Management and outcome of encephalitis in children

Mildred A Iro

Dominic F Kelly

Abstract

Encephalitis is a serious neurological disorder in childhood which can result in death or significant neurodisability. The clinical presentation can be non-specific and similar to many other important treatable conditions. Systematic investigation together with early diagnosis and treatment are critical to management. Here, we summarise the epidemiology and provide a practical approach to investigation and management of this condition.

Keywords encephalitis; HSV; management; meningoencephalitis; outcome

Encephalitis is a neurological condition characterised by brain inflammation occurring as a result of an infectious, post-infectious or autoimmune process. Inflammation of other parts of the central nervous system (CNS) can occur concurrently (e.g. the terms meningoencephalitis or encephalomyelitis indicate concurrent meningeal or spinal cord involvement respectively). In this article we focus on infection related encephalitis from a UK perspective.

Epidemiology

In England the population incidence for all-cause encephalitis has been estimated at 5.23–8.66/100,000/year[1] with the highest incidence in those less than 1 year and more than 65 years old.

Infection

Viruses are the most frequently identified pathogens causing encephalitis although numerous bacteria, parasites and fungi have also been implicated (Table 1). Whilst there are some pathogens that are common in all areas of the world (e.g. herpes simplex virus (HSV), varicella, and enteroviruses) other pathogens are regional (e.g. Japanese encephalitis in Asia, tick-borne encephalitis in Eastern Europe) and these can be the dominant pathogens with high burdens of disease during certain seasons.[2]

HSV encephalitis (HSVE) is the commonest cause of sporadic encephalitis, and in England accounts for around a fifth of all cases of encephalitis.[3] *Mycoplasma pneumoniae* has frequently been implicated as a cause of encephalitis although direct identification of the pathogen in CSF is unusual compared to indirect confirmation through serological tests. It is important to recognise that the spectrum of pathogens varies according to host factors (e.g. immunocompromise, immunisation status) and exposures (e.g. travel, animals) – see Table 1. Although a wide variety of infectious agents have been described as causing encephalitis, the aetiology remains unknown in 30–60% of cases, despite extensive investigations.

Immune forms of encephalitis – ADEM and antibody mediated

The immune forms of encephalitis include acute disseminated encephalomyelitis (ADEM) and antibody-mediated encephalitis. ADEM is an acute demyelinating condition characterised by multiple white matter lesions visible on magnetic resonance imaging (MRI) and can occur after infection, at an interval of a few days to several weeks, or more rarely after vaccination. Acute haemorrhagic leucoencephalitis (AHLE) is a rare but severe form of ADEM characterised by inflammatory demyelination and diffuse haemorrhagic necrosis. Antibody mediated encephalitis occurs due to the generation of neuronal autoantibodies. Well described important subtypes are those with antibodies against anti-N-methyl-D-Aspartate receptor (NMDAR) and anti-voltage-gated potassium channel (VGKC) complex. An association between anti-NMDAR antibody encephalitis and benign ovarian teratomas is well described.[7] With improved and more widely available diagnostic tests, antibody mediated forms of encephalitis are increasingly being identified and accounted for 9% of cases in immunocompetent individuals in a recent study in England.[3]

When should a clinician suspect a diagnosis of encephalitis?

Encephalitis should be suspected in any child presenting with a combination of features suggesting neurological involvement (e.g. confusion, seizures, headache or focal neurological signs) together with evidence of infection (e.g. fever, rash, focal signs of infection). However enecephalitis also needs to be considered in the setting of a more chronic evolution of neurological signs and symptoms and in children with encephalopathy without fever. A wide variety of other often treatable conditions can present in a similar manner (Table 2). Standardised case definitions of encephalitis have been developed mainly to facilitate epidemiological studies and clinical research. A recent consensus statement[4] suggested the presence of a 'major criterion' AND 2 (possible) or 3 (probable) 'minor criteria'. The major criterion was defined as 'Patients presenting to medical attention with altered mental status (defined as decreased or altered level of consciousness, lethargy or personality change) lasting ≥24 hours with no alternative cause identified'. The minor criteria included: documented fever ≥38 °C (100.4°F) within the 72 hours before or after presentation; generalized or partial seizures not fully attributable to a pre-existing seizure disorder; new onset of focal neurologic findings; CSF WBC count ≥5/cubic mm; abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new or appears acute in onset; abnormality on electroencephalography that is consistent with encephalitis and not attributable to another cause. However, no single clinical feature clearly distinguishes encephalitis from other causes of encephalopathy.

