Management of suspected viral encephalitis in children – Association of British Neurologists and British Paediatric Allergy, Immunology and Infection Group National Guidelines


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Introduction

Encephalitis is defined as a syndrome of neurological dysfunction caused by inflammation of the brain parenchyma. Encephalitis has many causes and some are specific to childhood, but fortunately it is relatively rare. However, doctors who treat acutely ill children should be aware of how to manage a child with suspected encephalitis as some of the individual causes of encephalitis will respond to specific treatments and delays in the diagnosis in these children can be devastating. Strictly speaking, inflammation of the brain parenchyma is a pathological diagnosis, however due to the practical limitations of this, surrogate clinical markers of inflammation are used (Table 1. Definitions).

Classification of encephalitis

Encephalitis can be caused by many individual disease processes but can broadly be divided into those associated with infection (either directly or indirectly) and non-infectious causes. Direct infections of the central nervous system (CNS) can be caused by many viruses, bacteria (especially intracellular bacteria such as Mycoplasma pneumoniae), parasites and fungi (Table 2. Viral encephalitis; Table 3. Non-viral causes of encephalitis or encephalopathy). Those indirectly associated with infection include an acute demyelinating process, which is often temporally related to a prior infection outside of the CNS. This process may also follow immunisation and is known as acute disseminated encephalomyelitis (ADEM). Non-infectious causes include antibody-mediated encephalitis, which may be paraneoplastic for example limbic encephalitis associated with ovarian teratomas or may be an isolated finding. Initially these disorders were reported in adults, but they are being increasingly recognised in children.1 Most viral encephalitides are acute, but sub-acute or chronic presentations are characteristic of particular pathogens, especially in the immunocompromised (Table 4. Sub-acute and chronic encephalitis).

Epidemiology

The incidence of encephalitis in children is difficult to establish as reported studies have used different case definitions, methodologies and different geographic locations and study populations. However, in western settings reported incidences range from 6.3 to 7.4 per 100,000 for all ages (adults and children) and approximately 10.5–13.8 per 100,000 children.2 In the UK, this should equate to 1–2 children per year in a typical district general hospital and 8–10 in a large tertiary children’s hospital. In industrialised nations, the most commonly diagnosed cause of encephalitis is herpes simplex virus (HSV) with an annual incidence of 1 in 250,000 to 500,000.3 The age specific incidence is bimodal, with peaks in childhood and the elderly. Most HSV encephalitis is due to HSV type 1 but about 10% is due to HSV type 2. The latter occurs typically in immunocompromised adults and in neonates in whom it can also cause a disseminated infection. Varicella zoster virus (VZV) is also a relatively common cause of viral encephalitis, especially in the immunocompromised, whilst cytomegalovirus (CMV) occurs almost exclusively in this group. Enteroviruses most often cause aseptic meningitis but can also be an important cause of encephalitis. Among the other non-infectious causes of encephalitis, immune mediated conditions are increasingly being recognised including ADEM and encephalitis associated with antibodies to the voltage-gated potassium channel complex, or N-methyl-D-aspartate antibody (NMDA) receptors.1,4

Summary

In the 1980s the outcome of patients with herpes simplex encephalitis was shown to be dramatically improved with aciclovir treatment. Delays in starting treatment, particularly beyond 48 h after hospital admission, are associated with a worse prognosis. Several comprehensive reviews of the investigation and management of encephalitis have been published. However, their impact on day-to-day clinical practice appears to be limited. The emergency management of meningitis in children and adults was revolutionised by the introduction of a simple algorithm as part of management guidelines.

In February 2008 a group of clinicians met in Liverpool to begin the development process for clinical care guidelines based around a similar simple algorithm, supported by an evidence base, whose implementation is hoped would improve the management of patients with suspected encephalitis.

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Table 1  Definitions.

**Encephalopathy**
- Clinical syndrome of altered mental status (manifesting as reduced consciousness or altered cognition, personality or behavior)
- Has many causes including systemic infection, metabolic derangement, inherited metabolic encephalopathies, toxins, hypoxia, trauma, vasculitis, or central nervous system infection

**Encephalitis**
- Inflammation of the brain
- Strictly a pathological diagnosis; but surrogate clinical markers often used, including inflammatory change in the cerebrospinal fluid or parenchymal inflammation on imaging
- Causes include viruses, small intracellular bacteria that directly infect the brain parenchyma and some parasites
- Can also occur without direct brain infection, for example in acute disseminated encephalitis myelitis (ADEM), or antibody-associated encephalitis
Aims and scope of the guideline

In the 1980s the outcome of HSV encephalitis in adults was shown to be dramatically improved by aciclovir treatment. Delays in starting treatment, particularly beyond 48 h after hospital admission, are associated with a worse prognosis. Several comprehensive reviews of the investigation and management of encephalitis have been published, but their impact on day-to-day clinical practice appears to be limited. The emergency

<table>
<thead>
<tr>
<th>Table 2 Causes of acute viral encephalitis, with geographical clues modified from (Solomon and Whitley 2004; Solomon, Hart et al. 2007). Note viral causes of chronic encephalitis such as JC viruses are not included here.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Groups</strong></td>
</tr>
<tr>
<td>Sporadic causes (not geographically restricted) listed by group</td>
</tr>
<tr>
<td>Herpes viruses (family Herpesviridae)</td>
</tr>
<tr>
<td>Herpes simplex virus type 2</td>
</tr>
<tr>
<td>Varicella zoster virus</td>
</tr>
<tr>
<td>Epstein–Barr virus</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Human herpes virus 6 &amp; 7</td>
</tr>
<tr>
<td>Enteroviruses (family Picornaviridae)</td>
</tr>
<tr>
<td>Enterovirus 71</td>
</tr>
<tr>
<td>Poliovirus</td>
</tr>
<tr>
<td>Coxsackievirus, Echovirus, Parechovirus</td>
</tr>
<tr>
<td>Paramyxoviruses (family Paramyxoviridae)</td>
</tr>
<tr>
<td>Mumps virus</td>
</tr>
<tr>
<td>Others (rarer causes)</td>
</tr>
<tr>
<td>Arthropod-borne and zoonotic viruses*</td>
</tr>
<tr>
<td>(family Flaviviridae)</td>
</tr>
<tr>
<td>Tick-borne encephalitis virus</td>
</tr>
<tr>
<td>Dengue viruses (types 1–4)</td>
</tr>
<tr>
<td>Alphaviruses (family Togaviridae)</td>
</tr>
<tr>
<td>Chikungunya virus</td>
</tr>
<tr>
<td>Bunyaviruses</td>
</tr>
<tr>
<td>Coltiviruses</td>
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<tr>
<td>Rhabdoviruses</td>
</tr>
<tr>
<td>Chandipura virus</td>
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<tr>
<td>Henipah Viruses</td>
</tr>
</tbody>
</table>

* Most are zoonotic — i.e. animals rather than humans are the main natural hosts, the exceptions being dengue and chikungunya viruses.
management of meningitis in children and adults was revolutionised by the introduction of a simple algorithm as part of management guidelines.15 In February 2008 a group of clinicians met in Liverpool to begin the development process for clinical care guidelines based around a similar simple algorithm (Fig. 1. Algorithm for the management of patients with suspected viral encephalitis, Table 3)

### Table 3 Non-viral causes of encephalitis and its mimics modified from (Solomon and Whitley 2004; Solomon 2009).80,110

<table>
<thead>
<tr>
<th>Encephalitis</th>
<th>Mimics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CNS Infections</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
</tr>
<tr>
<td>Small bacteria (mostly intracellular)</td>
<td></td>
</tr>
<tr>
<td>Mycoplasma</td>
<td><em>Mycobacterium tuberculosis</em></td>
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<tr>
<td><em>Chlamydia pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td><em>Rickettsiae</em> (including scrub typhus, Rocky Mountain spotted fever)</td>
<td></td>
</tr>
<tr>
<td><em>Ehrlichiosis</em> (anaplasmosis)</td>
<td></td>
</tr>
<tr>
<td><em>Coxiella burnetti</em> (Q fever)</td>
<td></td>
</tr>
<tr>
<td><em>Bartonella henselae</em> (cat scratch fever)</td>
<td></td>
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<tr>
<td><em>Tropheryma whipplei</em> (Whipple’s disease)</td>
<td></td>
</tr>
<tr>
<td><em>Brucella sp.</em> (brucellosis)</td>
<td></td>
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<tr>
<td><em>Listeria monocytogenes</em></td>
<td></td>
</tr>
<tr>
<td><em>Treponema pallidum</em> (Syphilis)</td>
<td>Leptospirosis</td>
</tr>
<tr>
<td><em>Borrelia burgdorferi</em> (Lyme neuroborreliosis)</td>
<td></td>
</tr>
<tr>
<td><em>Borrelia recurrentis</em> (relapsing fever)</td>
<td></td>
</tr>
<tr>
<td>Other bacteria</td>
<td></td>
</tr>
<tr>
<td><em>Nocardiosis</em></td>
<td>Infective endocarditis</td>
</tr>
<tr>
<td><em>Actinomycosis</em></td>
<td>Parameningeal infection</td>
</tr>
<tr>
<td><strong>Parasites</strong></td>
<td></td>
</tr>
<tr>
<td><em>Trypanosoma brucei gambiense</em> and <em>rhodesiense</em> (African sleeping sickness)</td>
<td>Malaria</td>
</tr>
<tr>
<td><em>Naegleria fowleri</em>, <em>Balamuthia mandrillaris</em> (Amoebic encephalitis)</td>
<td>Cysticercosis</td>
</tr>
<tr>
<td><em>Angiostrongylus cantonensis</em> (rat lung worm)</td>
<td>Trichinosis</td>
</tr>
<tr>
<td><strong>Fungi</strong></td>
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<tr>
<td><em>Coccidiodomycosis</em></td>
<td>Cryptococcosis</td>
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<tr>
<td><em>Histoplasmosis</em></td>
<td></td>
</tr>
<tr>
<td><em>North American blastomycosis</em></td>
<td></td>
</tr>
<tr>
<td><strong>Para/post-infectious causes</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Inflammatory</strong></td>
<td></td>
</tr>
<tr>
<td>Acute disseminated encephalomyelitis (ADEM)</td>
<td></td>
</tr>
<tr>
<td>Acute haemorrhagic leukoencephalopathy (AHLE)</td>
<td></td>
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<tr>
<td><strong>Systemic infection</strong></td>
<td></td>
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<tr>
<td>Septic encephalopathy</td>
<td></td>
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<tr>
<td>Shigellosis</td>
<td></td>
</tr>
<tr>
<td><strong>Non-infectious causes</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
<td></td>
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<tr>
<td>Vasculitis</td>
<td></td>
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<tr>
<td>Systemic lupus erythematosis</td>
<td></td>
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<tr>
<td>Behcet’s disease</td>
<td></td>
</tr>
<tr>
<td>Subarachnoid &amp; subdural haemorrhage</td>
<td></td>
</tr>
<tr>
<td>Ischaemic cerebrovascular accidents</td>
<td></td>
</tr>
<tr>
<td><strong>Neoplastic</strong></td>
<td></td>
</tr>
<tr>
<td>Paraneoplastic encephalitis</td>
<td>Primary brain tumour</td>
</tr>
<tr>
<td>Metastases</td>
<td></td>
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<tr>
<td><strong>Metabolic encephalopathy</strong></td>
<td></td>
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<tr>
<td>Hepatic encephalopathy</td>
<td></td>
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<tr>
<td>Renal encephalopathy</td>
<td></td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td></td>
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<tr>
<td>Toxins (alcohol, drugs)</td>
<td></td>
</tr>
<tr>
<td>Hashimoto’s disease</td>
<td></td>
</tr>
<tr>
<td>Septic encephalopathy</td>
<td></td>
</tr>
<tr>
<td>Mitochondrial diseases</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>Antibody-mediated encephalitis: VGKC complex or NMDA receptor</td>
<td></td>
</tr>
<tr>
<td>Encephalitis lethargica</td>
<td>Epilepsy</td>
</tr>
<tr>
<td>Haemophagocytic Lymphohistiocytosis (HLH) syndrome (usually children)</td>
<td></td>
</tr>
<tr>
<td><strong>Functional disorder</strong></td>
<td></td>
</tr>
<tr>
<td>Drug reactions</td>
<td></td>
</tr>
</tbody>
</table>

In this table some of the important aetiologies are classified into whether they cause an encephalitis, with inflammatory changes seen histopathologically in the brain parenchyma, or encephalopathy without inflammatory changes in the parenchyma, although for some aetiologies this is based on limited evidence. Abbreviations: VGKC, voltage-gated potassium channel; NMDA, N-methyl-D-Aspartic acid.
supported by an evidence base, whose implementation, it is hoped, would improve the management of patients with suspected encephalitis. The scope of the guideline is to cover the initial management of all patients with suspected encephalitis, up to the point of diagnosis and early treatment, in an acute care setting such as acute medical unit or emergency room. They are thus intended as a ready reference for clinicians encountering the more common causes of encephalitis, rather than specialists managing rarer causes. The guidelines also cover the specific treatments and further management of patients for whom a diagnosis of viral encephalitis is made, particularly that due to HSV, VZV and enteroviruses. Encephalitis due to CMV is almost exclusively seen in the immunocompromised and is not covered in HIV guidelines.\textsuperscript{18} At the end of the guidelines the special circumstances of returned travellers, immunocompromised patients and encephalitis associated with antibodies are discussed. Many patients with suspected viral encephalitis ultimately prove to have another infectious or non-infectious cause for their illness. The further management and treatment of such patients is beyond the scope of this guideline, but we have included a section on follow-up and support for patients with encephalitis in both the healthcare and voluntary sectors after discharge from hospital. Finally, we have included some suggestions for audit standards to assess practice before and after implementation of the guidelines.

