Acute encephalitis in children: Progress and priorities from an Australasian perspective

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Abstract: Encephalitis is a complex neurological syndrome caused by inflammation of the brain that occurs with highest incidence in children. It is challenging to diagnose and manage due to the variety of aetiologies and non-specific clinical presentations. We discuss the recent progress in clinical case definitions; review recent, large, prospective epidemiological studies; and describe aetiologies. We emphasise infectious causes relevant to children in Australasia but also consider emerging immune-mediated syndromes responsive to immune therapies. We identify priorities for future research in children, given the potential for climate change and international travel to influence the emergence of infectious agents in our region.

Key words: aetiology; Asia; Australia; child; encephalitis; epidemiology.

Encephalitis is a complex neurological syndrome caused by inflammation of the brain parenchyma. It is difficult to diagnose and manage because of the following: its hallmark clinical features overlap with other pathologies; it is often rapidly progressive; and there are a large number of aetiologic agents, few of which respond to targeted therapy.1 A confirmed aetiologic diagnosis is made in, at best, 60% of cases of encephalitis.2 The incidence of encephalitis is highest in children.3 Though viruses are the most common confirmed causes, immune-mediated encephalitides are increasingly recognised and may respond to early immune suppressive therapies.

Definitions

Although the term encephalitis implies a histopathological diagnosis, the condition is rarely diagnosed by histology. Instead, the pathology is inferred in a patient who presents with acute central nervous system (CNS) dysfunction in association with evidence of CNS inflammation on cerebrospinal fluid, CNS imaging or electroencephalogram. Some authors use the term ‘meningo-encephalitis’ interchangeably, highlighting the importance of CSF inflammation. Detailed case definitions have been developed for use in large epidemiological research studies and for international guidelines (Table 1). Though a strong consensus has emerged, these definitions need to be more widely tested in specific patient groups, for example, young infants/neonates and the immunocompromised. Encephalitis should be differentiated from encephalopathy associated with metabolic dysfunction, toxin exposure, other CNS pathologies and infections outside the brain (see Box 1). Earlier literature used heterogeneous case definitions and less rigorous attribution of causality for infectious agents, which has limited our understanding of the epidemiology of encephalitis.9 Infection-associated encephalopathies (IAEs), such as acute necrotising encephalopathy (ANE), pose a particular dilemma to classification. ANE is not associated with encephalitis histopathologically, and CSF pleocytosis is usually absent, yet it frequently meets encephalitis case definitions and is associated with infections identified outside the CNS (especially influenza).10 Other IAE described include mild encephalopathy with reversible splenial lesion and acute encephalopathy with biphasic seizures and late reduced diffusion.11

Key Points

1 Encephalitis is diagnosed in a child with encephalopathy and other features of central nervous system (CNS) dysfunction in association with evidence of CNS inflammation on cerebrospinal fluid, CNS imaging or electroencephalogram.
2 The most frequent causes of encephalitis in children are HSV, varicella zoster virus and the non-polio enteroviruses. A detailed history of specific risk factors and exposures assists in prioritising testing for the myriad other causes.
3 Paediatricians should be aware of the immune-mediated causes of encephalitis that likely respond to immune therapies. Where these are suspected, referral to a paediatric neurologist is warranted.

