples in early infection	Cerebral oedema, multifocal lesions, can resemble ADEM in acute setting
Mumps	CSF PCR (high sensitivity) or IgM and IgG; serum IgM or rising serum IgG; PCR from throat swab	Lesions in brainstem, hippocampus, and splenium of corpus callosum
Influenza virus	PCR or antigen testing of respiratory secretions; respiratory viral culture; CSF PCR is rarely positive	Neuroimaging is often normal, although abnormalities can include reversible splenial lesions, deep grey T2 abnormalities, diffuse oedema, and haemorrhagic and necrotising lesions of thalami, brainstem, and cerebellum
Arboviruses (including alphaviruses such as eastern equine encephalitis, and flaviviruses, such as Japanese encephalitis, West Nile and Zika viruses)†	CSF IgM, serum IgM and IgG (obtain paired samples); CSF PCR (low sensitivity unless tested early, during initial viraemia), urine PCR (Zika, West Nile virus); serological cross-reactivity with other arboviruses within the same family	Up to half will have normal brain MRI; abnormalities might involve deep grey matter (ie, thalamus, basal ganglia) and brainstem
Nipah virus	Serum or CSF IgM (sensitivity peaks several weeks after onset of illness); PCR of CSF, serum, and urine	Widespread punctate subcortical and deep white matter lesions
Rabies virus	PCR from saliva, nuchal skin biopsy; brain tissue DFA; and serum rabies virus neutralising antibodies (Rapid Fluorescent Focus Inhibition Test)	Multifocal abnormalities in temporal cortex, hippocampi, deep grey nuclei, substantia nigra, brainstem, cerebral white matter; grey matter>>white matter
Bacteria		
Borrelia spp	Serology (serial EIA and Western blot); C6 antibody; CSF antibody index; and CSF PCR (low sensitivity)	Multifocal lesions in subcortical white matter, potentially mimicking multiple sclerosis
Brucella spp	Serum and CSF IgG and IgM; CSF culture	Variably enhancing lesions with marked surrounding oedema
Listeria monocytogenes	Multiple blood and CSF cultures	In rhombencephalitis, multiple small rim-enhancing lesions with variable restriction of diffusion
Mycobacterium tuberculosis	Multiple studies from CSF and extra-CNS sites: AFB smear, culture, PCR, and direct examination; nucleic acid amplification test from multiple sites; large volume CSF culture (low sensitivity)	Basilar meningeal enhancement, hydrocephalus, rim-enhancing lesions, and strokes in deep gray matter or internal capsule
Rickettsia and related diseases (ie, *Anaplasma* spp, *Coxiella burnetti*, *Ehrlichia* spp, and *Rickettsia* spp)	Serum IgG and IgM (paired if possible); whole blood PCR; if rash, PCR or immunohistochemical staining of skin biopsy	Reversible splenial lesions; punctate areas of restricted diffusion
Treponema pallidum	Diagnosed via combination of serum treponemal antibody, CSF VDRL, CSF white count, protein	Variable mesial temporal lobe involvement has been described
Fungi		
Cryptococcus spp	CSF lateral flow assay, CSF India ink assay	Basilar meningeal enhancement and hydrocephalus; cryptococcomas are T1 hypointense and T2 hyperintense lesions in basal ganglia and midbrain
Others (coccidioides, histoplasma, and blastomyces)	CSF and serum antigen antibody testing; large volume CSF culture; urine antigen (for histoplasma and blastomyces)	Basilar meningeal enhancement, hydrocephalus, and rim-enhancing lesions
Parasites and free-living amoebae		
Acanthoemeba spp	CSF and brain tissue PCR; brain histopathology; serology	Haemorrhagic and necrotic rim-enhancing lesions
Balamuthia mandrillaris	CSF and brain tissue PCR; brain histopathology; serology	Multifocal T2-weighted hyperintensities with rim enhancement, surrounding oedema, and leptomeningeal extension
Baylisascaris procyonis	CSF and serum antibodies; peripheral or CSF eosinophilia	Multifocal or confluent white matter abnormalities and nodular enhancement
Naegleria fowleri	Wet mount preparation of warm CSF; brain histopathology; CSF and brain PCR	Necrotic and haemorrhagic lesions often in frontal lobes