**Methods**

A literature search was performed on the Medline database for the years 1998–2008, to identify for all (English language) publications using the key words ('Encephalitis' AND: 'Symptoms'; 'Signs'; 'Management'; 'Diagnosis'; 'Investigation'; 'Lumbar Puncture'; 'Cerebrospinal Fluid' (CSF); 'Computed Tomography (CT)'; 'Magnetic Resonance Imaging (MRI)'; 'Single Photon Emission Tomography (SPECT)'; 'Electroencephalography (EEG)'; 'Treatment'; 'Antiviral'; 'Aci-clovir'; 'Steroids/Dexamethasone') separately and in combination with the following MESH terms: ('Herpes Simplex Virus'; 'Varicella Zoster Virus'; 'Enterovirus'; 'Human Immunodeficiency Virus (HIV)'; 'Immune compromise'; 'Arbovirus'). This yielded a total of 6948 citations, including many case reports, which were grouped together in subject areas including clinical presentation, diagnosis, imaging, treatment, outcome, immune compromise. These groups of papers were each screened by at least 2 of the group and scored for relevance, level of evidence and need for inclusion. Further sources were added from review of the bibliographies of these articles, textbooks, other reviews and personal collections of the screening group.

Using these revised source reference lists each subsection of the manuscript was composed by two authors of the Guidelines Writing Group, from the fields of neurology, infectious diseases, microbiology, virology, acute medicine and the patient-sector. This included members from professional bodies including the British Infection Society (now British Infection Association), the British Paediatric Allergy Immunology and Infection Group, the British Paediatric Neurology Association, the Society for Acute Medicine and the Encephalitis Society. Each subsection was internally peer-reviewed. The contributions from the various sections of the guidelines that people wrote were assimilated into a single document in accordance with the principles of the AGREE (appraisal of guideline research and evaluation) collaboration.\textsuperscript{19} In rating the strength of evidence we have used the GRADE approach, in which the strength of recommendations is rated from A to D, and the quality of the evidence supporting the recommendation is rated from I to III (Table 5. GRADE).\textsuperscript{20}

This document has again been internally peer-reviewed twice by the Guidelines Development Group, and updated to include further comments from all contributing authors, incorporating references published in 2009–11. The guideline has also been peer-reviewed by the wider Guidelines Stakeholder Group. This included members from the Royal College of Paediatrics and Child Health, the Paediatric Intensive Care Society, the Children’s HIV Association and the Meningitis Research Foundation. The guidelines are structured to answer common clinical questions posed during the work-up of a patient with possible encephalitis.

**Definition of childhood for this document**

This guideline is for the management of suspected viral encephalitis in children aged older than 28 days (outside the

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**Table 4** Sub-acute and chronic central nervous system presentations — microbiological causes, modified from (Solomon, Hart et al., 2007; Solomon 2009).\textsuperscript{110,211}

<table>
<thead>
<tr>
<th>Group</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viruses</strong></td>
<td>In immunocompromised patients</td>
</tr>
<tr>
<td></td>
<td>Measles virus (inclusion body encephalitis)</td>
</tr>
<tr>
<td></td>
<td>Varicella zoster virus (causes a multi-focal</td>
</tr>
<tr>
<td></td>
<td>leukoencephalopathy)</td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td></td>
<td>Herpes simplex virus (especially HSV-2)</td>
</tr>
<tr>
<td></td>
<td>Human herpes virus 6</td>
</tr>
<tr>
<td></td>
<td>Enteroviruses</td>
</tr>
<tr>
<td></td>
<td>JC/BK\textsuperscript{a} virus (progressive multi-focal</td>
</tr>
<tr>
<td></td>
<td>leukoencephalopathy)</td>
</tr>
<tr>
<td></td>
<td>HIV (dementia)</td>
</tr>
<tr>
<td></td>
<td>In immunocompetent patients</td>
</tr>
<tr>
<td></td>
<td>JC/BK\textsuperscript{a} virus (progressive multi-focal</td>
</tr>
<tr>
<td></td>
<td>leukoencephalopathy)</td>
</tr>
<tr>
<td></td>
<td>Measles virus (sub-acute sclerosing panencephalitis)</td>
</tr>
<tr>
<td><strong>Bacteria</strong></td>
<td>Mycobacterium tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Treponema pallidum (syphilis)</td>
</tr>
<tr>
<td></td>
<td>Borrelia burgdorferi (Lyme neuroborreliosis)</td>
</tr>
<tr>
<td></td>
<td>Tropheryma whippelii (Whipple’s Disease)</td>
</tr>
<tr>
<td><strong>Fungi</strong></td>
<td>Cryptococcus neoformans</td>
</tr>
<tr>
<td><strong>Parasites</strong></td>
<td>Trypanosoma brucei spp. (African trypanosomiasis)</td>
</tr>
<tr>
<td></td>
<td>Toxoplasma gondii (toxoplasmosis)</td>
</tr>
<tr>
<td><strong>Prions</strong></td>
<td>Creutzfeldt-Jakob disease</td>
</tr>
</tbody>
</table>

\textsuperscript{a} JC and BK viruses are named after the initials of the patients from whom they were first isolated.
**Clinical contraindications to lumbar puncture without neuro-imaging**
- Moderate-severe impairment of consciousness
- Reduced or fluctuating GCS (<13 or fall)
- Focal neurological signs (e.g. unilateral, dilated or poorly responsive pupil)
- Abnormal posture or posturing
- Papilloedema
- Altered mental state (confused)
- Failure to respond to therapy
- Abnormal left-arm or right-leg movements
- Immune-compromised
- Seizure activity
- Systemic shock
- Coagulation abnormalities: Results (if obtained) outside the normal range
- Platelet count <100 x 10^9/L
- Anticoagulant therapy
- Local infection at lumbar puncture site
- Respiratory insufficiency
- Suspected meningococcal septicemia

**Clinical features suspicious of encephalitis**

- Assess ABCD and check glucose (+/- involve ICU)

**Clinical contraindication to immediate LP?**

No  Yes

**If delay (>6 hours) expected: Start IV aciclovir whilst results pending**

No  Yes

**If delay (>6 hours) expected: Start IV aciclovir whilst results pending**

No  Yes

**Additional Investigations**
- Consider swab
  - Throat
  - Rectal
  - Vesicle (if present)
- Sputum (if symptoms)
  - Urine (if Urine)
- If travel consider
  - CSF PCR for EBV + CMV
  - HSV PCR for HSV
  - CSF PCR for Herpesviridae
  - CSF PCR for Cytomegalovirus
  - CSF PCR for Varicella virus
  - CSF PCR for Epstein-Barr virus
  - CSF PCR for Mycoplasm
  - CSF PCR for Adenovirus

**HIV (all patients)**
- Consider
  - CSF PCR for HIV
  - CSF PCR for JC virus
  - CSF PCR for Coccidioides
  - CSF PCR for Cryptococcus neoformans

**If CSF HSV PCR not sent**
- Repeat CSF PCR on 2nd LP
- Consider HSV CSF IgG at 30-14 days

**EEG Indications**
- if subtle motor status epilepticus suspected
- if unclear if psychiatric cause or encephalopathy

**Aciclovir Dose**
- (adjust for renal failure)
- Given 8 hourly:
  - Neonate-3 months: 20 mg/kg
  - 3 months-12 years: 500 mg/m²
  - >12 years: 10 mg/kg

**Radiological contraindications to LP**
- Significant brain shift/swelling
- Tight basal cisterns
- Alternative diagnosis made

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Normal</th>
<th>Bacterial</th>
<th>Viral</th>
<th>Tuberculous</th>
<th>Fungal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opening Pressure</td>
<td>10-20 cmH2O</td>
<td>High</td>
<td>Normal/high</td>
<td>High</td>
<td>High/very high</td>
</tr>
<tr>
<td>Colour</td>
<td>Clear</td>
<td>Cloudy</td>
<td>&quot;Gin&quot; Clear</td>
<td>Cloudy/yellow</td>
<td>Clear/cloudy</td>
</tr>
<tr>
<td>Cells</td>
<td>&lt;5</td>
<td>High/very high</td>
<td>Slightly increased</td>
<td>Slightly increased</td>
<td>Normal/high</td>
</tr>
<tr>
<td>Differential</td>
<td>Lymphocytes</td>
<td>Neutrophils</td>
<td>Lymphocytes</td>
<td>Lymphocytes</td>
<td>Lymphocytes</td>
</tr>
<tr>
<td>Glucose</td>
<td>50-80 g/L</td>
<td>Low</td>
<td>Normal</td>
<td>Low-very low</td>
<td>Normal-low</td>
</tr>
<tr>
<td>Protein (g/L)</td>
<td>&lt;0.45</td>
<td>High</td>
<td>Normal/high</td>
<td>High-very high</td>
<td>Normal-high</td>
</tr>
</tbody>
</table>

**Figure 1  Algorithm for the management of patients with suspected viral encephalitis.**

Patients (when conscious level permits) and their next-of-kin should be made aware of the support provided by voluntary sector partners such as the Encephalitis Society (www.encephalitis.info)

Abbreviations: ABCD - Abbas Investigative score to determine risk; CSF - Cerebrospinal fluid; CT - Computed tomography; ESR - Epstein-Barr virus; EEG - Electroencephalography; GCS - Glasgow coma score; HIV - Human immunodeficiency virus; IV - Intravenous; MRI - Magnetic resonance imaging; PCR - Polymerase chain reaction; T3 - T3rd Criteria; VZV - Varicella zoster virus
neonatal period) and younger than 16 years. The management of neonatal encephalitis (including premature infants) is outside the scope of this document. National guidelines for the management of suspected viral encephalitis in adults are also available as a separate document (Solomon, Michael, et al. 2012).

Diagnosing encephalitis

Which clinical features should lead to a suspicion of encephalitis in children, how do they differ from other encephalopathies, and can they be used to diagnose the underlying cause?

Recommendation

- The constellation of a current or recent febrile illness with altered behaviour, personality, cognition or consciousness or new onset seizures or new focal neurological signs should raise the possibility of encephalitis, or another CNS infection, and should trigger appropriate investigations (A, II)
- The differential diagnosis of encephalopathy (due to metabolic, toxic, autoimmune causes or sepsis outside the CNS) should be considered early (B, III), especially if there are features suggestive of a non-encephalitic process, such as a past history of similar episodes, symmetrical neurological findings, myoclonus, clinical signs of liver failure, a lack of fever, acidosis or alkalosis (B, III)
- Patients presenting with a sub-acute (weeks to months) encephalitis should trigger a search for autoimmune, paraneoplastic, metabolic aetiologies (C, III)
- The priority of the investigations shown in Table 9 is determined by the patient’s clinical history and clinical presentation (C, III)

Evidence

The differential diagnosis of acute encephalitis in childhood is broad encompassing infectious, para-infectious immune-mediated, autoimmune, metabolic, vascular, neoplastic, paraneoplastic, and toxic aetiologies as well as brain dysfunction due to systemic sepsis (Tables 2 and 3). Nevertheless, defining the clinical features that should prompt the suspicion of acute encephalitis of childhood is essential in order to achieve prompt recognition, investigation and management because delays have been shown to impair outcome.

However, differentiating infection-associated encephalitis from the other causes of encephalopathy on the basis of clinical findings poses a significant diagnostic challenge, especially in children in whom the clinical picture can be vague. For example, of Chaudhuri and Kennedy’s list ‘useful clinical pointers to aid exclusion of non-infective causes of encephalopathy’, none are absolute. In adults, fever and abnormal mental status, often with severe headache, nausea and vomiting, are the classical clinical features of infective encephalitis. Eighty-five (91%) of 93 adults with HSV-1 encephalitis in one study were febrile on admission; even those not febrile on admission will often have a history of febrile illness (Table 6. History). Disorientation (76%), speech disturbances (59%) and behavioural changes (41%) were the most common features, and one third of patients had seizures. However, a normal Glasgow coma score at presentation was seen in some patients in this, and other studies, reflecting the fact that it is a crude tool for detecting subtle changes in behaviour. Alterations in higher mental function include lethargy, drowsiness, confusion, disorientation and coma (Table 7. Examination).

Definition of the spectrum of clinical findings at presentation, and the pattern of subsequent manifestations in children is more difficult as documentation of the clinical presentation of children with encephalitis is less well described. Several studies include adults and children together making it difficult to comment on whether children may have a different presentation. Furthermore, given that children are susceptible to different aetiological agents than adults and also present differently from adults with other causes of infection, the utility of the profiles defined in characterising encephalitis presentations in childhood is limited by the lack of breakdown by age. The most relevant studies have only reported findings in small populations.