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<table>
<thead>
<tr>
<th>Age</th>
<th>Brighton collaboration(^4)</th>
<th>California Encephalitis Project(^5)</th>
<th>French prospective cohort(^6)</th>
<th>UK prospective cohort(^2)</th>
<th>International Encephalitis Consortium(^7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Encephalopathic features</td>
<td>Any age</td>
<td>Depressed or altered level of consciousness, lethargy or a personality change lasting ≥24 h</td>
<td>≥26 months</td>
<td>≥28 days</td>
<td>Any age</td>
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<td>Depressed or altered level of consciousness lasting ≥24 h, lethargy or a personality change</td>
<td>Decreased consciousness; altered mental status</td>
<td>Altered consciousness lasting &gt;24 h including lethargy, irritability or a change in personality and behaviour</td>
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<td>Altered mental status (defined as decreased or altered level of consciousness, lethargy or personality change) lasting ≥24 h with no alternative cause identified.</td>
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<tr>
<td>B. Inflammatory features</td>
<td>Fever (≥38°C); CSF pleocytosis &gt;5 cells/mm(^3) in children &gt;2 months; &gt;15 cells/mm(^3) in children &lt;2 months; Neuroimaging consistent with encephalitis; EEG consistent with encephalitis</td>
<td>Fever; CSF pleocytosis (undefined); MRI changes consistent with encephalitis; EEG consistent with encephalitis</td>
<td>CSF WBC count ≥4 cells/mm(^3); CSF protein level ≥0.4 g/dL; temperature ≥38°C</td>
<td>Fever or a history of fever (≥38°C); CSF pleocytosis (≥4 cells/μL); Neuroimaging (CT or MRI) changes consistent with encephalitis; EEG consistent with encephalitis</td>
<td>Documented fever ≥38.8°C (100.4°F) within the 72 h before or after presentation; CSF WBC count ≥5/ mm(^3); Neuroimaging suggestive of encephalitis; EEG that is consistent with encephalitis and not attributable to another cause</td>
</tr>
<tr>
<td>C. Specific neurological features</td>
<td>Decreased or absent response†; seizure associated with loss of consciousness; focal or multifocal findings referable to the central nervous system‡</td>
<td>Seizure; focal neurological findings</td>
<td>Seizure; focal neurological signs</td>
<td>Seizure; focal neurological findings</td>
<td>Generalised or partial seizures not fully attributable to a pre-existing seizure disorder; new onset of focal neurologic findings</td>
</tr>
<tr>
<td>Summation</td>
<td>Unspecified part of A and ≥2 features from B and ≥1 feature from C</td>
<td>Unspecified part of A and ≥1 feature from B or C</td>
<td>At least one CSF abnormality and temperature ≥38°C and ≥1 feature from A or C</td>
<td>Unspecified part of A and ≥2 features from B or C</td>
<td>Unspecified part of A and possible if ≥2 features from B or C; confirmed if ≥3 features from B or C</td>
</tr>
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†Includes the following: decreased or absent response to environment as defined by response to loud noise or painful stimuli; decreased or absent eye contact; inconsistent or absent response to external stimuli; and decreased arousability. Includes the following: focal cortical signs (e.g. aphasia, alexia, agraphia, cortical blindness); cranial nerve abnormality/abnormalities; visual field defects; presence of primitive reflexes (Babinski’s sign, sucking reflex); motor weakness (diffuse or focal); sensory abnormalities (positive or negative); altered deep tendon reflexes (asymmetry, hypo/hyperreflexia); and cerebellar dysfunction (e.g. ataxia, dysmetria, cerebellar nystagmus). CSF, cerebro-spinal fluid; CT, computed tomography; EEG, electroencephalogram; WBC, white blood cell.
Infectious Aetiology

The causes of encephalitis can be broadly categorised as infectious, immune-mediated (or inflammatory) or unknown (see Box 2).

Infectious

Over 100 different infectious agents have been implicated as a cause of encephalitis. Viruses are the most frequently diagnosed pathogens; however, numerous bacteria, parasites and fungi can cause encephalitis. In most cases, encephalitis is a rare or uncommon clinical manifestation of infection. Host immunogenetic susceptibility are likely to be important as shown by reports of an autosomal recessive immune deficiency found in some children with herpes simplex virus (HSV) encephalitis (HSE).12

The strength of evidence for the causative role of infectious diseases varies. It is clear, for example, for HSV and flaviviruses but more controversial for HSV-1, HSV-2, VZV, Epstein Barr virus (EBV), cyto-megalo-virus (CMV), human herpes virus 6 (HHV6)

- Enteroviruses (coxsackieviruses, numbered including

- Parechoviruses
- Influenza virus
- Paramyxoviruses (measles, mumps)
- Flaviviruses (including Japanese encephalitis (JEV), West Nile (WNV), dengue virus, Murray Valley encephalitis (MVEV), Kunjin virus, St Louis encephalitis (SLEV), tick-borne encephalitis virus (TBEV), powassan virus (POSV))
- Alphaviruses (including Chikungunya, Me Tri Virus, Eastern Equine (EEEV), Western Equine (WEEV), Venezueulan Equine (VEEV))
- Bunyaviruses (including La crosse (LACV) and other Californian serogroup viruses, Toscana (TOSV))
- Colorado tick fever (CTFV)
- Lyssaviruses (rabies, Australian bat (ABLV), European bat (EBLV))
- Henipaviruses (Hendra, Nipah)
- Human immunodeficiency virus (HIV)
- JC virus

Bacterial

- Listeria monocytogenes
- Mycoplasma pneumoniae
- Borrelia (Lyme disease)
- Treponema Pallidum (Syphilis)
- Burkholderia pseudomallei
- Mycobacterium tuberculosis
- Leptospira sp.
- Brucella sp.
- Bartonella sp.