ADEM=acute disseminated encephalomyelitis. AFB=acid fast bacillus. CSF=cerebrospinal fluid. DFA=direct fluorescent antibody. EIA=enzyme immunoassay. EV=enterovirus. HSV=herpes simplex virus. VDRL=venereal disease research laboratory. VZV=varicella zoster virus. *Coordinate testing with local, state, and national health departments. †When IgM/IgG testing is performed, acute and convalescent titres are typically obtained 1–4 weeks apart. Seroconversion and four-fold or greater rise in titre using paired sera is supportive of infection.

Table 3: **Laboratory testing and neuroimaging characteristics of selected pathogens**

timing of imaging and extent and severity of illness contribute to heterogeneity of MRI findings. Abnormalities on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences in the temporal lobes and to a lesser extent orbitofrontal and cingulate cortices are highly suggestive of HSV encephalitis,[35] particularly when asymmetrical; the presence of bilateral, symmetrical abnormalities confined to the mesial temporal

lobes is suggestive of autoimmune limbic encephalitis (figure 1).[20] Temporal lobe involvement can occur with HSV-1 or, less commonly, HSV-2; and also with VZV.[20,62] If a vasculitis is present in VZV, the MRI changes can predominantly involve the grey-white matter interface and are more typically ischaemic than haemorrhagic.[63] Of note, neurosyphilis can rarely present acutely with lesions in the temporal lobe.[20] Involvement of other brain locations can also suggest distinct causes. Deep grey matter abnormalities on T2/FLAIR can be seen in arboviral encephalitis, influenza-associated encephalitis and encephalopathy, or CNS tuberculosis, whereas mesodiencephalic abnormalities would suggest anti-Ma encephalitis.[25]

Other MRI characteristics can support different causes of encephalitis. On one hand, the presence of enhancement of the basilar meninges and hydrocephalus, for example, suggests tuberculosis, fungal infections, or *Balamuthia mandrillaris*; similar considerations emerge if rim-enhancing lesions indicative of abscesses are seen, although if such lesions are present mainly in the brainstem listeria would be a prime suspect. However, incomplete c-shaped rims of enhancement are suggestive of ADEM or other demyelinating causes. Evidence of haemorrhage can suggest HSV-1, VZV, influenza-associated acute necrotising encephalopathy, arbovirus infection, or haemorrhagic variants of ADEM depending on the location and distribution of lesions.[64]

Although brain MRI is abnormal in the acute setting in about two-thirds of cases of autoimmune limbic encephalitis, in most other autoimmune encephalitides the MRI is normal or shows non-specific changes.[65] For instance, brain MRI is normal in 70% of patients with anti-NMDA receptor encephalitis; when present, abnormalities can involve grey or white matter in the cortex, subcortex, or cerebellum and might be transient.[16,66] A notable exception is anti-GABAa receptor encephalitis, in which multifocal, asynchronous cortical, and subcortical lesions are typical and can be mistaken for ADEM.[67] In LGI-1 encephalitis, transient basal ganglia T1 and T2 hyperintensities have been reported.[68] Because of the heterogeneity in presence and patterns of MRI abnormality in autoimmune encephalitis, there has been interest in the use of other neuroimaging modalities. Current consensus criteria include fluorodeoxyglucose (FDG)-PET hypermetabolism of the mesial temporal lobe as meeting radiographical criteria for autoimmune limbic encephalitis.[2] Other potentially useful FDG-PET biomarkers include cortical hypometabolism, parieto-occipital hypometabolism in anti-NMDAR encephalitis, and basal ganglia hypermetabolism in LGI-1 encephalitis, although prospective validation will be necessary.[19,69,70]