Table 5  GRADE rating system for the strength of the guidelines recommendations and the quality of the evidence (Atkins, Best et al., 2004).20

<table>
<thead>
<tr>
<th>Strength of the recommendation</th>
<th>Quality of the evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Strongly recommended</td>
<td>I Evidence from randomised controlled trials</td>
</tr>
<tr>
<td>B Recommended,</td>
<td>II Evidence from non-randomised studies</td>
</tr>
<tr>
<td>but other alternatives</td>
<td>III Expert opinion only</td>
</tr>
<tr>
<td>C Weakly recommended:</td>
<td></td>
</tr>
<tr>
<td>seek alternatives</td>
<td></td>
</tr>
<tr>
<td>D Never recommended</td>
<td></td>
</tr>
</tbody>
</table>

Table 6 Questions to consider in the history when assessing a patient with suspected encephalitis, modified from (Solomon, Hart et al., 2007).110

- Current or recent febrile or influenza-like illness?
- Altered behaviour or cognition, personality change or altered consciousness?
- New onset seizures?
- Focal neurological symptoms?
- Rash? (e.g. varicella zoster, roseola, enterovirus)
- Others in the family, neighbourhood ill? (e.g. measles, mumps, influenza)
- Travel history? (e.g. prophylaxis and exposure for malaria, arboviral encephalitis, rabies, trypanosomiasis)
- Recent vaccination? (e.g. ADEM)
- Contact with animals? (e.g. rabies)
- Contact with fresh water (e.g. leptospirosis)
- Exposure to mosquito or tick bites (e.g. arboviruses, Lyme disease, tick-borne encephalitis)
- Known immunocompromise?
- HIV risk factors?

Abbreviations: ADEM Acute disseminated encephalomyelitis; HIV Human immunodeficiency virus.
numbers of children and the entry criteria were not proven encephalitis, but suspected encephalitis and are primarily hospital-based.\textsuperscript{14,21,27} In the Toronto Acute Childhood Encephalitis study, 50 children with suspected encephalitis were reported with the most common presenting features being fever (80%), seizures (78%), focal neurological signs (78%) and decreased consciousness (47%).\textsuperscript{27} In Wang’s study from Taiwan, 101 children with a final diagnosis of encephalitis were reported to have the following features; change in personality or reduction in consciousness (40%), seizures (33%), new neurological signs (36%) and meningism 22%. The number presenting with fever was not reported.\textsuperscript{28} In the more recent Liverpool study, 51 children were treated for suspected encephalitis and their most common presenting features included confusion, irritability or a behaviour change (76%), fever (67%), seizures (61%), vomiting (57%) and focal neurological signs (37%).\textsuperscript{14} However, 14 of these children were ultimately not felt to have viral encephalitis and should not have received aciclovir so the list of presenting symptoms is likely to be inaccurate. Ill children are different to adults, young children cannot often adequately describe symptoms such as headache and infants frequently have non-specific symptoms and signs for many acute illnesses including feeding and respiratory difficulties. In Wang’s study 54% of the children had concomitant signs of a respiratory infection and 21% had gastrointestinal symptoms.\textsuperscript{28}

With the advent of CSF PCR more subtle presentations of HSV encephalitis have been recognised and described in adults and children.\textsuperscript{20} These include low-grade pyrexia rather than a high fever, speech disturbances (dysphasia and aphasia), and behavioural changes which can be mistaken for psychiatric illness, or the consequences of drugs or alcohol, occasionally with tragic consequences.\textsuperscript{31}

### Table 7 Examination findings of importance in assessing a patient with suspected encephalitis modified from (Solomon, Hart et al., 2007).\textsuperscript{10}

- Airways, Breathing, Circulation
- Mini-mental state, cognitive function, behaviour (when possible)
- Evidence of prior seizures (tongue biting, injury)
- Subtle motor seizures (mouth, digit, eyelid twitching)
- Meningism
- Focal neurological signs
- Papilloedema
- Flaccid paralysis (anterior horn cell involvement)
- Rash (purpuric — meningococcus; vesicular — hand foot and mouth disease; varicella zoster; rickettsial disease)
- Injection sites of drug abuse
- Bites from animals (rabies) or insects (arboviruses)
- Movement disorders, including Parkinsonism

### Distinguishing HSV encephalitis from other encephalopathies

Several studies have documented the potential mimics of HSV encephalitis in adults and children.\textsuperscript{12—14,32,33} Whitley et al. demonstrated that of 432 (168 < 18 years old) patients undergoing brain biopsy for presumed HSV encephalitis: 195 (45%) had the diagnosis proven histologically and in a further 95 patients (22%) an alternative, often treatable, diagnosis was established.\textsuperscript{33} However, the clinical presenting features of these two groups were very similar. Chataway et al. found that, of those patients initially considered to have HSV encephalitis, inflammatory aetiologies such as ADEM or multiple sclerosis were the most frequent mimics.\textsuperscript{32} Some of the rarer paediatric diagnoses included epileptic encephalopathies such as Rasmussen’s encephalitis and Alper’s syndrome. Kneen et al. showed the broad range of final diagnoses in children initially treated with aciclovir for possible HSV encephalitis in children and Bell et al. and Michael et al. demonstrated that this was also similar in adult practice.\textsuperscript{12—14}

The clinical picture clearly varies with disease severity but can also vary with aetiological agent; of the many viruses that cause acute encephalitis in children, some have a predilection for localised parts of the brain which can determine the initial clinical picture and the subsequent clinical course.\textsuperscript{34} Although, De Tiege et al.\textsuperscript{35} endorse the view that the concept of a ‘‘classical’’ picture of HSV encephalitis in children is now out-dated and remind clinicians that the most common reason for failure to diagnose HSV encephalitis is non-specific initial clinical presenting symptoms and signs.\textsuperscript{7}

Seizures are more frequently found in patients presenting with encephalitic processes affecting the cortex, which are more often infectious in aetiology, as opposed to encephalitic processes predominantly affecting subcortical white matter that more frequently have an immune-mediated pathogenesis (e.g. ADEM). However, seizures and movement disorders are also often seen in children with encephalitis due to autoimmune antibody-mediated disease (see ‘Special circumstances’ section). Seizures can also be subtle and include subtle motor status: a syndrome of subtle continuous motor seizure activity. This often follows overt convulsive seizures or status epilepticus or non-convulsive status epilepticus (NCSE): a syndrome of encephalopathy with no overt motor seizure activity but an electrical seizure correlate on the EEG. A study of 144 (134 children) patients with encephalitis due to Japanese encephalitis virus found that 40 had witnessed seizures in hospital. Of these, 25 had one or more episodes of status epilepticus including 15 who went onto develop subtle motor status. Patients with witnessed convulsive or subtle motor status epilepticus were more likely to die ($p = 0.0003$).\textsuperscript{36} However, it is very unusual for patients with encephalitis or other CNS infections and encephalopathy to present with de novo NCSE. A study of 236 consecutive intensive care unit patients (11% < 16 years) during the first 3 days of an illness with coma (and no witnessed overt or subtle seizures) identified that 19 (8%) were in NCSE. Of these, 2 were children. Only one adult had a CNS infection (diagnosis unspecified).\textsuperscript{37} In another study of 45 consecutive adults diagnosed with NCSE, 20 had no previous diagnosis of epilepsy. Twenty-eight of the 45 patients had a remote risk factor for developing epilepsy including previous CNS infections in some (number not specified).\textsuperscript{38} Despite its relative rarity, NCSE can only be diagnosed with an EEG and as there are specific treatments available,
an EEG should be considered in all patients with undiagnosed encephalopathy. 39

In adult clinical practice the most frequently encountered infection-associated encephalopathy is septic encephalopathy, being found in 50–70% of septic patients. 40 This syndrome usually occurs in elderly patients with an extracranial focus of sepsis where the encephalopathy cannot be attributed to other organ dysfunction. Clinically, the diagnosis is one of exclusion. The syndrome is characterised neurologically by progression from a slowing of mentation and impaired attention to delirium and coma. Neurological examination findings are usually symmetrical. This syndrome is uncommon in paediatric practice but it can occur and is most frequently seen in association with bacterial infections of the urinary tract. It can also be seen in association with other rarer infective encephalopathies such as shigella or in association with typhoid fever. 41,42

Diagnostic features for specific aetiologies
The history is important in defining the spectrum of agents potentially responsible for encephalitis as this is influenced by age, immunocompetence, geography and exposure. Geographical restrictions are laid out in the Table 2. These are particularly significant for arthropod-borne infections.

As indicated above the features for HSV are non-specific: many patients with suspected HSV encephalitis ultimately prove to have a different diagnosis. In adults, the finding of labial herpes (cold sores) has no diagnostic specificity for HSV encephalitis and is merely a marker of critical illness. However, in children who are more likely to develop encephalitis with a primary HSV infection, labial herpes may be noted. 43,44 Lahat reported 2 children with recent labial herpes in a series of 28 children aged from 3 months to 16 years with proven HSV encephalitis due to a primary infection 45 and Elbers reported active or a recent history of labial herpes in 4 out of 16 children with proven HSV encephalitis. 44,46 Elbers also reported that 3 further children with positive CSF PCR for HSV-1 were excluded from his series because of an atypical presentation. These children all had a milder illness (all had fever, one had multiple seizures, one had a single seizure and ataxia and one had lethargy and headache) and normal cranial imaging. Elbers concluded that the CSF PCR results may be false positives or due to reactivation of the virus but it is also conceivable that HSV can cause a mild encephalitis and for this reason it should be considered in the differential diagnosis of children with less severe symptoms. A mild HSV encephalitis has also been reported in 2 previous children aged 3.5 and 15 years who recovered without treatment with aciclovir. 31

Children with HSV encephalitis may also present with an acute opercular syndrome (disturbance of voluntary control of the facio-linguo-glosso-pharyngeal muscles leading to oro-facial palsy, dysarthria and dysphagia). 45,46 CNS disease caused by HSV-2 is rare outside the neonatal period. The most common manifestation in adults is aseptic meningitis which may be recurrent. 47,48 This has also been reported in children and the possibility of sexual abuse may need to be considered. 49

Varicella zoster virus (VZV) can cause central nervous system manifestations through a post-infective immune-mediated cerebellitis, an acute infective viral encephalitis or a vasculopathy; the neurological presentation may be preceded by the vesicular rash of by days or weeks, though it occasionally occurs before the rash or even in patients with no rash. 50–52 Encephalitis is more common in adults, especially those with cranial dermatome involvement or a disseminated rash or the immunocompromised. The presentation may be acute or sub-acute with fever, headache, altered consciousness, ataxia and seizures. A more common neurological presentation associated with VZV infection in children is post-infectious cerebellitis particularly in young children. This is usually a relatively mild and self limiting disorder but children can become unwell due to hydrocephalus secondary to swelling of the cerebellum in more severe cases. 53,54 Children usually present with a short history of unsteadiness or limb ataxia and nystagmus. The other relatively common association in childhood is between VZV infection and arterial ischaemic stroke, and is thought to account for up to one third of cases of arterial strokes in paediatric practice. The majority present with acute but permanent hemiparesis, acute chorea or facial weakness which is commonly transient; 55 seizures and visual or speech disturbances also occur. Patients usually present after the rash has cleared and the time period can be very delayed with a mean of 3 months (range 1 week to 48 months) reported in a recent London study. 55 However, early manifestations can occur within days of exposure, 50 well before the vesicular eruption, which may be uncharacteristically mild, 52 making diagnosis more challenging, especially as onset of encephalitic features can be abrupt or gradual. 51 PCR for VZV DNA in the CSF is positive in around a third of patients. A more sensitive test (positive in over 90% patients) is measuring VZV specific IgG antibodies in CSF. The levels can be compared to a concomitant serum sample as a reduced serum/CSF ratio of VZV IgG confirms intrathecal synthesis. 56

Epstein–Barr virus (EBV) encephalitis most commonly affects teenagers (median age 13 years; but generally presents in the absence of signs of the typical mononucleosis clinical picture. 57 In Doja’s series of 21 patients, 17 had a non-specific prodrome of fever and 14 had headache. Manifestations of EBV encephalitis and encephalomyelitis may also include an altered level of consciousness, seizures and visual hallucinations. 57–59 However, the temporal relationship between symptoms is highly variable, including CNS disease as the presenting manifestation, making aetiological diagnosis difficult on clinical grounds and highlighting the need to consider EBV in all cases of childhood encephalitis irrespective of symptoms. 57