Parasitic

- Toxoplasma gondii
- Angiostrongylus cantonensis
- Neurocysticercosis
- Amoeba (Naegleria fowleri, Balamuthia mandrillis)
- Trypanosomiasis

Other

- Rickettsia sp.
- Ehrlichia sp.
- Coxiella burnetii (Q fever)
- Anaplasma sp.

Immune mediated

- Acute disseminated encephalomyelitis (ADEM)
- Acute haemorrhagic leuko-encephalopathy (AHLE)
- Antibody mediated (e.g. anti-N-methyl-D-Aspartate receptor (NMDAR), anti-VGKC-complex)
- Basal ganglia encephalitis

Non-polio enteroviruses cause a variety of neurological diseases in children including encephalitis. In some recent studies of childhood encephalitis, using molecular diagnostics, enteroviruses were the most commonly identified cause.
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20–30% mortality. JEV vaccination can prevent associated encephalitis annually, 75% in children. Pacific remain suboptimal.47 encephalitis, but coverage and implementation in the Asia

Box 3 Defining the causal relationship between a pathogen and encephalitis (adapted from Granerod et al.19)

High likelihood or ‘confirmed’
Organism identified within the central nervous system (CNS) (culture, polymerase chain reaction (PCR), histopathology) ± demonstration of an intrathecal specific antibody response

Moderate to high likelihood or ‘probable’
Organism identified in a sterile site (blood, cerebro-spinal fluid (CSF), pleural/pericardial fluid, joint) ± demonstration of a systemic specific antibody response

Moderate likelihood or ‘probable’
Organism identified in a non-sterile site (possible carriage) ± demonstration of a systemic specific antibody response

Low likelihood or ‘possible’
Organism identified in a non-sterile site (possible carriage) and no specific antibody response

Certain subtypes appear to be more neurotropic and/or produce more severe disease. In Asia, enterovirus 71 causes epidemics of hand, foot and mouth disease and encephalomyelitis. Parechoviruses, originally considered part of the enterovirus genus, also show the potential to cause encephalitis. An epidemic of parechovirus in New South Wales in late 2013 has caused encephalitis in some young babies (unpublished results).

In immunocompetent hosts, EBV and adenovirus encephalitis occur almost exclusively in children. M. pneumoniae has been frequently associated with encephalitis, although its causative role is unclear. The controversy is that M. pneumoniae is rarely detected in the CNS, and most cases are diagnosed based on a single positive IgM titre, a test with poor specificity. Influenza is associated with ANE and other IAE during seasonal epidemics with highest frequency in children.42,45

Vector-borne pathogens (e.g. flaviviruses) have a restricted geographic range and a seasonal predilection associated with the behaviour of specific vectors. In Asia, childhood encephalitis is most often caused by the flavivirus Japanese encephalitis virus (JEV). JEV causes an estimated 67 900 cases of encephalitis annually, 75% in children <15 years old with 20–30% mortality. JEV vaccination can prevent associated encephalitis, but coverage and implementation in the Asia Pacific remain suboptimal.47

In Europe, North America and Australia, measles (including subacute sclerosing pan-encephalitis (SSPE)), mumps and rubella were prominent causes now virtually eradicated by immunisation. These pathogens continue to be identified in Asia, likely related to poor vaccine coverage. Similarly, in Europe, the burden of tick-borne encephalitis virus (TBEV) in some countries has been reduced by immunisation.49

Immunocompromise associated with HIV/AIDS or following transplant and chemotherapy is associated with reactivation of latent infection potentially causing encephalitis (e.g. CMV, EBV, HHV-6) and with susceptibility to opportunistic CNS pathogens (e.g. Toxoplasma, Cryptococcus).