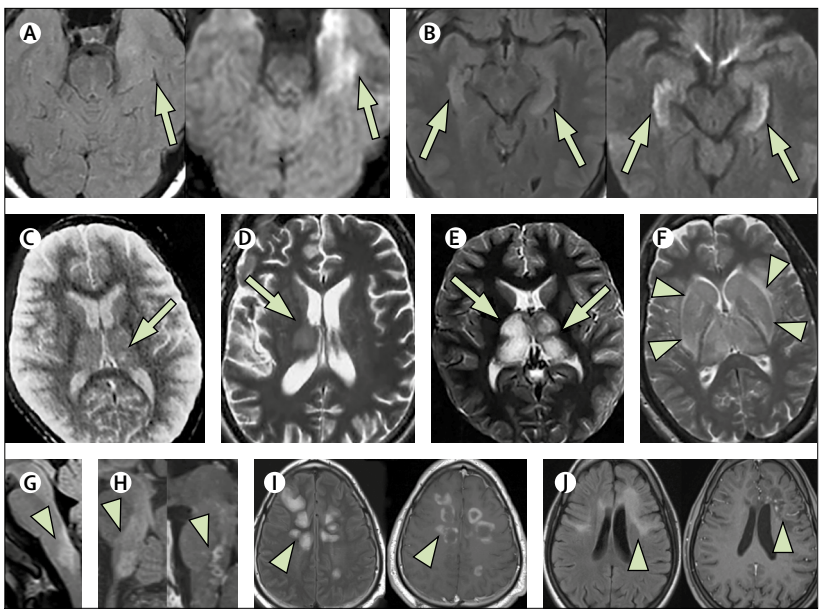

Figure 1: **MRI findings in acute encephalitis**
Representative images from infectious and autoimmune encephalitides are shown. (A) Early herpes simplex encephalitis; left temporal lobe abnormalities are more clearly seen on diffusion weighted imaging (DWI) (right) than fluid-attenuated inversion recovery (FLAIR), (left). (B) Autoimmune limbic encephalitis; bilateral mesial temporal lobe abnormalities seen on both DWI (right) and FLAIR (left)—note the symmetric nature of the lesions. (C–F) Arboviral encephalitis; T2-weighted images of patients with (C) Japanese encephalitis, (D) West Nile encephalitis, (E) Murray Valley encephalitis, and (F) Eastern equine encephalitis show increased signal intensity and swelling in the deep grey matter. (G) Neuromyelitis optica; FLAIR image of a patient who presented with brainstem encephalitis and found to have antibodies to aquaporin-4. (H) *Listeria* brainstem encephalitis; FLAIR (left) and post-gadolinium (right) images show T2 abnormalities similar to neuromyelitis optica (NMO) but also multiple rim-enhancing brainstem lesions typical of Listeria. (I) In acute disseminated encephalomyelitis multifocal areas of T2 hyperintensity are seen on FLAIR (left) with characteristic incomplete rims of enhancement following gadolinium administration (right). (J) In myelin oligodendrocyte glycoprotein encephalomyelitis multifocal and confluent lesions can be seen on FLAIR imaging (left) and post-gadolinium imaging (right) shows patchy areas of enhancement. Images in C,D, and E are reproduced from Solomon T,[60] by permission of Massachusetts Medical Society. Image 1F is reproduced from Solomon Harvala et al,[61] by permission of Elsevier. Images in J are courtesy of M Levy.

Electroencephalography

EEG has two main uses in the evaluation of potential encephalitis. First, because CSF and MRI can be normal, particularly in cases of autoimmune encephalitis, the identification of encephalopathic changes on EEG can help to distinguish this from a primary psychiatric diagnosis.[4] For example, in anti-NMDA receptor encephalitis 80% of patients have generalised slowing and epileptiform activity can be seen in 50%. Additionally, when identified, the extreme delta brush pattern on EEG is associated with anti-NMDA receptor encephalitis.[22,71] More generally non-specific features might be identified, such as lateralised periodical discharges or focal slowing.

Second, in patients with altered consciousness, EEG can identify patients in subtle motor or non-convulsive status epilepticus, which might present de novo or evolve from a convulsive to non-convulsive picture in the setting of encephalitis.

Serum and other fluid testing

Serum laboratory studies that should be done on all adults with encephalitis include full blood counts with differential, electrolytes, renal and liver function tests, blood cultures, treponemal, and HIV testing. Exposure to cats should prompt testing for *Bartonella henselae*.