Encephalitis may be associated with respiratory illnesses in children: most common pathogens include the influenza viruses, paramyxoviruses and the bacterium M. pneumoniae. There may be no preceding respiratory symptoms prior to the development of encephalitis in a significant proportion of patients. 60,61 In a recent study of patients with M. pneumoniae encephalitis, the affected children were an older cohort (median age 11 years old), presenting with a short prodrome of fever (70%), lethargy (68%), and altered consciousness (58%), while gastrointestinal (45%) and respiratory (44%) symptoms were less common. 60 Their clinical course progressed rapidly (median 2 days from onset to hospitalization), and commonly required intensive
care (55%). Seizures were less common in the clinical picture. Symptoms of progressive symmetrical external ophthalmoplegia typify Bickerstaff brainstem encephalitis in association with M. pneumonia and can serve as a clue to diagnosis especially when accompanied by ataxia.62 Influenza has been reported to be associated with a spectrum of neurological disorders in adults and children ranging through a mild encephalopathy with seizures, encephalitis, ADEM, encephalopathy with posterior reversible encephalopathy syndrome, malignant brain oedema syndrome and acute necrotising encephalopathy (ANE).65,66 Patients with influenza (particularly influenza B) can also have associated severe myositis.63,64 Patients with influenza encephalopathy/encephalitis rarely have viral antigens or viral nucleic acid in CSF or neural tissue and the mechanisms for causing neurological illness are still unclear. Influenza A in particular, has been reported in association with ANE, a severe encephalopathy often associated with fever and in which typical MRI abnormalities have been reported in the thalami, brainstem and cerebral white matter.65–67 ANE has most frequently been reported in young children in small outbreaks in Japan and other Southeast Asian countries. This disorder has been found to have an autosomal dominant inheritance pattern in some families with genetic mutations identified.68 There is some very recent evidence that the H1N1 strain of Influenza A that emerged in 2009 may cause more neurological manifestations than seasonal flu. Ekstrand reported 18 children with H1N1 and compared them to 16 with seasonal flu. Children with the H1N1 strain were more likely to have encephalopathy, focal neurological signs, aphasia and an abnormal EEG.69

Encephalitis associated with gastrointestinal symptoms includes infection with enteroviruses, rotavirus and human parechoviruses. Enteroviral encephalitis can be associated with a brainstem syndrome. Large outbreaks of encephalitis have been reported with enterovirus 71 in Bulgaria 1975, Hungary 1997, Malaysia 1997 and Taiwan 1997. Children under 5 are more commonly affected70 and the highest mortality is in those aged 6–12 months.71,72 Clues to infection with this virus include the typical papular lesions on the hands, feet and in the mouth but those with encephalitis often develop neurogenic pulmonary oedema73 on day 2–3 of illness which can rapidly progress to fatal cardiorespiratory collapse despite intervention.71 Rotavirus encephalopathy has been reported to cause convulsions and cerebellar signs in some children.74,75

Rashes may be seen in other encephalitides; for example a maculopapular or vesicular rash is seen in Rickettsial infections or the highly typical rash of measles virus infection. Measles can cause three separate encephalitides and is of particular concern given the recent rise in cases reported in children and young adults across Europe. The first is either an acute encephalitis or acute disseminated encephalomyelitis associated with the acute infection, although patients may present without the typical rash.76 The second is a sub-acute encephalopathy around six months after the primary infection in the immunocompromised with measles inclusion bodies in the brain often without a rash. The third is sub-acute sclerosing panencephalitis (SSPE) in the immunologically normal which can occur several years after the primary infection. Patients with the sub-acute forms usually present with a dementia, visual problems and later with seizures.77

HHV6 (and possibly HHV7) is a cause of encephalitis causing severe disease and long-term sequelae far beyond self-resolving febrile convulsions.78 Typical below age 2 years79 ataxia and prolonged convulsions are the major neurological manifestations and gastrointestinal symptoms can accompany the high fever and rash systemically, thus can be indistinguishable from the viral encephalitides typified by gastroenteritis.

Sometimes the pattern of neurological deficit can be a clue as to the possible aetiology. Thus autonomic dysfunction, myoclonus and cranial neuropathies can indicate brainstem encephalitis, which is seen in listeriosis, brucellosis, some viral infections or rarely tuberculosis (Table 8. Brainstem encephalitis); there may be tremors and other movement disorders if the thalamus and other basal ganglia are involved, as seen in flaviviruses, such as West Nile virus and Japanese encephalitis, and alphaviruses such as Eastern equine encephalitis virus.80,81 An encephalitis with an acute flaccid paralysis is characteristic of polio, and other enteroviruses, such as enterovirus 71, as well as flaviviruses.82

Which patients with suspected encephalitis should have a lumbar puncture (LP), and in which should this be preceded by a computed tomography (CT) scan?

Recommendation

- All patients with suspected encephalitis should have a lumbar puncture as soon as possible after hospital

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Table 8 Brainstem encephalitis (rhombencephalitis) - clues and causes, from (Solomon, Hart et al., 2007).110

<table>
<thead>
<tr>
<th>Suggestive clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Lower cranial nerve involvement</td>
</tr>
<tr>
<td>- Myoclonus</td>
</tr>
<tr>
<td>- Respiratory drive disturbance</td>
</tr>
<tr>
<td>- Autonomic dysfunction</td>
</tr>
<tr>
<td>- Locked-in syndrome</td>
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<tr>
<td>- MRI changes in the brainstem, with gadolinium enhancement of basal meninges</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Enteroviruses (especially EV-71)</td>
</tr>
<tr>
<td>- Flaviviruses, e.g. West Nile virus, Japanese encephalitis virus</td>
</tr>
<tr>
<td>- Alphaviruses, e.g. Eastern equine encephalitis virus</td>
</tr>
<tr>
<td>- Rabies</td>
</tr>
<tr>
<td>- Listeriosis</td>
</tr>
<tr>
<td>- Brucellosis</td>
</tr>
<tr>
<td>- Lyme borreliosis</td>
</tr>
<tr>
<td>- Tuberculosis</td>
</tr>
<tr>
<td>- Toxoplasmosis</td>
</tr>
<tr>
<td>- Primary or secondary central nervous system malignancy</td>
</tr>
<tr>
<td>- Paraneoplastic syndromes</td>
</tr>
</tbody>
</table>
admission, unless there is a clinical contraindication (Table 10. Contraindications to immediate lumbar puncture) (A, II)

- Clinical assessment and not cranial CT should be used to determine if it is safe to perform a LP (A, II)
- If there is a clinical contraindication indicating possible raised intracranial pressure due to or causing brain shift, a CT scan should be performed as soon as possible, (A, II). An immediate LP following this should ideally be considered on a case by case basis, unless the imaging reveals significant brain shift or tight basal cisterns due to or causing raised ICP, or an alternative diagnosis, or the child’s clinical condition changes (B, III).
- If an immediate CT is not indicated, imaging (CT or, preferably, MRI) should be performed as soon as possible after the LP (A, II)
- In anticoagulated patients, adequate reversal (with protamine for those on heparin and vitamin K, prothrombin complex concentrate, or fresh frozen plasma for those on warfarin) is mandatory before lumbar puncture (A, II). In patients with bleeding disorders, replacement therapy is indicated (B, II). If unclear how to proceed, advice should be sought from a haematologist (B, III)
- If an initial LP is non-diagnostic, a second LP should be performed 24-48 hours later (B, II)
- Children and young adults should be stabilised before performing a CT scan, and an anaesthetist, paediatrician or intensivist should be consulted. (A, III)
- Lumbar punctures should be performed with needles that meet the standards set out by the National Patient Safety Agency (A, III)

Table 9  Additional investigations to consider in the differential diagnosis of encephalitis.

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Investigations to consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Para-infectious immune-mediated</td>
<td>MRI brain and spine&lt;br&gt;AntiDNase B and ASO titre, influenza A and B PCR and/or antibody in CSF and serum&lt;br&gt;CSF examination&lt;br&gt;Brain and meningeal biopsy</td>
</tr>
<tr>
<td>encephalitis</td>
<td></td>
</tr>
<tr>
<td>Autoimmune/Inflammatory</td>
<td>FBC, ESR, CRP, ANA, ENA, dsDNA, ANCA, C3, C4, lupus&lt;br&gt;antiacoagulant, cardiolipin, thyroglobulin, thyroperoxidase antibodies, ferritin, fibrinogen, triglycerides&lt;br&gt;Voltage-gated potassium channel complex and NMDA receptor antibodies&lt;br&gt;Serum and CSF ACE, Serum 25OH Vitamin D, 24hr urinary calcium&lt;br&gt;Whole body CT&lt;br&gt;Biopsy: Brain, meninges, skin, lymph node, peripheral nerve/muscle</td>
</tr>
<tr>
<td>encephalitis</td>
<td></td>
</tr>
<tr>
<td>Metabolic</td>
<td>Renal, liver, bone &amp; thyroid profiles&lt;br&gt;Arterial blood gas analysis&lt;br&gt;Plasma and CSF lactate, ammonia, pyruvate, amino acids, very long-chain fatty acids, urinary organic acids&lt;br&gt;Porphyrrins: blood/urine/faeces&lt;br&gt;Biopsy: skin, lymph node, peripheral nerve/muscle</td>
</tr>
<tr>
<td>Vascular</td>
<td>CT or MRI head with venogram and/or angiogram&lt;br&gt;CT or PET chest, abdomen and pelvis&lt;br&gt;Biopsy of non CNS viscera&lt;br&gt;Alpha fetoprotein, beta human chorionic gonadotrophin</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Anti-neuronal and onconeural antibodies&lt;br&gt;CT or PET chest, abdomen and pelvis&lt;br&gt;Biopsy of non CNS viscera</td>
</tr>
</tbody>
</table>
Evidence

A lumbar puncture (LP) is an essential investigation in the management of children with suspected encephalitis to confirm the diagnosis and rule out other causes. Therefore all children with suspected encephalitis should have a LP unless a specific contraindication exists. Contraindications have been published in an evidenced based guideline for the management of decreased level conscious level in children (Table 10. Contraindications to immediate lumbar puncture). The risk of presenting with viral encephalitis following a febrile seizure is not known although the risk for bacterial meningitis following febrile seizures is quoted to occur in between 0.4 and 5%. This figure increases to 18% in children who present with febrile status epilepticus. In addition, young children may present with meningitis without any signs of meningeal irritation; 6 children aged less than 18 months in a series of 95 children who presented with a simple (n = 87) or complex febrile seizure (n = 8) and without signs of meningial irritation had underlying bacterial meningitis. Although others have reported that only 0.4–1.2% of children who present with a fever and a seizure, in the absence of signs of meningeal irritation will have bacterial meningitis. Nevertheless, children who do not make a full recovery within an hour following a typical, simple febrile convulsion should have a LP.

There has been considerable controversy over the role of computer tomography (CT) and LP in patients with suspected central nervous system infection, in particular whether a CT is needed before an LP. Although there are few studies that specifically address this issue in patients with suspected encephalitis, much of the literature about suspected bacterial meningitis is pertinent because of overlap in the clinical presentations. As in patients with meningitis, in encephalitis the CT scan is not a reliable tool for the diagnosis of raised intracranial pressure, and should not be used to for this. In patients with suspected encephalitis, an early CT scan has two roles: suggesting the diagnosis of viral encephalitis and indicating an alternative diagnosis. An initial CT scan soon after admission will show a suggestive abnormality in about 80% of patients with herpes simplex virus (HSV) encephalitis, almost all those with HSV encephalitis, and a negative initial scan will have abnormalities on a second scan. The sensitivity of the CT scan for detecting abnormalities is increased with the use of intravenous contrast media, however, it is not, on its own, diagnostic.

The second role of an early CT scan is suggesting an alternative diagnoses, so that LP may no longer be necessary. For example in one study of 21 adults with suspected encephalitis, 2 (10%) patients did not have a LP after the CT scan showed a stroke; however, in a larger study only 2 (1%) of 153 patients with suspected CNS infections who had a CT first did not subsequently need a LP.

If clinical contraindications to an immediate LP are present then an urgent CT should be performed. If this identifies shift of brain compartments or tight basal cisterns, due to mass lesions and/or oedema a subsequent LP may be dangerous. In patients with brain shift, a LP, by reducing the cerebrospinal fluid (CSF) pressure below the lesion, may precipitate herniation of the brainstem or cerebellar tonsils. For example this may occur in patients with brain abscess, subdural empyema, tumour, or a necrotic swollen lobe in HSV encephalitis. However unselected CT scanning all patients before a LP can cause unnecessary delays in many patients, in whom there were no contraindications to an immediate LP. For example in one recent study of 21 adults with suspected encephalitis, 17 had a LP, which was delayed for a CT scan in 15, though only one of them had any contraindications to an immediate LP. The median time to CT scan was 6 h, but the median time to LP was 24 h. For example this may occur in patients with brain abscess, subdural empyema, tumour, or a necrotic swollen lobe in HSV encephalitis. However unselected CT scanning all patients before a LP can cause unnecessary delays in many patients, in whom there were no contraindications to an immediate LP. For example in one recent study of 21 adults with suspected encephalitis, 17 had a LP, which was delayed for a CT scan in 15, though only one of them had any contraindications to an immediate LP. The median time to CT scan was 6 h, but the median time to LP was 24 h. Furthermore, in a larger study of 217 patients with suspected CNS infections who had a CT first did not subsequently need a LP.

Table 10 Contraindications to an immediate lumbar puncture in patients with suspected CNS infections, modified from (Kneen, Solomon, et al., 2002; Michael, Sidhu, et al., 2010; Hasbun, Abrahams, et al., 2002; NICE).