Mildred A Iro *MBBS, MRCPCH, PgDip Doctorate of Philosophy student, Department of Paediatrics, University of Oxford and the NIHR Oxford Biomedical Research Centre, Oxford, UK.*

Dominic F Kelly *PhD is a BRC Consultant in Paediatrics and Vaccinology with the Oxford Vaccine Group, Department of Paediatrics, University of Oxford and the NIHR Oxford Biomedical Research Centre, Oxford, UK.*

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Infectious causes of encephalitis (adapted from Britton et al., 2014[5]). Unless otherwise indicated potential for occurrence globally. Pathogens which cause encephalitis more commonly in the immunocompromised child are underlined

A. Viruses

Occur globally

- Herpesviruses (HSV-1, HSV-2, VZV, CMV, EBV,HHV6)
- Enteroviruses (coxsackieviruses, EV71, Poliovirus[V])
- Parechoviruses
- Influenza
- Measles[V], Mumps[V]
- Adenovirus
- Rotavirus
- Human immunodeficiency virus (HIV)
- JC virus

Geographic variation in prevalence

- Flaviviruses (e.g. Japanese encephalitis, West Nile, dengue virus, tickborne encephalitis virus, Murray Valley encephalitis, St Louis encephalitis)
- Alphaviruses (e.g. Chikungunya, Eastern Equine, Western Equine, Venezeulan Equine)
- Bunyaviruses (e.g. La crosse)
- Henipaviruses (Hendra (horses), Nipah (pigs)) — Asia—Pacific region
- Lyssaviruses (rabies, European bat) — animal bites, bats

B. Bacteria

- *Listeria monocytogenes*
- *Mycobacterium tuberculosis*
- *Mycoplasma pneumoniae*
- *Borrelia burgdorferi* (Lyme disease)
- *Treponema Pallidum* (Syphilis)
- *Brucella* sp. (domestic animals — cattle, sheep, goats, pigs — or products (e.g milk/urine/placenta))
- *Bartonella henselae* (cat-scratch disease)

C. Parasites

- *Toxoplasma gondii*
- Amoeba (*Naegleria fowleri*, *Balamuthia mandrillis*)
- *Angiostrongylus cantonensis* (principally Asia)
- Trypanosomiasis (African, South-American)
- Neurocysticercosis

Other

- Rickettsia sp. (Spotted Fever Group (e.g. RMSF — N/S America), Typhus Group (e.g. Scrub Typhus - Asia))
- *Coxiella burnetti* (Q fever) — mammals (cattle, sheep, goats, cats, dogs, rabbits), birds (pigeons)
- *Cryptococcus neoformans*

V = consider if no vaccine given; RMSF = Rocky Mountain Spotted Fever. CMV, cytomegalovirus; EBV, Epstein—Barr virus; HHV-6, human herpes virus 6; HSV, herpes simplex virus; VZV, varicella zoster virus; EV = enterovirus.

Table 1

Examples of the range of differential diagnoses to be considered in a child presenting with possible encephalitis

Infectious and parainfectious

Bacterial meningitis, intracerebral abscess.
Cerebral malaria, TB meningitis

Metabolic/Endocrine

Hypoglycaemia, toxins (alcohol, drugs)
Inborn errors of metabolism (e.g. urea cycle defects, organic acidopathies)
Mitochondrial disorders
Hepatic or renal encephalopathy,
Reyes syndrome
Addison's' disease, hypo/hyperthyroidism

Vascular

Stroke, venous thrombosis, migraine

Haemorrhagic

Traumatic, spontaneous (e.g. arteriovascular malformation, coagulopathy)

Malignancy

Primary brain tumour, metastatic disease

Other

Epilepsy, psychiatric, functional

Table 2

Initial management of children with suspected encephalitis

Children with suspected encephalitis often have seizures and a deteriorating level of consciousness and maybe systemically unwell. Prompt resuscitation involving management of airway, breathing and circulation together with the management of seizures and raised intra-cranial pressure are a priority in order to prevent secondary morbidity. The need for admission to the paediatric high dependency unit (PHDU) or intensive care unit (PICU) should be considered early. An approach focussed on the investigation and management of suspected encephalitis is outlined in Figure 1. Given the range of infectious and metabolic conditions that may present in a similar manner investigation of other treatable conditions should be undertaken in parallel to those for encephalitis (Table 2). The following section focusses specifically on the diagnosis and management of encephalitis.

History/Examination

In a child presenting with features suggestive of encephalitis a detailed history and examination are important. The history should be directed at i) excluding other causes of encephalopathy (see Table 2), ii) seeking evidence of associated infections and iii) considering whether the child has risk factors for more unusual causes of encephalitis: foreign travel (e.g. Japanese Encephalitis, tick borne encephalitis, rabies); lack of immunisation (e.g. measles, mumps, polio); exposure to animals (rabies, cat-scratch, Q-fever) or immunocompromise (HIV, CMV, measles, toxoplasma, Listeria). Examination should be directed at assessing the extent of neurological involvement (Glasgow coma score, focal neurology including brain-stem involvement, evidence of raised intra-cranial pressure or ongoing seizures) and looking for evidence of infection (e.g. meningism, rash, respiratory tract infection).