Patients with altered consciousness and fever either in or returning from malaria endemic areas should always be tested by thick and thin blood film or rapid diagnostic test for malaria antigen. Dengue and chikungunya are also common cause of fever in returning travellers, and are sometimes associated with neurological disease.[72] In cases of suspected demyelinating disorders, serum testing for antibodies to aquaporin-4 or MOG can confirm the diagnosis.

Peripheral eosinophilia can be found in some fungal and parasitic conditions, most notably infection by *Baylisascaris procyonis*.[40] Hyponatraemia is found in many forms of encephalitis.[73] In autoimmune encephalitis with LGI-1-antibodies, hyponatraemia is found in 60% of cases and this can have an inverse correlation with antibody titre perhaps reflecting hypothalamic involvement.[74] HIV test antibody and RNA tests are important because the presentation of meningo-encephalitis might be due to an HIV seroconversion illness. In patients with longstanding HIV infection a wider range of opportunistic pathogens that can cause CNS disease needs to be tested for.[4]

In many patients in whom CSF and MRI might show evidence of inflammation of the CNS, no pathogen is diagnosed by PCR, culture, or IgG and IgM analysis of the CSF. Therefore, it is recommended to assess for pathogens outside the CNS that could nevertheless be the cause of encephalitis, either by direct invasion or by para-infectious and post-infectious immune-mediated processes. Particular examples include viral culture or PCR of skin lesions (for VZV or enteroviruses), throat and rectal swabs (for enteroviruses), and respiratory samples (for influenza).[1,75] The greatest diagnostic confidence is for pathogens identified from sterile sites (eg, vesicles); there is less confidence with non-sterile sites and those where there could be asymptomatic shedding such as throat, and faecal or rectal samples.[4]

Neoplasia screening

In all cases of autoimmune encephalitis, screening for malignancy is advised because of the potential that the disease represents a paraneoplastic condition. For example, malignancy is identified in up to 40% of anti-NMDA receptor patients, predominantly ovarian teratomas in women, although other tumours are reported in older adults.[16,49,50,76] Although the preferred modalities and follow-up in autoimmune encephalitis are unclear, the European Federation of Neurological Societies has proposed guidelines for paraneoplastic conditions[77] that are applicable: for screening of the thorax a CT is recommended and if negative FDG-PET should be obtained; breast cancer screening is by mammography followed by MRI; and for the pelvic region, ultrasound is the investigation of choice. If testing is negative, repeat assessment in 3–6 months is reasonable when the autoantibody found is strongly associated with malignancy.

Novel diagnostics and biomarkers

There is increasing interest in the utility of multiplex or unbiased assays for pathogen detection. The BioFire FilmArray panel, a multiplex PCR-based system for detection of pathogens in the CSF, has shown some promise although continued validation is needed to establish its potential.[78] Next generation sequencing represents an exciting and increasingly affordable modality to attempt to identify the cause in cases for whom no cause of encephalitis is identified. A systematic review of published cases in which a pathogen was identified by metagenomic next generation sequencing reported 44 cases with analysis of CSF or brain biopsy tissue; the approach seemed especially useful in those with immunocompromise.[79] A well recognised pathogen known to cause encephalitis was identified in 22 cases, a known pathogen but one not recognised to cause encephalitis was identified in three, and a novel pathogen was identified in 19. There are numerous limitations to this approach in routine practice, including the restriction to pathogens with homology to those known in specific databases, cost, time, and the poor applicability for those causes of encephalitis in which the CNS manifestations are para- infectious or post-infectious. Nevertheless, rare and novel causes of encephalitis such as *Balamuthia mandrillaris* and *Astrovirus* are being increasingly identified with these techniques.[80,81]

Bead-array and proteomic approaches to assess the host inflammatory responses are increasingly being explored to investigate the pathophysiological processes that could be amenable to targeted immunomodulatory therapies.[82,83] However, whether these profiles predict cause is less clear. Although one study has reported distinct cytokine profiles between patients with infectious as opposed to immune-mediated encephalitis, further investigation is warranted.[82]

Management

After patients with encephalitis have had initial assessment of airway, breathing, circulation, and blood sugar, the focus is on seizures and raised intracranial pressure, followed by specific treatments appropriate to the suspected causes (figure 2).