Australia has a number of novel and endemic causes of encephalitis including Murray valley encephalitis virus, Kunjin virus, Australian bat lyssavirus (ABLV) and Hendra virus (See Box 4). Regionally important causes of encephalitis at risk of emergence within Australia include JEV, dengue and Nipah.59

Immune mediated

The immune-mediated encephalitides include acute disseminated encephalomyelitis (ADEM), acute haemorrhagic leuko-encephalopathy (AHLE) and the antibody-mediated encephalitides. ADEM is an inflammatory, demyelinating condition of the CNS with a well-defined histopathology. Magnetic resonance imaging (MRI) is central to the diagnosis; features include multiple, asymmetrically distributed lesions most evident on T2-weighted and fluid-attenuated inversion recovery sequences involving the sub-cortical, central and periventricular white matter and deep grey matter (thalamus, basal ganglia (BG)). It is a common form of encephalitis that is often temporally associated with infection or vaccination. AHLE can be considered a hyper-acute form of ADEM but is rare, and there is a probable overlap with CNS vasculitis.61

The antibody-mediated encephalitides are being identified more frequently. The most important sub-types are anti-N-methyl-D-Aspartate receptor (NMDAR), anti-voltage-gated potassium channel (VGKC) and BG encephalitis.

• Anti-NMDAR encephalitis typically presents with psychiatric symptoms, seizures, memory loss and mutism. The syndrome evolves to include movement disorders, dysautonomia and sometimes hypoventilation. Although initially described as a para-neoplastic disorder with ovarian teratoma, this tumour association is uncommon in young children. It is diagnosed by identifying CSF or serum antibodies against the NR1 subunit of the NMDA receptor. Immunomodulatory therapy improves outcomes.

• VGKC-complex encephalitis in children presents with temporal lobe focal seizures, status epilepticus and encephalopathy. It is diagnosed by identifying serum antibodies that bind to the VGKC-complex, although low-titre antibodies are of questionable significance. Immunomodulatory therapy should probably be similarly efficacious as in NMDAR encephalitis although there is less evidence.

• BG encephalitis presents with movement disorders such as Dystonia-Parkinsonism and chorea with associated psychiatric symptoms but without seizures. Imaging is normal or may show localising BG involvement. BG encephalitis is likely to be immune mediated, and patients often have antibodies against dopamine-2 receptor. There is some evidence for the benefit of immune therapy.

It is likely that other immune-mediated encephalitis syndromes will be identified in future.
Pathogenesis

The pathogenesis of encephalitis is complex and incompletely understood. There are a number of potential mechanisms. Direct invasion of the brain by an infectious agent, most commonly a virus, followed by replication within the CNS can induce a mixture of direct viral neuronal cytotoxicity, primarily of the grey matter (e.g. HSV) and tissue-damaging inflammation (e.g. West Nile Virus, WNV).24 The agent may enter the brain by acute retrograde neuronal transport (e.g. HSV, rabies, enterovirus 71), by reactivation of latent virus within neurons or other cells (e.g. herpesviruses), by crossing the blood brain barrier during viraemia (e.g. WNV, JEV, enteroviruses) or by carriage within immune cells (e.g. HIV).24,40,41,72 Another mechanism for neuronal tissue damage is ischaemia due to infection-induced vasculitis. This typically occurs with VZV infection.40 ADEM results from an aberrant immune response within the CNS.60 It primarily involves the white matter though can involve deep
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Box 4  Infectious encephalitides endemic to Australia

Murray Valley encephalitis virus

Murray Valley encephalitis virus (MVEV), a mosquito-borne flavivirus, has caused three large outbreaks of encephalitis since its first description in 1951. It is maintained in enzootic mosquito-water bird cycles in North-Western Australia. It causes occasional sporadic cases in South-Eastern Australia potentially associated with periods of high rainfall and flooding. In 2011, 16 confirmed cases (three children <4 years old) of MVEV encephalitis and three deaths were recorded across Australia. Encephalitis is estimated to occur in less than 1% of infections. The major clinical features overlap with other causes of encephalitis; however, MVEV is associated with limb paresis/paralysis and features of brainstem involvement including cranial nerve dysfunction. On MRI, MVEV shows a predilection for the deep grey matter (especially thalami), cerebral peduncles, brainstem and cervical spinal cord. Treatment is supportive, and mortality occurs in up to 30% of cases, with neurological sequelae in up to half.

Kunjin virus

Kunjin virus (KUNV), a mosquito-borne flavivirus, is a subtype of West Nile Virus first described in 1960. It is thought to have a very similar epizootological characteristics as MVEV. Twenty-seven confirmed cases have been reported across Australia in the last 10 years. A large outbreak was reported in horses in NSW in 2011 with no associated human cases. Like MVEV and other flaviviruses, encephalitis likely occurs in only a fraction of total infections. It appears to cause a more mild illness than MVEV with no deaths recorded and fewer severe sequelae. Radiological changes are similar to those of MVEV. Treatment is supportive.