<table>
<thead>
<tr>
<th>Imaging needed before lumbar puncture (to exclude brain shift, swelling, or space occupying lesion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Moderate to severe impairment of consciousness (GCS &lt; 13) or fall in GCS of &gt;2</td>
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<tr>
<td>• Focal neurological signs (including unequal, dilated or poorly responsive pupils)</td>
</tr>
<tr>
<td>• Abnormal posture or posturing</td>
</tr>
<tr>
<td>• Papilloedema</td>
</tr>
<tr>
<td>• After seizures until stabilised</td>
</tr>
<tr>
<td>• Relative bradycardia with hypertension</td>
</tr>
<tr>
<td>• Abnormal ‘doll’s eye’ movements</td>
</tr>
<tr>
<td>• Immunocompromise</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Systemic shock</td>
</tr>
<tr>
<td>• Coagulation abnormalities:</td>
</tr>
<tr>
<td>o Coagulation results (if obtained) outside the normal range</td>
</tr>
<tr>
<td>o Platelet count &lt;100 × 10^9/L</td>
</tr>
<tr>
<td>o Anticoagulant therapy</td>
</tr>
<tr>
<td>• Local infection at the lumbar puncture site</td>
</tr>
<tr>
<td>• Respiratory insufficiency</td>
</tr>
<tr>
<td>• Suspected meningococcal septicaemia (extensive or spreading purpura)</td>
</tr>
</tbody>
</table>

There is no agreement on the depth of coma that necessitates imaging before lumbar puncture; some argue Glasgow coma score < 12, others Glasgow coma score < 9.

• Patients on warfarin should be treated with heparin instead, and this stopped before lumbar puncture.

• Consider imaging before lumbar puncture in patients with known severe immunocompromise (e.g. advanced HIV).

• A lumbar puncture may still be possible if the platelet count is 50 × 10^9/L; Seek haematological advice.
A series of studies have examined which clinical signs can be used to determine which patients with suspected bacterial meningitis need a CT scan before LP. In one study of 696 episodes of community acquired acute bacterial meningitis it was concluded that CT scan should precede LP in patients with new onset seizures, focal neurological signs, excluding cranial neuropathies, or moderate to severe impairment of consciousness, as indicated by a Glasgow coma score of 10 or less. Papilloedema, a di- erate to severe impairment of consciousness, as indicated by neurological signs, excluding cranial neuropathies, or moderate meningitis it was concluded that CT scan should precede LP study of 696 episodes of community acquired acute bacte- to make a diagnosis and guide treatment. In one retrospec- similar cases in patients with viral encephalitis; and most LP has been reported in patients with bacterial meningitis whatever the scan shows. Occasionally deterioration after whether a low coma score is an absolute contraindication, should then be performed at all, if the scan is normal, or whether a low coma score is an absolute contraindication, whatever the scan shows. Occasionally deterioration after LP has been reported in patients with bacterial meningitis and an apparently normal CT; but we are not aware of similar cases in patients with viral encephalitis; and most would argue that the information from the LP is essential to make a diagnosis and guide treatment. In one retrospec- tive series of 222 adults with suspected encephalitis less than 5% of patients had imaging changes suggestive of raised intracranial pressure.

Other contraindications to LP include local skin infection at the site of puncture, a clinically unstable patient with circulatory shock or respiratory insufficiency, and any clinical suspicion of spinal cord compression. LP may also be harmful in patients with coagulopathy, because of the chance of needle-induced subarachnoid haemorrhage or of the development of spinal subdural and epidural haematomas. The standard recommendation is to perform a lumbar puncture only when the patient does not have a coagulopathy and has a platelet count of 100 × 10^9/L or greater, although platelet counts of 20 × 10^9/L or greater have also been recommended. A rapidly falling count is also a contraindication. Haemorrhage can occur in patients anticoagulated with heparin or warfarin, but in one large study, preoperative antplatelet therapy with aspirin or nonsteroidal anti-inflammatory medications and subcutaneous heparin on the operative day were not risk factors for spinal haematoma in patients undergoing spinal or epidural anaesthesia.

In summary, many children will need a CT before a LP, because of their clinical contraindications to an immediate LP; such patients should have a CT, and then ideally a LP should be considered on a case by case basis (if still indicated and no radiological contraindications are identified) within 6 h and then decisions made on antiviral treatment based on these results. In some children who do not have a clinical contraindication to immediate LP, and in whom CT is not immediately available, a prompt LP may be the most useful approach to get an early diagnosis.

Lumbar punctures should be performed with needles that meet the standards set out by the National Patient Safety Agency.

What information should be gathered from the LP?

**Recommendations**

- CSF investigations should include:
  - Opening pressure when possible (A, II)
  - Total and differential white cell count, red cell count, microscopy, culture and sensitivities for bacteria (A, II)
  - If necessary, the white cell count and protein should be corrected for a bloody tap
  - Protein, lactate and glucose, which should be com- pared with a plasma glucose taken just before the LP (A, II)
  - A sample should be sent and stored for virological inv- estigations or other future investigation as indicated in the next section (A, II)
  - Culture for Mycobacterium tuberculosis when clinically indicated (A, II)

- If there is a strong clinical diagnosis of encephalitis in a child, but the initial CSF results are normal, a second LP should be undertaken and all CSF tests repeated, in- cluding consideration for antibody detection (A, II)

**Evidence**

Patients with HSV encephalitis typically have moderate elevation of CSF opening pressure, a moderate CSF pleocytosis from tens to hundreds of cells × 10^6/L, a mildly elevated CSF protein and normal CSF to plasma glucose ratio. Whilst measuring the CSF opening pressure is part of a standard LP, it is often more difficult to achieve this in children and is frequently omitted. Whilst the evidence base would recommend undertaking opening pressure, it is recognised that it is often impractical to do this in a child so the clinician responsible for undertaking the LP will have to make a balanced judgement as to the value of trying to achieve this. However, if the child is being anaesthetised for the procedure, the opening pressure should be measured with arterial blood gas results stabilised and CO2 noted. Occasionally polymorphonuclear cells predominate, or the CSF may be normal, especially early in the illness: in approximately 3–5% of adults with proven HSV encephalitis an initial CSF may be normal with no pleocytosis and a negative HSV PCR. The figure is even higher in patients with immunocompro- mise and in children, especially infants. However, if the first CSF is normal in HSV encephalitis, a second CSF examination 24–48 h is likely to be abnormal with a positive HSV PCR, although the viral load does reduce when patients are receiving aciclovir.

A series of studies have shown the apparent difficulty in measuring plasma glucose at the same time as CSF.
glucose, but without the former, interpretation of the CSF results is very difficult. HSV encephalitis can be haemorrhagic, and the CSF red cell count is elevated in approximately 50% of cases. An acellular CSF is also described for other viruses, VZV, EBV and CMV, and occurs more frequently in patients with immunocompromise.

Although a lymphocytic CSF pleocytosis is typical of viral CNS infections, non-viral infection, particularly tuberculosis and listeriosis, and partially treated acute bacterial meningitis can give a similar picture. Usually the clinical setting and other CSF parameters (low glucose ratio and higher protein) will suggest these possibilities. CSF lactate may be helpful in distinguishing bacterial meningitis from viral CNS infections; in particular a CSF lactate of <2 mmol/l is said to rule out bacterial disease. A high CSF lactate may also be an indicator of a metabolic disorder, in particular a mitochondrial encephalopathy. If ADEM is in the differential diagnosis, the CSF (with a paired serum sample) should be sent for oligoclonal bands.

In a traumatic tap white blood cells and protein from the blood can contaminate the cerebrospinal fluid. There is little good evidence to support how to correct for this in children. However, the standard approximation would be to subtract 1 white cell for every 700 red blood cells × 10⁶/L in the CSF and 0.1 g/dl for every 100 red blood cells. This approximation will suffice in most circumstances, though more complicated formulae allowing for anaemia etc are available. However, in patients with HSV encephalitis a blood-stained CSF sample may reflect the haemorrhagic pathophysiology of the condition, this is more likely if serial CSF specimens are blood-stained.

What virological investigations should be performed?

Recommendation

- All patients with suspected encephalitis should have a CSF PCR test for HSV (1 and 2), VZV and enteroviruses as this will identify 90% of known viral cases and EBV considered (B, II)
- Further testing should be directed towards specific pathogens as guided by the clinical features such as travel history and animal or insect contact (B, III)

Evidence

Although the list of viral causes of encephalitis is long, HSV types 1 & 2, VZV, and enteroviruses are the commonest causes of viral encephalitis in immunocompetent individuals in Europe & the United States. Our ability to diagnose encephalitis caused by herpes viruses & enteroviruses has been improved greatly by using polymerase chain reaction (PCR). CSF PCR for HSV during day 2–10 of illness has overall sensitivity and specificity of >95% for HSV encephalitis in immunocompetent adults. Although HSV PCR may be negative in the first few days of the illness a second CSF taken 2–7 days later will often be HSV positive, even if aciclovir treatment has been started.

Further microbiological investigations should be based on specific epidemiological factors (age, animal and insect contacts, immune status, recreational activities, geography and recent travel history, season of the year and vaccination history) and clinical findings (hepatitis, lymphadenopathy, rash, respiratory tract infection, retinitis, urinary symptoms and neurological syndrome (Table 11. Microbiological investigation of encephalitis)).

Table 11 Microbiological investigations in patients with encephalitis, modified from (Solomon, Hart et al., 2007).

<table>
<thead>
<tr>
<th>CSF PCR</th>
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<tbody>
<tr>
<td>1. All patients HSV-1, HSV-2, VZV Enterovirus, parechovirus</td>
</tr>
<tr>
<td>2. If indicated EBV/CMV (especially if immunocompromised) HHV6,7 (especially if immunocompromised, or children) Adenovirus, influenza A &amp; B, rotavirus (children) Measles, mumps Erythrovirus B19 Chlamydia</td>
</tr>
<tr>
<td>3. Special circumstances Rabies, West Nile virus, tick-borne encephalitis virus (if appropriate exposure)</td>
</tr>
</tbody>
</table>

Antibody testing (when indicated — see text)

1. Viruses: IgM and IgG in CSF and serum (acute and convalescent), for antibodies against HSV-1 & 2, VZV, CMV, HHV6, HHV7, enteroviruses, RSV, Erythrovirus B19, adenovirus, influenza A & B
2. If associated with atypical pneumonia, test serum for Mycoplasma serology chlamyphila serology

Ancillary investigations (when indicated - These establish carriage or systemic infection, but not necessarily the cause of the CNS disease)

- Throat swab, nasopharyngeal aspirate, rectal swab, faeces, urine PCR/culture of throat swab, rectal swab, faeces for enteroviruses PCR of throat swab for mycoplasma, chlamyphila PCR/antigen detection of nose/throat swab or nasopharyngeal aspirate for respiratory viruses, adenovirus, influenza virus (especially children) PCR/culture of parotid duct swab following parotid massage or buccal swab for mumps PCR/culture of urine for measles, mumps and rubella
- Vesicle electron microscopy, PCR and culture Patients with herpetic lesions (for HSV, VZV) Children with hand foot and mouth disease (for enteroviruses)

Brain Biopsy

For culture, electron microscopy, PCR and immunohistochemistry

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a Antibody detection in the serum identifies infection (past or recent depending on the type of antibodies) but does not necessarily mean this virus has caused the CNS disease.

b Viral culture and electron microscopy less sensitive than PCR.
What antibody testing should be done on serum & CSF?

Recommendation

- Guidance from a specialist in microbiology, virology or infectious disease specialists should be sought in deciding on these investigations (B, III)
- In patients with suspected encephalitis where PCR of the CSF was not performed acutely, a later CSF sample (at approximately 10–14 days after illness onset) should be sent for HSV specific IgG antibody testing (B, III)
- In suspected flavivirus encephalitis CSF should be tested for IgM antibody (B, II)
- Acute and convalescent blood samples should be taken as an adjunct to diagnostic investigation especially when EBV, arboviruses, Lyme disease, cat scratch disease, rickettsiosis or ehrlichiosis are suspected (B, II)

Evidence

Whilst all patients with suspected encephalitis should have PCR requested for the common viruses, decisions about antibody testing of serum and CSF are best made in conjunction with the specialist microbiology/virology or infectious diseases service.

Cerebrospinal fluid

Intrathecal synthesis of HSV-specific IgG antibodies is normally detected after 10–14 days of illness, peaks after one month and can persist for several years. The detection of intrathecally synthesized HSV IgG antibodies, when available, may help to establish the diagnosis of HSV encephalitis in patients where the CSF is taken after day 10–12 of the illness. This is especially useful in patients for whom an earlier CSF was not taken, or was not tested for HSV by PCR. A European consensus statement recommended the combined approach of testing CSF by PCR and antibody detection, such that a negative HSV-PCR result early in the disease process coupled with a negative HSV-specific IgG antibody study sampled 10–14 days after symptom onset effectively ruled out the disease; however, intrathecal immune responses may be delayed or absent when antiviral therapy is started early. Additionally, many laboratories do not provide CSF antibody detection services. The detection of oligoclonal bands in the CSF is a non-specific indicator of an inflammatory process in the CNS; immunoblotting of the bands against viral proteins from HSV can be used to detect anti-HSV antibody, although this is not routinely available. Antibody detection can also be particularly useful in VZV encephalitis.

The detection of virus specific IgM in CSF is usually indicative of an intrathecal antiviral immune response; this is especially useful for flaviviruses and other RNA viruses, which tend to be primary infections, rather than DNA viruses, which are often reactivations.

Blood

Acute and convalescent blood samples should be taken for appropriate serological testing based on the likely organisms identified from specific epidemiological and clinical features. Examples of infectious causes of encephalitis that can be diagnosed from serological investigations of blood include: EBV, arthropod-borne viruses (arboviruses), Borrelia burgdorferi (lyme disease), Bartonella hensae (cat scratch disease), rickettsioses, ehrlichiosis, and mycoplasma. Serological testing for antibodies in autoimmune encephalitis is covered in the ‘Special circumstances’ section of the guideline.