Neurological emergencies

Rapid bedside assessment and neurological imaging (ie, head CT) should be done in any patient for whom there is concern about raised intracranial pressure and brain shift on the basis of the coma score and focal neurological signs. The management of cerebral oedema is summarised in the appendix.[84,85] Status epilepticus is common in acute encephalitis, occurring in approximately 20% of patients, with about a quarter developing persistent status despite use of first-line and second-line drugs, a condition termed refractory status epilepticus.[86–88] Although protocols for management of status epilepticus

are well established (appendix), there are few conclusive data to guide clinicians with respect to primary and secondary prevention of seizures in encephalitis.[89]

Cause-specific management

Initially, the aetiological treatment is broad with subsequent tailoring as more information becomes

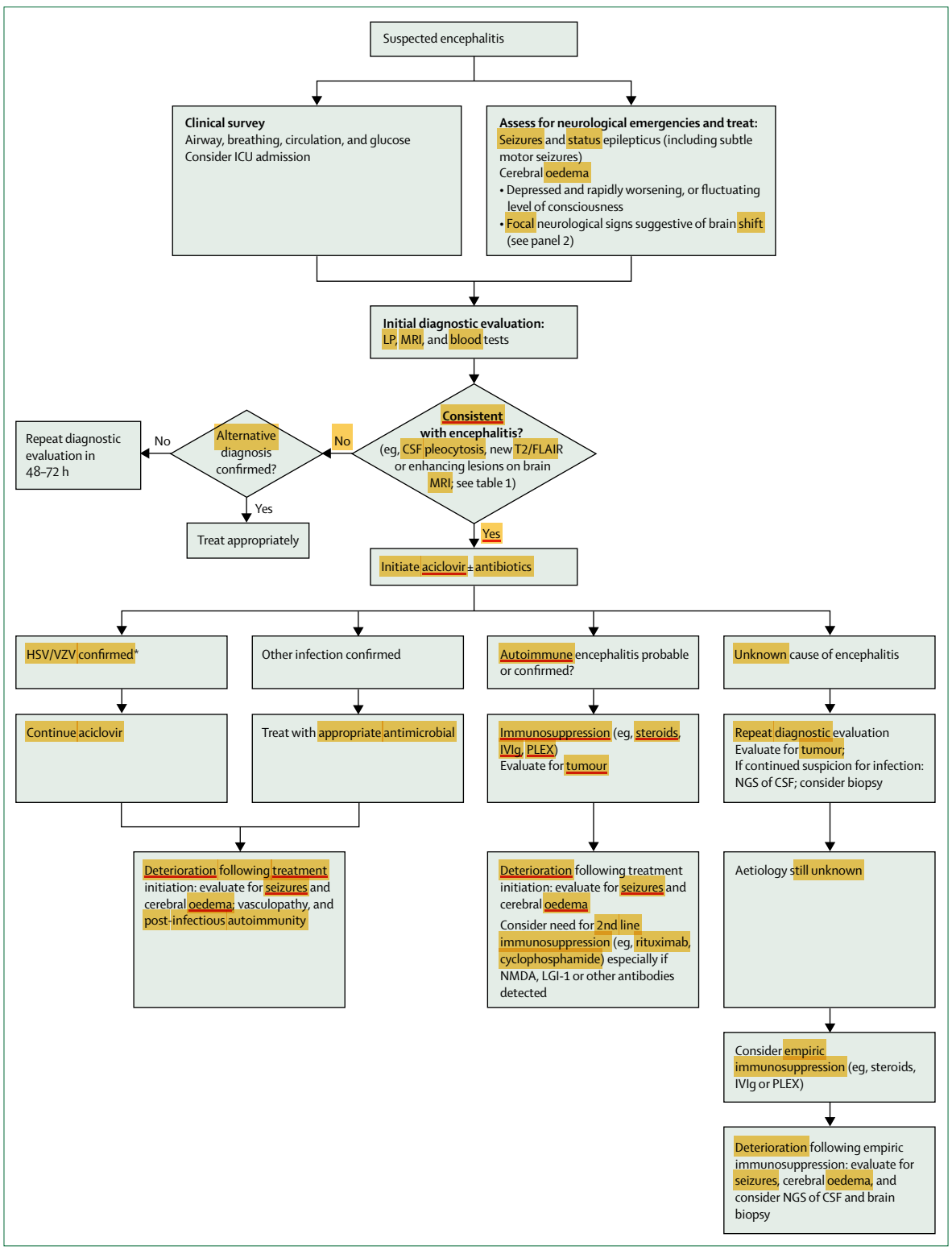

***Figure 2*: Overview of management of patients with suspected encephalitis**
Following recognition and treatment of systemic and neurological emergencies, the evaluation is focused on confirming the diagnosis of encephalitis and distinguishing infectious from autoimmune causes to guide treatment. If deterioration occurs following initiation of treatment, further evaluation for alternate diagnoses and neurological complications of brain inflammation is warranted. CSF=cerebral spinal fluid. HSV=herpes simplex virus. ICU=intensive care unit. IVIg=intravenous immunoglobulin. LGI-1=leucine-rich glioma-inactivated protein 1. LP=lumbar puncture. NGS=next-generation sequencing. NMDA=N-methyl-D-aspartate. PLEX=plasma exchange. VZV=varicella zoster virus. *If HSV and VZV not initially confirmed but strong clinical suspicion exists, continue aciclovir and repeat CSF PCR in 2–3 days.

available. Because of the frequency and the morbidity and mortality associated with delayed treatment of HSV encephalitis, empirical aciclovir (10 mg/kg intravenously every 8 h in individuals with normal renal function) should be initiated and continued until the diagnosis of HSV has been excluded.