Hendra virus

Hendra virus (HeV), a member of the henipavirus genus of paramyxoviruses, was first described to cause human respiratory and neurological disease in 1994. Its natural reservoir is in Flying Foxes, though periodic spillover into horses occurs causing clinical disease. These events have been reported in Queensland and, more recently, Northern NSW. Transmission between horses and humans can occur, though no human-to-human transmission has been recorded. Seven human cases and four deaths have been reported, all from Queensland. Clinical features in humans include a primary influenza-like illness that may resolve or progress to encephalitis that has been universally fatal. Late neurological progression/relapse occurred in one patient 13 months following initial illness. MRI features include cortical, subcortical and brainstem lesions and leptomeningeal enhancement. Treatment and post-exposure prophylaxis with ribavirin has been proposed though its benefit is uncertain. Post-exposure prophylaxis with a specifically designed monoclonal antibody can be considered in individual cases and is available through Queensland Health.

Australian bat lyssavirus

Australian bat lyssavirus (ABLV), a phylogroup 1 lyssavirus, was first discovered in 1996. The virus is genetically very similar to rabies virus (RABV). ABLV can be found in bats across Australia with low frequency. Three human cases have been diagnosed. All of the cases occurred in Queensland, all with a history of contact with bats, two adults and one child. All showed clinical features and neuropathology consistent with classical rabies, and all three cases resulted in death. Rabies vaccine alone or in addition to rabies immunoglobulin are recommended for pre-exposure and post-exposure prophylaxis, respectively.

grey matter structures. Whether or not preceding infection or immunisation are triggers is debated. There is increasing evidence that CNS infection can trigger CNS autoimmunity (e.g. in post-HSV chorea associated with anti-NMDAR antibodies), which highlights the overlap of infectious and autoimmune mechanisms, a key future research direction.

Epidemiology

Three recent, large, prospective studies including some children have made major contributions (see Box 5). Most published childhood-specific studies are small- to moderate-sized cohorts or case series.

Two systematic reviews attempt to estimate the incidence of encephalitis; the first found the overall incidence was between 0.07 and 12.6 per 100 000 person years without significant regional differences; the second found the minimum incidence in industrialised countries to be 10.5 per 100 000 children and 2.2 per 100 000 adults. Higher incidence rates have been published in very young infants. Most studies report a slightly higher incidence in males.

Two estimates of the incidence of ADEM of 0.4 and 0.64 per 100 000 person years have been published. It is most common in children (mean age 5–8 years old), and there may be a slight male predominance. A seasonal increase in winter/ spring has been reported.

The epidemiology of antibody-mediated encephalitides is emerging. In one study, NMDAR encephalitis was more common than any single viral cause of encephalitis.

Australia

There have been two population-based studies of encephalitis in Australia, one of national mortality data from 1979 to 2006 and the second of ICD-coded encephalitis hospitalisations in NSW between 1990 and 2007. The proportion of childhood deaths...
and hospitalisations was small, but the hospitalisation rate was highest in children. Over the study period, there was a significant decline in encephalitis-associated deaths, particularly for infectious causes, although the proportion of deaths without a cause identified increased (‘unknown’ encephalitis). The average annual hospitalisation rate was 5.2/100,000 population with an average annual case fatality rate of 4.6%. The most commonly identified pathogen was HSV. Toxoplasma encephalitis and SSPE declined significantly. There was a high proportion of ‘unknown’ encephalitis (69.8%, range 61.5–78.7%). The highest rates of hospitalisation and death were in the <1 year age group. Around half of hospitalised cases had no cause assigned.

Box 5 Summary of recent large prospective clinical epidemiologic studies

California Encephalitis Project

Summary
Encephalitis cases in immunocompetent patients (see Box 1) referred by physicians across California 1998–2005; case history form completed by referring doctor; samples of CSF, respiratory secretions, acute and convalescent serum collected; structured testing algorithm; aetiology classified as confirmed, probable or possible; 1570 patients included; 56% male, median age 23 years, 45% children; confirmed or probable infectious cause identified in 248 patients (16%) – 170 viral (encephalitis virus (EV) 25%, HSV-1 24%, VZV 14%, WNV 11%, EBV 10%), 78 non-viral (M. tuberculosis 24%, Bartonella sp 17%); M. pneumoniae most common possible cause found; non-infectious cause identified in 122 patients (8%); no aetiology found for 63% of patients; 10 clinical profiles recognised (six generalised and four focal) defined by clinical characteristics and neuroimaging; EBV and EV more common in children; EV and WNV most common in summer; 162 deaths (11%).