What PCR/culture should be done on other samples (e.g. throat swab, stool, vesicle etc)?

Recommendation

- Investigation should be undertaken through close collaboration between a specialist in microbiology, virology, infectious diseases and the clinical team (B, III)
- In all patients with suspected viral encephalitis throat and rectal swabs for enterovirus investigations should be considered; and swabs should also be sent from vesicles, if present (B, II)
- When there is a recent or concomitant respiratory tract infection, throat swab or sputum/lavage should be sent for PCR for respiratory viruses (B, II)
- When there is suspicion of mumps CSF PCR should be performed for this and parotid gland duct or buccal swabs should be sent for viral culture or PCR (B, II)

Evidence

Investigation of sites outside the CNS can be useful to provide pointers as to possible aetiology (Table 11 Microbiological investigations); however it must be remembered that such infection might be coincidental rather than causal; this is especially the case for non-sterile sites, or sites where long term shedding of virus occurs (e.g. in the stool). In enterovirus encephalitis, the virus may be isolated by swabbing the throat and rectum, or, if present, vesicles. Of these vesicular swabs are most useful because they indicate acute and systemic infection, whereas carriage in the faeces, and to some extent the throat may be long term. Although many patients with enterovirus CNS infections do not have vesicles, if the clinical illness suggests a recent respiratory infection, samples taken from the respiratory tract (throat swab, nasal swab, nasopharyngeal aspirate, nasal washings, tracheal aspirate or bronchoalveolar lavage) can be tested by PCR for respiratory viruses.

Mumps encephalitis is most accurately confirmed by PCR of the CSF; serum or salivary mumps antibodies are also helpful. Viral culture or PCR performed on parotid gland duct swabs, taken after massaging the parotid gland for 30 s, or buccal (saliva) swabs are useful for the diagnosis of recent mumps virus infection, within 9 days of the onset of symptoms. A urine sample is less sensitive but may be positive for at least 5 days after detection in the mouth. Urine analysis if also useful if measles is suspected.

Viral infection may be demonstrated by culture, detection of viral genomes (by PCR), viral antibodies (by serology), viral antigens (by direct immunofluorescence), or, if available, viral particles (by electron microscopy), although PCR is the most sensitive.
Which children with encephalitis should have an HIV test?

Recommendation

- We recommend that an HIV test be performed on all patients with encephalitis, or with suspected encephalitis irrespective of apparent risk factors (A, II)

Evidence

HIV is directly capable of causing an encephalopathy in young children but infection with the virus also predisposes children to CNS infections from other specific pathogens. Antenatal screening for HIV infection is offered to all pregnant women in the United Kingdom and has a high uptake (90%). However it is not compulsory, and Mother to Child transmission of HIV can still occur in the UK. Migrants and travellers to the UK, from areas defined by the WHO as areas with high endemicity of HIV infection, particularly from sub-Saharan Africa, and Asia, including major parts of the former Soviet Union, should be regarded as being at risk of Mother to Child Transmission of HIV. It must be remembered that while HIV infection is rapidly progressive in 20% of infants, late presentation of perinatally acquired HIV infection can occur at 13 years of age or older. HIV should be considered in children with suspected encephalitis for three reasons. Children with undiagnosed advanced HIV disease can present with CNS infections from a number of the less common infectious causes, such as cytomegalovirus. Secondly some of the more common CNS infections, such as Streptococcus pneumoniae or Mycoplasma tuberculosis have an increased incidence in patients with HIV. Thirdly, although uncommon in children, primary HIV-1 infection can present with an acute meningoencephalitis as part of a seroconversion illness. The current UK guidelines on HIV testing emphasise that “all patients presenting for healthcare where HIV, including primary HIV infection, enters the differential diagnosis” should be tested for HIV and offers detailed guidance on the testing of infants, children and young people.

What is the role of brain biopsy in children with suspected viral encephalitis?

Recommendation

- Brain biopsy has no place in the initial assessment of suspected acute viral encephalitis in immunocompetent children. Stereotactic brain biopsy should be considered in a child with suspected encephalitis in whom no diagnosis has been made after the first week, especially if there are focal abnormalities on imaging and if the findings could change the child’s management.
- If imaging shows nothing focal, an open biopsy, usually from the non-dominant frontal lobe, may be preferable.
- The biopsy should be performed by an experienced paediatric neurosurgeon and the histology should be examined by an experienced neuropathologist (B, III)

Evidence

For many years brain biopsy was the preferred method for diagnosing HSV encephalitis, because clinically many conditions mimic HSV encephalitis, the chances of culturing the virus from the CSF were low, and a biopsy was one of the few reliable means of making the diagnosis; although its sensitivity was low, specificity was high. Subsequently CSF PCR for HSV DNA was developed, and proved a rapid and reliable diagnostic test, largely replacing biopsy for the diagnosis HSV encephalitis. However biopsy still has a role in the investigation of other patients. Although until recently it was considered highly invasive with a significant mortality and morbidity (through intracranial haemorrhage, or biopsy site oedema), with modern stereotactic approaches the incidence of serious adverse events is low, and it is now considered a relatively safe investigation.

There is no role for a brain biopsy in the initial assessment of patients with suspected HSV encephalitis. However it may have a role in patients with suspected HSV encephalitis who are PCR negative and deteriorate despite aciclovir, or to identify alternative causes, such as vasa-...
patients. Early MRI changes occur in the cingulate gyrus and medial temporal lobe, and include gyral oedema on T-1 weighted images, and high signal intensity on T2-weighted and T2 fluid attenuated inversion recovery (FLAIR) images. Later there may be haemorrhage. Diffusion-weighted MRI may be especially sensitive to early changes. Specific sequences, such as FLAIR and STIR (short-tau inversion recovery) sequences may be of particular value in young children due to normal brain maturation processes. The MRI should be interpreted by an experienced neuroradiologist.

The changes seen on MRI are reported to be specific (87.5%) for PCR-confirmed HSV encephalitis but can also identify alternative (often treatable) diagnoses in patients that are negative for HSV. Thus it is important that an MRI is performed urgently. In small studies, the extent of MRI abnormality seen acutely in HSV encephalitis did not correlate with the clinical evolution of the disease nor with depression afterwards, though a correlation between number of seizures in acute HSV encephalitis, and subsequent brain atrophy on MRI has been demonstrated. In VZV CNS disease in immunocompetent children, the most common pathogenesis is a large vessel vasculitis, which presents with an ischaemic or haemorrhagic infarct often seen on MRI and angiography. In immunocompromised children, VZV may cause a multifocal leukoencephalopathy which may be seen to follow a clear arterial distribution. Other pathogens may have typical abnormal findings. M. pneumoniae may show focal cortical lesions, deep white matter lesions and large areas of demyelination. Japanese B encephalitis typically involves the thalamus and basal ganglia with T2 hyperintensity. Enterovirus may result in generalised parenchymal destruction, or may predominately affect the brainstem, occasionally spreading posteriorly to involve the cerebellar denate nuclei or superiorly to involve the thalami and basal ganglia. In young children, white matter oedema is not easily distinguished from unmyelinated white matter, and without contrast may result in incorrect reporting.

Although MRI is the investigation of choice, in young, acutely ill, comatose or confused children a general anaesthetic is usually required posing practical difficulties for many hospitals. In one series 70% of children required sedation or general anaesthesia. Some would recommend that sedation not be used in this patient group and only anaesthetic support and formal anaesthesia used. In these circumstances, CT scanning may be the only urgent imaging available. However, the CT scan may be normal in children with CNS infections including severe bacterial meningitis and encephalitis so should not be relied upon to make or refute the diagnosis of these conditions.

A pragmatic approach is to perform a CT scan as the first cranial imaging investigation and then an MRI can be undertaken as soon as it can be arranged, often after transfer to the local tertiary centre.

Other modalities
MR spectroscopy identifies and quantifies concentrations of various brain metabolites, and so may help distinguish normal from diseased brain tissue, and characterise the nature of the damage, particularly distinguishing inflammatory from neoplastic processes; however there are no prospective studies assessing its diagnostic role. Single photon emission computed tomography (SPECT) may show focal hypoperfusion persisting after recovery from acute viral encephalitis. However, it has been used mainly as a research tool and appears to have little application in suspected acute encephalitis in practice. Fluorodeoxyglucose positron emission tomography (PET) shows abnormalities in acute viral encephalitis with regions of FDG-PET hypermetabolism seen most frequently in the medial temporal lobes (sometimes reflecting seizure activity). However PET scanning is not practical or sufficiently informative to be used in children with suspected acute viral encephalitis.

Which children with suspected viral encephalitis should have an electroencephalogram (EEG)?

**Recommendation**

- An EEG should not be performed routinely in all patients with suspected encephalitis; however, in patients with mildly altered behaviour, if it is uncertain whether there is a psychiatric or organic cause an EEG should be performed to establish whether there are encephalopathic changes (B, II)
- EEG should also be performed if subtle motor, or subclinical seizures are suspected (B, II)
- An EEG should be performed in children with suspected chronic viral encephalitis for example SSPE (B, II)

**Evidence**
The EEG is abnormal in most patients with encephalopathy, including more than 80% of those with acute viral encephalitis. When patients have a more subtle presentation, it can be helpful in determining whether abnormal behaviour is due to psychiatric causes or is an early feature of encephalopathies. EEG is also useful in determining whether an individual has non-convulsive or subtle clinical seizures, which occur in both HSV encephalitis and other encephalopathies.

In HSV encephalitis EEG abnormalities include non-specific diffuse high amplitude slow waves, sometimes with temporal lobe spike-and-wave activity and periodic lateralised epileptiform discharges (PLEDs). Even though PLEDs occur in many cases of HSV encephalitis and were at one stage considered pathognomonic, they are now recognised in other viral encephalitides and non-infectious conditions, and it is accepted that there are no EEG changes diagnostic of HSV encephalitis. For example when PLEDs are identified in patients with a sub-acute or chronic encephalopathy this would be suggestive of SSPE.

**Treatment of viral encephalitis**

For which patients should aciclovir treatment be started empirically?

**Recommendation**

- Children with suspected encephalitis should have intravenous aciclovir started if the initial CSF and/or imaging findings suggest viral encephalitis, and definitely
within 6 hours of admission if these results are awaited (A, II).
- If the first CSF microscopy or imaging is normal but the clinical suspicion of HSV or VZV encephalitis remains, aciclovir should still be started within 6 hours of admission whilst further diagnostic investigations (as outlined below) are awaited (A, II)
- The dose of intravenous aciclovir should be:
  - 3 months-12 years 500mg/m² 8 hourly
  - >12 years 10mg/kg 8 hourly
- The dose of aciclovir should be reduced in patients with pre-existing renal impairment (A, II)
- Patients with suspected encephalitis due to infection should be notified to the appropriate Consultant in Communicable Disease Control (In Scotland, only patients with a proven aetiology or those occurring as part of an unusual outbreak are notifiable) (A, III)
- If meningitis is also suspected, the child should also be treated in accordance with the NICE meningitis guideline (A, II)

Evidence

Aciclovir is a nucleoside analogue with strong antiviral activity against HSV and related herpes viruses, including VZV. Two randomised trials have shown that aciclovir (10mg/kg three times a day) improves the outcome in adults with HSV encephalitis from a mortality of about 70% to less than 20–30%.5,6 Even with aciclovir treatment the outcome is often still poor, especially in patients with advanced age, a reduced coma score, or delays of more than 48 h between hospital admission and starting treatment.7,8 Because HSV encephalitis is the most commonly diagnosed viral encephalitis in industrialised countries, treatment with aciclovir is usually started once the initial CSF and/or imaging findings suggest viral encephalitis, without waiting for confirmation of HSV by PCR. However, unlike meningococcal septicaemia, where children can die within a few hours and thus immediate treatment with antibiotics is needed, in a patient with encephalopathy who has only mild confusion, investigation with a lumbar puncture before considering treatment is sensible; especially given the very wide differential diagnosis, and relative rarity of HSV encephalitis. Moreover, empirical use of antimicrobial and antiviral agents can prematurely halt the diagnostic pathway because clinicians feel falsely reassured, and this delays the identification of other aetiologies for which different treatments might be appropriate.

Experience from paediatrics has shown that the practice of presumptive antiviral treatment for all patients with encephalopathy, with no regard to the likely diagnosis, is not beneficial.14 However if there is a strong clinical suspicion of encephalitis, and there will be delays before a lumbar puncture can be performed, or if the child is very sick or deteriorating, then aciclovir should be started sooner, as should treatment for possible bacterial meningitis.15 Even if aciclovir has already been started in a patient with HSV encephalitis the CSF PCR is likely to remain positive for up to 7–10 days,11 meaning that a later lumbar puncture can still confirm the diagnosis.

Although aciclovir is relatively safe there are important side effects, particularly renal impairment secondary to crystalluria and obstructive nephropathy.161 This reversible nephropathy usually manifests after 4 days of intravenous therapy and can affect up to 20% of patients.162,163 The risk of nephropathy can be reduced by maintaining adequate hydration and monitoring renal function. In addition, the dose of aciclovir should be reduced in patients with pre-existing renal impairment, because it is excreted via the kidneys. Other rare adverse events include hepatitis, bone marrow failure and encephalopathy.