[90] This treatment should be continued for at least 2 weeks. Some advocate repeating the lumbar puncture at that stage, and if the patient is still positive for the virus then the treatment should be continued for a further week, and repeated until the virus has cleared.[4] The occurrence of autoimmune encephalitis after HSV encephalitis is increasingly recognised: patients who are recovering from appropriately treated HSV encephalitis and develop new or relapsing neurological symptoms are noted to develop anti-neural antibodies either to the NMDA receptor or to other antigens, and respond to immune treatments.[35,91] Such cases reflect the complex interplay between CNS infection and the onset of autoimmunity in the pathogenesis of encephalitis.[92] Regarding the use of adjunctive corticosteroids more broadly in patients with HSVE, the German trial of acyclovir and corticosteroids in herpes simplex virus encephalitis[93] was stopped because of under-recruitment; a similar study in the UK and France is ongoing and recruiting to target. Although the results of this trial are awaited, corticosteroids are sometimes given to patients in whom there is substantial vasogenic oedema and mass effect (appendix).

Aciclovir, usually given at a higher dose is used in VZV encephalitis, and adjunctive corticosteroids can also be beneficial especially if there is concomitant vasculopathy.[38] Ganciclovir or foscarnet are used in encephalitis caused by HHV-6 or cytomegalovirus. There are no proven antiviral or immunomodulatory treatments for any arboviral infection. Interferon alpha, ribavirin, minocycline, intravenous immunoglobulin, and dexamethasone have been assessed for Japanese encephalitis in trials of varying size and quality, but none has been shown to be efficacious.[94] Some of these drugs have also been tried in small numbers of patients with West Nile virus encephalitis.[95]

In addition to aciclovir, other antimicrobial drugs directed against viral, bacterial, mycobacterial, or other infectious organisms should be empirically initiated on the basis of specific epidemiological or clinical factors.[1,38] Such treatments can be tailored further pending subsequent CSF culture, PCR assays, antigen assays, and antibody assessments.