Comments
Case definition ‘tuned’ to achieve sensitivity; case ascertainment problematic (<15% population WNV encephalitis included); high percentage of children; immunodeficient patients excluded; <40% aetiological diagnosis may reflect referral bias; limited outcome data.

French National Encephalitis Study

Summary
Encephalitis cases (see Box 1) referred by physicians across France 2007; standardised questionnaire completed by referring doctor including case history with subsequent patient chart review; diagnostic testing performed locally according to structured testing algorithm as per French national recommendations; no neuroimaging reported; aetiology classified as confirmed, probable or possible; 253 patients included; 61% male, median age 55 years, 10% children; confirmed or probable infectious cause identified in 119 patients (47%) – 83 viral (HSV 66%, VZV 19%), 36 non-viral (M. tuberculosis 44%, L. monocytogenes 33%); VZV and M. tuberculosis most common possible causes found; no aetiology found for 48% of patients; 118 ICU admission (47%), median hospital stay, 20 days, 26 deaths (10%); on discharge, 62% of patients had persisting neurological signs, and 10% had behavioural disorder; factors associated with death were increased age, cancer, immunocompromise, mechanical ventilation, coma and sepsis.

Comments
Abnormal CSF central to case definition; lack of neuroimaging findings; excluded ‘mild’ cases (i.e. length of stay <5 days and survival); patients with HIV excluded; low percentage children; early outcome data.

UK National Encephalitis Study

Summary
Encephalitis cases (see Box 1) recruited from 24 hospitals (three regions) of England for 2 years (from 2005/2006); direct interview with patient or next of kin; specimens of CSF, respiratory secretions, urine, stool, acute and convalescent serum collected; structured testing algorithm with involvement multidisciplinary expert panel; aetiology classified as confirmed, probable or possible; 203 patients included; 54% male, median age 30 years, 34% children; confirmed or probable infectious cause identified in 128 patients (63%) – 57 viral (HSV 66%, VZV 18%, EV 5%), 25 non-viral (M. tuberculosis 40%, Streptococci 16%), 42 immune mediated (acute disseminated encephalomyelitis (ADEM) 55%, antibody mediated 38%); no aetiology found for 37% of patients; normal MRI likely with antibody-mediated encephalitis; abnormal imaging most likely with ADEM and HSV; median hospital stay 28 days, 24 deaths (12%); at 6 months, 43% of patients had a ‘good recovery’, 22% moderate disability, 23% severe disability; immunocompromise, TB, VZV and antibody-mediated encephalitis associated with death; TB and antibody-mediated encephalitis associated with worst outcomes; ADEM associated with best outcomes.

Comments
Approximately one-third referred patients excluded as encephalitis mimics allows for quantification of ‘specificity’ of case definition i.e. ~ 70%; most inclusive study; relatively low proportion of cases with unknown cause; cases of infectious encephalitis without CSF pleocytosis or fever identified; immune-mediated encephalitis well identified and reported; high numbers of antibody-mediated encephalitis a novel finding; moderate percentage children; 6-month follow-up outcome data.
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Diagnosis and Management

Clinical assessment

A comprehensive history and examination is essential (Box 6). Defining encephalopathy can be difficult in young children; persistent irritability, lethargy and reduced interest in feeding are the main features. In prospective studies, no clinical pattern predicted aetiology accurately. Some presentations, however, are classical (e.g. hydrophobia and hypersalivation for rabies), and other associated clinical clues may suggest a specific aetiology: flaccid paralysis (flaviviruses, EV71), rash (VZV, enteroviruses, HHV6, measles), parotitis (mumps), pneumonia (respiratory viruses, mycoplasma, Henipaviruses) and brainstem dysfunction (EV71, flaviviruses, listeria, TB). Features suggesting the antibody-mediated encephalitides include the following: absence of fever at presentation, subacute progression, prominent psychiatric and cognitive disturbance, and movement disorders.