How long should aciclovir be continued in proven HSV encephalitis, and is there a role for oral treatment?

Recommendation

- In children with proven HSV encephalitis, intravenous aciclovir treatment should be continued for 14–21 days (A, II), and a repeat LP considered at this time to confirm the CSF is negative for HSV by PCR (B, II); particularly if there are concerns that the treatment is ineffective (severe disease, immune-compromise, previous relapses).
- If the CSF is still positive for HSV by PCR, aciclovir should continue, with weekly CSF PCR until it is negative (B, II)
- In children aged 3 months-12 years a minimum of 21 days of aciclovir should be given before repeating the LP (B, III)

Evidence

The original randomised trials of aciclovir for HSV encephalitis were for 10 days. However, reports of clinical relapse after 10 days of treatment were published subsequently.164,165 In children, relapse rates may be as high as 26–29%, particularly if the duration of treatment is <14 days.166 Although an on-going immune-mediated and inflammatory reaction to the infection is now thought by many to be the major pathogenic process,164–167 there is evidence for continuing viral replication in some cases.8,164,166,168 As a consequence most clinicians now use at least 14–21 days intravenous treatment in confirmed cases, though later relapses can occur.8 The risk of relapse may be highest in children aged 3 months-12 years, up to 29%, and some have advocated that this group should receive a minimum of 21 days of intravenous aciclovir.151

Some advocate repeating a CSF examination at 14–21 days, and continuing treatment until the CSF is negative for virus by PCR110, this is supported by a European Consensus Statement.39

Oral aciclovir does not achieve adequate levels in the CSF and is not suitable for treating HSV encephalitis; however its valine ester valaciclovir has good oral bioavailability, and is converted to aciclovir after absorption.169 Valaciclovir has been occasionally used in paediatric practice to treat HSV encephalitis after at least 10–14 days of intravenous aciclovir, when maintaining intravenous access proved difficult.170 Although CNS penetration is difficult to monitor some have reported CSF trough levels that are >50% of plasma trough levels.171 However valaciclovir is not licenced for use in children
and is only available in tablet form. The American National Institute of Allergy and Infectious Disease Collaborative Antiviral Study Group is assessing the role of high dose valaciclovir (2 g three times daily) for three months.\(^{172}\)

**When can presumptive treatment with aciclovir be safely stopped, in patients that are HSV PCR negative?**

**Recommendation**

- Aciclovir can be stopped in an immunocompetent child, if
  - An alternative diagnosis has been made, or
  - HSV PCR in the CSF is negative on two occasions 24-48 hours apart, and MRI imaging (performed \(>72\) hours after symptom onset), is not characteristic for HSV encephalitis, or
  - HSV PCR in the CSF is negative once \(>72\) hours after neurological symptom onset, with normal level of consciousness, normal MRI (performed \(>72\) hours after symptom onset), and a CSF white cell count of less than \(5 \times 10^6/L\) (B, III)

**Evidence**

For most patients with suspected HSV encephalitis, presumptive aciclovir treatment is started on the basis of a clinical picture and initial CSF findings consistent with viral encephalitis. This initial CSF may subsequently reveal an alternative diagnosis such as bacterial infection, in which case aciclovir can be stopped. However, an initial CSF PCR can occasionally be negative in HSV encephalitis, especially if it is taken early in the illness (<72 h after symptom onset), or after some days on aciclovir treatment when the virus has cleared. Thus if viral encephalitis is still strongly suspected, aciclovir treatment should not be stopped on the basis of a single negative CSF PCR only. A European consensus statement recommended the combined approach to diagnosis of testing CSF by PCR and antibody detection, such that a negative HSV-PCR result early in the disease process coupled with a negative HSV-specific CSF antibody study sampled 10–14 days after symptom onset effectively ruled out the disease.\(^{169}\) Given that CSF antibody studies can only rule out diagnosis late in the disease process and that there can be considerable delay in obtaining results from these assays, an alternative strategy has been proposed for halting aciclovir treatment.\(^{113}\) This proposes that if a negative HSV PCR result is obtained from CSF sampled \(>72\) h into the disease process and the patient has a low probability of HSV encephalitis (e.g. normal neuroimaging, CSF \(<5 \times 10^6/L\) WBCs/mm\(^3\), and normal level of consciousness) then aciclovir treatment might be safely halted. However in reality, a more common situation is the patient with a negative initial CSF PCR who continues to have altered consciousness, or has a CSF pleocytosis, or imaging abnormalities. In this situation many clinicians would repeat the CSF examination at 24–48 h to determine whether it is still negative for HSV by PCR; HSV encephalitis is very unlikely in such patients if there are two negative CSF PCRs for HSV.

**What is the role of corticosteroids in HSV encephalitis?**

**Recommendation**

- Whilst awaiting the results of a randomised placebo-controlled trial corticosteroids should not be used routinely in patients with HSV encephalitis (B, III)
- Corticosteroids may have a role in patients with HSV encephalitis under specialist supervision, but data establishing this are needed and the results of a prospective RCT are awaited (C, III)

**Evidence**

The role of steroids in the treatment of HSV encephalitis is not established.\(^{173}\) Even before antiviral drugs became available, many clinicians considered that corticosteroids were beneficial in HSV encephalitis, though others disagreed.\(^{174,175}\) Since the advent of aciclovir, corticosteroids have often be used, especially in patients with marked cerebral oedema, brain shift or raised intracranial pressure, but their role remains controversial because as well as reducing swelling, corticosteroids have strong immunomodulatory effects, which in theory could facilitate viral replication. However a retrospective analysis of 45 patients with HSV encephalitis showed that older age, lower Glasgow coma score at admission and lack of administration of corticosteroids were significant independent predictors of a poor outcome.\(^{176}\) An accompanying editorial made a strong case for a randomised placebo-controlled trial,\(^{177}\) which is now being carried out across several European countries.\(^{177}\)

**What should be the specific management of VZV encephalitis?**

**Recommendation**

- No specific treatment is needed for VZV cerebellitis (B, II).
- For VZV encephalitis, whether a primary infection or a reactivation, intravenous aciclovir \(500\)mg/m\(^2\) (if aged 3 months-12 years) or \(10-15\)mg/kg (if aged \(>12\) years) three times daily is recommended (B, II);
- If there is a vasculopathy (i.e. stroke), there is a case for using corticosteroids (B, II)

**Evidence**

In immunocompetent children, VZV can cause CNS disease through three mechanisms; a post-VZV cerebellitis, an acute VZV encephalitis and a VZV vasculopathy.

In cerebellitis caused by VZV, antiviral treatments are not normally used because the disease is usually self limiting, resolving in one to three weeks, and the primary pathogenic process is thought to be immune-mediated demyelination, rather than viral cytopathology.\(^{178}\) Although there are no good studies in primary VZV encephalitis, this condition is usually treated with antiviral drugs and, possibly corticosteroids.\(^{178}\) Aciclovir \(10\)mg/kg three times daily is often recommended,\(^{179}\) but because VZV is less sensitive to aciclovir than HSV, \(15\) mg/kg three times daily has also been suggested if renal function is normal,\(^{146}\) for up to \(14\) days,\(^{180}\) especially if it
can be started within a few days of symptom onset.\textsuperscript{179} A VZV vasculopathy presents with an acute stroke-like episode following VZV infection and is routinely treated with both aciclovir, as outlined, and corticosteroids, although there is limited evidence to support this.\textsuperscript{181}

The course of steroids (for example 60–80 mg of prednisolone daily for 3–5 days) is often given, because of the inflammatory nature of the lesion.\textsuperscript{146} In immunocompromised patients with VZV encephalitis a prolonged course of intravenous aciclovir may be needed.

**What should be the specific management of enterovirus meningoencephalitis?**

**Recommendation**

- No specific treatment is recommended for enterovirus encephalitis; in patients with severe disease pleconaril (if available) or intravenous immunoglobulin may be worth considering (C, III)

**Evidence**

Pleconaril is a drug that binds within a hydrophobic pocket at the base of the receptor-binding canyon in the viral capsid protein of enteroviruses, thus inhibiting the virus from binding to its cellular receptor. The drug has broad activity against most enteroviruses at low concentrations (<0.1 μg per mL), and has good oral bioavailability. In phase III clinical trials pleconaril reduced symptoms of aseptic meningitis, particularly headache, by approximately two days, compared with placebo controls, but it is not used widely for this condition.\textsuperscript{182} The drug has also been used in patients with chronic enterovirus infection due to agammaglobulinaemia, enterovirus myocarditis, poliovirus vaccine associated paralysis and neonatal infection. However there have been no trials assessing its role in enterovirus encephalitis, and it is often not available.

Intravenous immunoglobulin is used in patients with chronic enterovirus meningitis,\textsuperscript{183} and may also be useful in patients with severe enterovirus 71 infection, though no randomised trials have been conducted.\textsuperscript{184}

**What acute facilities should be available and which patients should be transferred to a specialist unit?**

**Recommendation**

- Patients with falling level of consciousness require urgent assessment by paediatric Intensive Care Unit staff for airway protection and ventilatory support, management of raised intracranial pressure, optimisation of cerebral perfusion pressure and correction of electrolyte imbalances. (A, III).
- Patients with suspected acute encephalitis should have access to a paediatric neurological specialist opinion and should be seen as soon as possible and definitely within 24 hours of referral (B, III)
- There should be access to neuroimaging (both MRI and CT), under general anaesthetic if needed, and neurophysiology (EEG), which may mean transfer to a specialist paediatric neuroscience unit (B, III)
- As CSF diagnostic assays are critical to confirming diagnosis, the results of CSF PCR assays should be available within 24-48 hours of a lumbar puncture being performed. (B, III)
- When a diagnosis is not rapidly established or a patient fails to improve with therapy, transfer to a paediatric neurological unit is recommended. The transfer should occur as soon as possible and definitely within 24 hours of being requested (B, III)

**Evidence**

Currently in the UK there is sparse evidence and little guidance for the inpatient care of patients with suspected viral encephalitis. A charity-commissioned nationwide survey of encephalitis patients’ experiences of hospital care revealed that only 39% were cared for on a neurological ward.\textsuperscript{185} Many patients with suspected acute encephalitis are critically ill. Their behaviour is often disturbed and they are at risk of seizures, malignant raised intracranial pressure, aspiration, systemic complications of infection, electrolyte disturbances, and death. Because it is a relatively rare condition, medical teams caring for patients with encephalitis often have limited experience of the condition. Patients require close monitoring in a quiet environment but do not routinely require isolation. Unlike stroke in adults, where clear evidence exists to support patient management in specialist units, no such studies have been undertaken for encephalitis.\textsuperscript{186} Appropriate environments for managing patients with encephalitis include neurological wards, high dependency units, or intensive care units.

The acute care of a child with suspected encephalitis is multidisciplinary, potentially requiring the input of not only paediatric neurologists, but infectious disease paediatricians, virologists, microbiologists, neuropathologists, neuroradiologists, paediatric neurosurgeons, neurologically and/or psychiatrically-trained nursing staff, and paediatric intensive care staff. Many of these personnel are only available through specialist paediatric neuroscience centres at tertiary hospitals. The role of members of the multidisciplinary team varies during the acute illness and rehabilitation.

**What rehabilitation and support services should be available for children affected by encephalitis and their families?**

**Recommendation**

- Parents and older children (where their cognitive ability permits) should be made aware of the support provided by voluntary sector partners such as the Encephalitis Society (www.encephalitis.info) (B, III)
- At the time of discharge, children should have either a definite or suspected diagnosis. Arrangements for outpatient follow-up and plans for on-going therapy and/or rehabilitation should be formulated at a discharge meeting (A, III)
- All children should have access to assessment for rehabilitation (A, III)
Evidence
The sequelae of encephalitis may not be immediately apparent when a patient is discharged from hospital following the acute illness. However, anxiety, depression and behavioural problems such as intrusive obsessive behaviour, challenging behaviour or hyperactivity/concentration difficulties often become evident subsequently, and may be more likely after encephalitis than other causes of acute brain injury. A charity-commissioned study of encephalitis patients found that 33% were discharged without out-patient follow-up although 96% reported on-going complications from their illness.

A broad and comprehensive approach to both assessment and rehabilitation is necessary, with neuropsychology and child and adolescent mental health teams as central components, and access to speech and language therapists, neuro-physiotherapists, and occupational therapists. Access to specialist brain injury rehabilitation services is key to recovery in many cases.

Children affected by encephalitis, their families and other people involved in supporting them, such as teaching staff, require information on the condition and its consequences and directions on how access this information. In one survey one third of patients were discharged from hospital without them or their families being informed of the diagnosis. Information and support reduces isolation, helps family adjustment and can provide useful signposting to other services as appropriate.

Special circumstances

What is the management of suspected encephalitis in children returning from travelling overseas?

Recommendation

- Patients returning from malaria endemic areas should have rapid blood malaria antigen tests and ideally three thick and thin blood films examined for malaria parasites (A, II). Thrombocytopenia, or malaria pigment in neutrophils and monocytes may be a clue to malaria, even if the films are negative.
- If cerebral malaria seems likely, and there will be a delay in obtaining the malaria film result, anti-malarial treatment should be considered and specialist advice obtained (A, III)
- The advice of the regional paediatric infectious diseases units, and national specialists testing laboratories is needed in deciding on appropriate investigations.