When the initial evaluation does not support an infectious cause and an autoimmune cause is suspected, treatment is directed toward systemic immunosuppression. Such treatment is usually started presumptively because of the time required for diagnostic results to return (appendix). There is some support for the use of second-line drugs (eg, rituximab) as early treatment in an attempt to reduce the risk of clinical relapse.[96] Risks of broad immunosuppression in such cases include potentiation of clinical worsening in the setting of an undiagnosed infectious condition or masking of causes such as lymphoma. There is increasing interest in more targeted immunotherapies such as blockade of the pro-inflammatory interleukin-6 or interleukin-1 pathways or depletion of antibody-producing plasma cells via the protease inhibitor bortezomib.[97–99]

Notably, there are no data from randomised controlled trial is to guide the selection of one therapy over another, even for first-line treatment, and therefore patient comorbidities and associated side-effects of each treatment are used to guide treatment selection (appendix).[2,100] For the autoimmune encephalitides associated with antibodies to neuronal cell surface antigens (table 1), which directly impair neuronal function, rapid clearance of antibodies can result in rapid and robust improvement. However, even in such cases, T-cell-mediated mechanisms can additionally contribute to disease pathogenesis.[101] When the target of the antibodies is intracellular, T cell or other mechanisms are probably driving disease pathogenesis, and cyclophosphamide or other broad spectrum chemotherapeutic drugs might be more effective.[3,100] ADEM and other demyelinating disorders are similarly treated in the acute setting with first-line drugs.[33,102]

In cases in which an underlying cancer is detected, treatment of the cancer can have a substantial effect and has an important therapeutic role. For example, resection of an ovarian teratoma in the setting of anti-NMDA receptor encephalitis might be considered as adjunctive first-line treatment and can potentially abrogate the need for escalation of immunosuppression.[16]

In patients with no pathogen or autoantibody identified but in whom there is clinical suspicion of possible autoimmune encephalitis,[2] some recommend a trial of immunotherapy with corticosteroids and IVIg.[100] Because of the risks and costs of such treatment a randomised controlled trial is needed. In all patients close clinical monitoring following initiation of empirical immunosuppression is paramount, particularly as clinical or radiographical deterioration would support consideration of brain biopsy to establish a definitive diagnosis.[103]

Prognosis

Overall, mortality rates for encephalitis range between approximately 5–15%.[104] However, there are few data with longitudinal follow-up and there are no standardised outcome measures which have been validated across the range of causes, across different geographical, ethnic, and resource settings, and which have been developed with integrated patient and public engagement. The extended Glasgow outcome score or the modified Rankin score are often used, although the modified Rankin score in particular has relative insensitivity in capturing the cognitive sequelae of encephalitis. Tools such as the Liverpool outcome score developed for follow-up of paediatric populations in southeast Asia and general measures of cognitive function such as the Wechsler

Intelligence scale have also been applied to encephalitis populations.[80,105]

In HSV encephalitis, even with aciclovir treatment, there is a 10–15% mortality rate and severe neurological and neuropsychiatric sequelae in 43–67% of cases.[106,107] Although 27% might superficially appear to have recovered completely, neuropsychological assessment and measures of quality of life reveal substantial deficits.[37] In addition to delayed treatment, poor outcome is associated with older age, a lower Glasgow coma scale on admission, restricted diffusion on brain MRI, and impaired immune status that might not be improved immediately.[37,106,108] A favourable outcome has been associated with dominant α or θ activity in the absence of δ, lateralised periodical discharges, or burst-suppression on routine EEG in one small series.[109]

Approximately 20–30% of patients with JEV and 10% with West Nile virus encephalitis die, and around 50% of survivors from either flavivirus have neurological sequelae.[110,111] Longitudinal follow-up of affected children in Nepal found functional impairment in 68% after JEV, particularly in behaviour, language, and limb use, with a median cost of 10 times the family monthly income in those moderately and severely affected.[112] Nevertheless, 49% showed some improvement using a validated scoring system at follow-up, supporting the need for ongoing rehabilitation.[105]