Investigations

CSF is central to the diagnosis, and lumbar puncture should be performed as soon as possible if not clinically contraindicated. CSF pleocytosis akin to that in viral meningitis is common though can be absent. Other markers such as CSF neopterin or oligoclonal bands can demonstrate inflammation with additional sensitivity. MRI is the imaging modality of choice and, if possible, should be performed on all children with suspected encephalitis. It is the most sensitive modality for the inflammatory changes characteristic of encephalitis (especially diffusion-weighted sequences) and highly sensitive for alternate pathologies. CT is useful but has a lower yield. It remains important in some situations prior to lumbar puncture in excluding haemorrhage, space-occupying lesions and features of raised intracranial pressure. Electroencephalogram (EEG) is sensitive for identifying cerebral dysfunction in encephalitis but non-specific. Nucleic acid identification tests including polymerase chain reaction (PCR) have enabled earlier diagnosis of viral encephalitis and revealed a wider spectrum of disease, in particular for HSV and enteroviruses. However, PCR remains inadequately sensitive for flavivirus encephalitis; for this and other vector-borne viral diseases, diagnosis is primarily based on serology including CSF antibodies.

The antibody-mediated encephalitides are diagnosed by detecting anti-neuronal antibodies in the serum though CSF antibodies may be more specific. For infectious pathogens, a confirmed serological diagnosis requires the collection of acute and convalescent specimens to demonstrate seroconversion or a rise in pathogen-specific IgG. A single positive IgM, though suggestive of acute infection, can be non-specific. The very large number of pathogens associated with encephalitis cannot all be investigated, and therefore, a staged, targeted approach should be pursued in consultation with an infectious diseases specialist and microbiologist.

Management

Aciclovir reduces mortality in HSE and should be used empirically in clinical encephalitis until HSV is excluded. In children, duration of treatment for HSE is controversial; many authors recommend 21 days. Other specific treatments based on lesser quality evidence include aciclovir with corticosteroids for VZV, ganciclovir and/or foscarnet for CMV and HHV-6, and oseltamivir for influenza. New antivirals are being developed. For bacteria, fungi and parasites, effective antimicrobials are available in many cases; their use in encephalitis are beyond the scope of this review.

Box 6 Clinical assessment of a child with encephalitis

History

Timing and onset of symptoms?
Behavioural disturbance? Lethargy? Irritability?
Weakness? Abnormal gait? Bladder/bowel dysfunction?
Clumsiness?
Abnormal movements? Seizures? Loss of consciousness?
Fever?
Focal symptoms of infection – coryza, cough, mouth ulcers, skin rash, vomiting, abdominal pain, diarrhoea?
Exposure history including the following:
Travel – domestic and international?
Insect bites – mosquito, tick?
Animal exposures – wild/exotic (e.g. bats, monkeys) or domestic (e.g. horses, dogs)?
Contact with sick persons?
Parent occupations?
Outdoor activities – hiking, camping and swimming/water sport?
Ingestion of uncooked foods or untreated water?
Host risk factors:
Age?
Immunisation history?
Immunocompromise – immunosuppressive medications, HIV, primary immunodeficiency?

Physical examination

Objectively assess consciousness (e.g. GCS)
Temperature and other vital signs (note possible raised intracranial pressure or autonomic dysfunction)
Describe mental state (e.g. behaviour, disorientation, hallucinations)
Detailed neurologic examination should identify specific signs and their localisation:
• Cranial nerves
Abnormal movements
• Seizure activity (can be subtle, including eye deviation, nystagmus, focal facial/limb clonic movements)
Weakness
• Abnormal reflexes
• Sensory disturbance
• Sphincter tone
Aetiologic clues:
Rash or other cutaneous marks (bites, eschar)
Mouth/palate ulcers
Lymphadenopathy
Hepatosplenomegaly

predicted aetiology accurately. Some presentations, however, are classical (e.g. hydrophobia and hypersalivation for rabies), and other associated clinical clues may suggest a specific aetiology: flaccid paralysis (flaviviruses, EV71), rash (VZV, enteroviruses, HHV6, measles), parotitis (mumps), pneumonia (respiratory viruses, mycoplasma, Henipaviruses) and brainstem dysfunction (EV71, flaviviruses, listeria, TB). Features suggesting the antibody-mediated encephalitides include the following: absence of fever at presentation, subacute progression, prominent psychiatric and cognitive disturbance, and movement disorders.
The role of immunomodulation in infectious encephalitis is largely unresolved. A randomised controlled trial showed that interferon-α is not effective for JEV.102 There is some evidence that adjunctive corticosteroids may be of benefit for HSE;103,104 Intravenous immunoglobulin (IVIG) is widely used in Southeast Asia for Ev71 encephalomyelitis without compelling evidence.105 Corticosteroids are used to treat ADEM, though not based on high-level evidence.62 Other immune therapies used include IVIG and plasma exchange. There is moderate evidence to support immune modulation in NMDAR encephalitis; in a recent cohort, patients who failed first-line immune therapy (corticosteroids, IVIG, plasmapheresis) did better if given second-line immune therapy (rituximab, cyclophosphamide).46 Other antibody-mediated encephalitides are treated similarly with less evidence.