Evidence

Children travelling overseas are at risk of a range of infectious causes of encephalitis and encephalopathy, in addition to those found in the UK. More common causes of encephalopathy in returning travellers include malaria and tuberculous meningitis, and encephalopathy related to diarrhoea and dehydration. There are typically 5-15 deaths every year in the UK from malaria. Malaria is diagnosed by examination of thick and thin blood films for malaria parasites. Thrombocytopenia, or malaria pigment in neutrophils and monocytes may be a clue to malaria, even if the films are negative. Testing for malaria is important even in patients that have taken anti-malarial prophylaxis, or residents from endemic areas who are thought to be immune, because in both cases disease can occur. If cerebral malaria seems likely, and there will be delays in diagnostic tests, then treatment should be started.

Children with TB meningitis often have a history of recent tuberculosis contact and their family often originates from an area with a high incidence of TB. UK guidelines on the management of the TB have recently been produced.

In addition occasional cases have been reported of dengue encephalopathy, rabies, Japanese encephalitis, eastern equine encephalitis, West Nile virus encephalitis, and tick-borne encephalitis.

Table 2 gives an indication of the geographical risk factors associated with these viral CNS infections. Close liaison with the paediatric infectious diseases units, and national specialists testing laboratories is needed in deciding on appropriate investigations.

Other relatively rare non-viral causes of encephalopathy in returning travellers include eosinophilic meningitis, typhoid encephalopathy and trypanosomiasis (sleeping sickness).

Cysticercosis and schistosomiasis typically present with space occupying lesions (often causing seizures in the case of cysticercosis), rather than an encephalitis.

What differences are there in the management of suspected encephalitis in the immunocompromised?

Recommendations

- Encephalitis should be considered in immunocompromised patients with altered mental status, even if the history is prolonged, the clinical features are subtle, or there is no febrile element (A, III)
- In patients with known severe immunocompromise a CT scan before LP should be considered (B, III). If a patient’s immune status is not known, there is no need to await the result of an HIV test before performing a LP
- MRI should be performed as soon as possible in all patients (A, II)
- Diagnostic microbiological investigations for all immunocompromised patients with suspected CNS infections include (B, II):
  - CSF PCR for HSV 1 & 2, VZV and enteroviruses
  - CSF PCR for EBV, and CMV
  - CSF acid fast bacillus staining and culture for Mycobacterium tuberculosis
  - CSF and blood culture for Listeria monocytogenes
  - Indian ink staining and/or cryptococcal antigen (CRAG) testing of CSF and serum for Cryptococcus neoformans
  - Antibody testing of serum and if positive CSF PCR for Toxoplasma gondii
  - Antibody testing of serum and if positive CSF PCR for syphilis (B, II)

Other investigations to consider, depending on the circumstances, include (C, III):
- CSF PCR for HHV 6 and 7
- Erythrovirus B19
- Measles
- West Nile virus encephalitis
- CSF PCR for JC/BK virus
- CSF examination for Coccidioides species, and Histoplasma species
- Children with HIV suffering from severe infections or other complex problems should be treated in a regional hub or London Lead Centre (A, II)
- Immunocompromised patients with encephalitis caused by HSV-1 or 2, should be treated with intravenous aciclovir (10mg/kg three times daily) for at least 21 days, and reassessed with a CSF PCR assay; following this long term oral treatment should be considered until the CD count is >200x10^6/L, or if CD4%, 15% if <5 years old (A, II)
- Acute concomitant VZV infection causing encephalitis should be treated with intravenous aciclovir (A, II)
- CNS CMV infections should be treated with ganciclovir, oral valganciclovir, foscarnet or cidofovir (A, II)
- Children with VZV encephalitis should be treated with intravenous aciclovir 500mg/m² for at least 10 days, although immunocompromised children may require longer treatment (B, III)

Evidence
Immune compromise presents specific challenges in all aspects of the management of patients with suspected encephalitis, including the range of causative pathogens, and presenting clinical features, and differences in the investigations, and treatment. Although many of the principles of management of the immunocompromised are the same as those covered for the immunocompetent, above, there are some specific features, as outlined below.

Causes
In patients with immune compromise there is a wider range of pathogens that may cause an encephalitis presentation; these include bacterial diseases such as tuberculous meningitis or listeria, fungi, such as cryptococcus, parasitic diseases, for example toxoplasma, and viruses; the viruses implicated include cytomegalovirus, particularly in very advanced HIV with CD4 cell counts less than 50 x 10^6/L, measles and EBV. Progressive multi-focal encephalopathy (PML), due to JC and possibly BK viruses, is very rare in children and usually presents with features of dementia, rather than acute encephalitis. Non-infective considerations include primary CNS lymphomas, which are usually EBV-driven. In one study looking for herpes viruses in 180 non-selected CSF samples from 141 adult and paediatric patients, 23 patients were HIV positive among these CMV was the virus most frequently identified (13%), followed by EBV (10.6%), VZV (5.3%) and finally HSV-1 and HSV-2 (both 1.3%). HSV-2, EBV and VZV were detected in the 11 HIV-negative immunocompromised patients.

In addition to the pathogens outlined above, for which all immunocompromised patients with suspected encephalitis should be investigated, less common pathogens to consider, depending on the circumstances, include Coccidioides species, Histoplasma capsulatum and West Nile virus.

History
Immunocompromised patients are more likely to have subtle and sub-acute presentations of viruses which cause an acute encephalitis in the immunocompetent, such as HSV and enterovirus, as well as for viruses specific to the immunocompromised, such as HHV6 (Table 4 Sub-acute and chronic).

Role of imaging
Because of an impaired inflammatory and immune response, severely immunocompromised patients may have lesions on CT which are not associated with focal neurological presentations or papilloedema, prompting some to suggest that a CT scan should be performed in all immunocompromised patients before LP. There are no studies comparing imaging options in patients with suspected viral encephalitis with or without immunocompromise. However, immunocompromised patients are vulnerable to a broader range of encephalitides (including PML) and the clinical changes may be masked by immunocompromise. MRI is therefore the imaging modality of choice in immunocompromised patients.

CSF findings
In immunocompromised patients with encephalitis, the CSF is more likely to be acellular, even though such patients are at increased risk of CNS infection. Thus CSF investigations for microbial pathogens should be performed irrespective of the CSF cell count.

Treatment
The UK Standards for HIV clinical care recommend that children with HIV suffering from severe infections or other complex problems should be referred to the regional hub or the London Lead Centre. The initial treatment of HSV encephalitis in immunocompromised patients is the same as for the immunocompetent; however, achieving viral clearance can be harder, and prolonged treatment may be needed. Although there are no good trials for CMV encephalitis, open label studies suggest that ganciclovir (and valganciclovir), foscarnet or cidofovir may be helpful.

What differences are there in the presentation and management of encephalitis associated with antibodies?

Recommendations
- Antibody-mediated encephalitis should be considered in all patients with suspected encephalitis as they have a poorer outcome if untreated. Moreover the clinical phenotypes of these recently described disorders are still expanding (B, III)
- Clinical features, such as limbic encephalitis, a sub-acute presentation, speech and movement disorders and intractable seizures may suggest an antibody-mediated encephalitis, although these features are not exclusive to antibody-mediated disease (B, III)
- Although tumours occur less frequently in children, all patients with proven VGKC or NMDAR-receptor antibody associated encephalitis should have screening for a neoplasm (C, III), and extended surveillance for several years (C, III)
- Annual tumour screening should be conducted in patients with NMDA-receptor antibody associated
encephalitis if no tumour has been found, especially if
the patient has a poor response to therapy or there are
relapses (B, III)
- Early immune suppression and tumour removal should
be undertaken when possible (B, III)

Evidence
In children with an acute or more commonly sub-acute onset of
encephalitis, immune-mediated encephalitis should be con-
sidered as the treatment is very different and early inter-
vention significantly improves outcome. A growing number of
cases immune-mediated encephalitis have been reported in
children, comprising of autoantibodies targeting the voltage-
gated potassium channel (VGKC)-complex proteins, 202,203
N-methyl-D-Aspartic acid (NMDA) receptor, 204–206 and other
CNS antigens. 207 In a multicentre UK Health Protection Agency
(HPA) aetiology of encephalitis study4 20% of patients that
were identified to have an autoantibody aetiology were chil-
dren (Granerod and Crowcroft; unpublished observation). In
particular, all patients should have appropriate imaging to
identify an associated tumour, such as an ovarian tertoma.

Encephalitis associated with antibodies to the
voltage-gated potassium channel (VGKC)-complex
proteins

Presentation
VGKC-complex antibodies are beginning to be identified in
children. In a small case series of children presenting with
limbic encephalitis, 4/12 (30%) of patients were positive for
VGKC-complex antibodies. 207 In another series of children
presenting with encephalopathy and status epilepticus, 4/
10 (40%) of patients were found to be VGKC-complex anti-
bodies positive. 203 Finally, in a review of children with
VGKC autoimmunity, a proportion of these children had en-
cephalopathy or neuroregression probably representing a
sub-acute encephalopathy. 202 These case series are small
and appear to focus on specific subgroups thus making di-
rect comparison between them and the overall encephalitis
literature difficult. Nevertheless, cases reported of VGKC-
complex antibody-associated encephalitis in children shares
similar features with adult patients when presenting as
limbic encephalitis (disorientation and confusion with
seizures). However, the low plasma sodium found in about
60% of adult patients does not appear to be reported in
these childhood cases. 208

Investigative findings
The MRI may reveal either features of limbic encephali-
tis, 202,207 basal ganglia changes202 or other white matter
and sub-cortical changes. 203 The EEG reveals generalised
slowing with or without an ictal focus. 203 Significant CSF ab-
normalities are uncommon. Association with tumours like
neuroblastomas has been reported. 202

Treatment
In all of the reported series, the latency to treatment has
been long (months to years), and hence any interpretation
of treatment efficacy is unreliable. Treatment started
within 4 weeks of symptom onset confers the best re-
cov ery. 202 Although prompt immunosuppression is
advocated, there is no definitive evidenced based approach
to treating VGKC-complex autoimmunity. Immunosuppres-
sion as reported in the case series comprise of high dose in-
travenous corticosteroid use and regular IVIG therapy, used
independently or in conjunction. Mild to moderate response
to treatment have been reported particularly in patients
presenting with seizures and limbic encephalitis. 202

What are the differences in patients with
encephalitis associated with antibodies to
N-methyl-D-Aspartic acid (NMDA) receptor?

Presentation
Unlike VGKC-complex antibodies, antibodies targeting the
NMDA receptor are more commonly observed in children
and adolescents than adults. 205,206 In a comprehensive sin-
gle national reference centre study of patients presenting
anti-NMDA-receptor antibody associated encephalitis, 40%
(32/81) were age 18 or below. 204 In this study, an overall fe-
male preponderance and tumour preponderance in female
patients were identified. The risk of a tumour was lower in
younger girls (56% in women >18 years old, 31% in girls
<19 years old, and 9% in girls <15 years old). Of the 32 chil-
dren and adolescents, 87.5% had a history of behavioural or
personality change, sometimes associated with seizures
and frequent sleep dysfunction; 9.5% with dyskinesias or
dystonia; and 3% with speech impairment. On admission.
53% had clinical evidence of severe speech deficits. Eventu-
ally, 77% developed seizures, 84% stereotyped movements,
86% autonomic instability, and 23% hypoventilation; mirr-
oring the biphasic presentation noted in adults where the cor-
tical features (seizures, confusion, amnesia and psychosis)
appear to precede the sub-cortical features (cerebellar and
oro-facial dyskinesia, fluctuations in conscious level,
dysautonomia and central hypoventilation). 205

Investigation findings
The CSF is frequently abnormal in patients consisting of a
lymphocytosis (27/31), an elevated protein (4/13) and
presence of oligoclonal bands. 204 Brain MRI is abnormal in
up to 30% of patients and abnormalities often represent ei-
ther FLAIR or T2 signal intensity in one or more areas (me-
dial temporal lobe, periventricular, cerebellar). EEG is
often abnormal with focal or diffuse slowing, and demon-
strates epileptic activity in only 30% of patients. 204
protracted behavioural symptoms. Overall, 74% had full or substantial recovery at 1 year, after immunotherapy or tumour removal.204 Indeed, as described in adults, children who had a teratoma and were treated with tumour removal and immunotherapy had more frequent full recovery.204,209 In patients that relapse or appear unresponsive to treatment, escalation of immunosuppression to include treatments like rituximab have been used with some success.210 Tumour screening should be performed annually for several years particularly if the treatment response is poor or relapses occur.

Guideline implementation and audit

These clinical guidelines have been written to aid early recognition and appropriate investigation and management of patients with suspected encephalitis. There are many barriers to the implementation of such guidelines. The first step needed to convince clinicians to change behaviour is often the performance of a simple operational audit, to identify levels of good and poor practice. This can encourage use of standardised clinical approaches to management, the success of which can be re-audited.

- We have included a table of suggested clinical and operational issues that are relatively easy to audit in a standardised manner, and which can be adapted for local use (Table S1. Audit parameters for national encephalitis guideline, available to download from Science Direct).

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Supplementary material


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