Mortality rates in autoimmune encephalitis are generally lower than in infectious cases; however, prolonged recovery and potential for relapse make longer-term management challenging. For anti-NMDA receptor encephalitis mortality is up to 6% and is associated with dysautonomia requiring intensive care. Moreover, 12–25% might relapse, predominantly in non-paraneoplastic cases, perhaps reflecting undertreatment.[16,49,50,113] A systematic review incorporating 80 children with anti-NMDA receptor encephalitis found that earlier immune treatment was associated with a better outcome.[114] A need for intensive care management and a maximum modified Rankin score of more than four are associated with a worse outcome overall[16,96] as was prolonged elevation of the chemokine CXCL13 in the CSF in one small study.[115] After completion of immunotherapy, improvements in cognition can be seen over months to years; although impairments might not be captured by routine neurological assessments, this emphasises the importance of specialised rehabilitation services.[4,116,117] Mortality rates are likely lower for anti-LGI-1 encephalitis than anti-NMDA receptor encephalitis, although longer-term relapse rates might be higher.[22,57,118] Functional neuroimaging parameters have been shown to be disrupted following autoimmune encephalitis and, although numbers are small, volumetric studies have identified correlations between subregional hippocampal atrophy and various cognitive domains following anti-NMDAR and anti-LGI-1 encephalitis.[119–122] In FDG-PET studies the time to resolution of occipital hypometabolism correlates with outcome in some patients with anti-NMDA receptor encephalitis.[68,123] In a retrospective review of all cases of autoimmune encephalitis, the outcome was worse for those with a longer duration of symptoms before immunotherapy.[125]

Several prognostic biomarkers have been explored in cohorts of patients with encephalitis of any cause, with CSF as opposed to serum markers seemingly most promising. For example, elevated levels of the neuronal protein tau, glial proteins S100B, glial fibrillary acidic protein, or rising levels of neurofilament heavy chain have been found in those with encephalitis or encephalopathy and poor outcome.[125,126] Several host response mediators have also been found to correlate with a poor prognosis, including CSF levels of interleukin (IL)-6 and the chemokine CCL5. In one large study, which recruited a broad range of causes, the CSF and serum balance between the pro-inflammatory cytokine IL-1 and its antagonists IL-1 receptor antagonist and IL-10 correlated with coma score, outcome score, the volume of oedema on neuroimaging, and a marker of blood–brain–barrier permeability.[82] Nevertheless, these markers remain to be validated and the only widely available biomarker is an EEG, which if normal early in admission has been associated with a positive outcome.[127]

Future directions

Although the field of encephalitis has changed dramatically over the past decade with characterisation of novel autoantibody-mediated syndromes, emergence of new infectious causes, and better ways of diagnosing infectious and autoimmune causes, several uncertainties remain (panel 3). Next-generation sequencing and FDG-PET have shown promise as diagnostic tools, but their sensitivity and specificity have yet to be defined in broad populations of patients with acute neurological disease. Despite extensive testing, a substantial proportion of cases of encephalitis remain without an identified cause and therefore further efforts should focus on understanding of T-cell-mediated, para-infectious, and other causes of acute CNS inflammation. Optimal immunotherapy regimens

Panel 3: **Controversies and uncertainties in diagnosis and management of acute encephalitis**

- Role of next generation sequencing in evaluation of patients
- Role of PET scanning in evaluation of autoimmune encephalitis and distinction from infectious encephalitides and neurodegenerative disorders
- When to biopsy patients with encephalitis of unknown cause
- Role of corticosteroids in herpes simplex virus encephalitis
- Best options for initial treatment of autoimmune encephalitis, including choice and duration of therapy
- When to use empirical immunosuppression in cases with unknown cause

for autoimmune encephalitis remain unknown, including choice of first-line drugs, duration of treatment, and timing of monoclonal antibody therapy in those with confirmed disease. Treatment trials that are carefully conducted with defined outcomes are needed. Lastly, current immunotherapies broadly suppress the immune system, and thus place patients at risk for opportunistic infections and malignancies. The evaluation of personalised immune therapies targeting specific pathways might provide opportunities to optimise treatment benefits while limiting risks.

Contributors

AV organised the manuscript. All authors contributed equally to the writing of this Seminar.

Declaration of interests

TS is an adviser to the GSK Ebola Vaccine programme and chairs a Seimens Diagnostics Clinical Advisory Board. All other authors declare no competing interests.

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