Supportive management is vital and might include seizure control, management of raised intra-cranial pressure, circulatory and respiratory support, fluid and electrolyte balance, nutritional support, pressure area care, and prevention of hospital-acquired infections. Multidisciplinary rehabilitation services may be required using brain injury models of care.

Comprehensive guidelines have been published from the UK, continental Europe and America,7-9,98,106,107 but not from Australasia.

**Outcome**

The overall mortality of encephalitis is approximately 10% in recent studies (see Box 3). Many paediatric studies report a lower rate (see Table 2) with the exception of Asian cohorts that showed mortality in excess of 20%. Up to half of patients will suffer a significant short- to medium-term neurological sequelae, which are severe in 20%. As may be expected, markers of disease severity (coma at presentation, ICU admission, mechanical ventilation, length of stay) are associated with more severe neurological sequelae and death.50,51,84,95 In addition, focal neurologic signs, abnormal MRI, status epilepticus, very young age, immunocompromise, JEV, TB, HSV and M. pneumoniae have all been associated with worse outcomes.5,48,50,52,93

The long-term outcome of encephalitis in children has not been well characterized; however, the evidence is concerning for high rates of neurocognitive and behavioural sequelae. A study from Finland showed cognitive and personality problems in over half,108 and an Israeli study showed moderate to severe sequelae in 63% of children with high rates of behavioural problems; low IQ scores, attention deficit hyperactivity disorder and learning disorders were overrepresented.109

**Prevention**

Vaccine-preventable causes of encephalitis include measles, mumps, rubella, VZV, influenza, JEV, rabies/ABLV and TBEV. From a regional perspective, scaling up the availability and delivery of JEV vaccine is a clear priority. Bacille Calmette-Guérin immunisation is up to 80% effective in preventing TB meningo-encephalitis.110 Post-exposure prophylaxis (PEP) for rabies/ABLV includes prompt wound management and the administration of vaccine and immunoglobulin.111 In the case of classical rabies, failure-appropriate PEP is rare.112 There is a significant progress in vaccine development for dengue and enteroviruses.41 Avoidance of exposure to vectors should be emphasised (e.g. mosquito nets).

**Future Research**

Encephalitis requires active surveillance in Australia; it is a potentially preventable cause of mortality and morbidity in children for which there are limited epidemiologic data. There is evidence that passive surveillance is ineffective86 and that non-clinical approaches are limited.113 Controlled trials of treatment of the immune-mediated encephalitides are needed. We call for well-designed, prospective cohort studies with focus on the following: the clinical epidemiology of encephalitis in children; the implementation of diagnostic algorithms; the collection and storage of specimens from cases without a confirmed aetiology (‘unknown’ encephalitis); and comprehensive follow-up to better understand neuropsychological sequelae.

**References**

Acute encephalitis in children


Multiple Choice Questions

1 Which of the following statements is FALSE?

a. Encephalitis is an uncommon clinical manifestation of many infections.
b. MRI is more sensitive than CT for diagnosing encephalitis.
c. Aciclovir is the treatment of choice of HSV encephalitis.
d. Flaviviral encephalitis is best diagnosed with PCR testing on CSF.
e. Corticosteroids are the first-line treatment of ADEM.

Answer: d.

Currently molecular tests (PCR) on CSF are less sensitive than serological techniques for the diagnosis of flaviviral encephalitis. PCR can be used as an adjunctive test where it is available.

2 The following features may assist clinicians in identifying the antibody-mediated encephalitides EXCEPT

a. Absence of fever at presentation
b. Focal weakness
c. Prominent psychiatric disturbance
d. Movement disorder
e. Subacute progression

Answer: b.

3 The following causes of encephalitis are vaccine preventable EXCEPT

a. Influenza
b. VZV
c. Echovirus 11
d. Rubella
e. Rabies

Answer: c.

The non-polio enteroviruses, of which echovirus 11 is one, are not currently vaccine preventable. This is in flux, however, with recent trials of an enterovirus 71 vaccine showing efficacy in preventing Ev71-associated hand, foot and mouth disease and Ev71-associated neurological disease.
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