Management of suspected viral encephalitis in adults — Association of British Neurologists and British Infection Association National Guidelines

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Accepted 13 November 2011
Available online 18 November 2011

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0163-4453/$36 © 2012 Published by Elsevier Ltd on behalf of The British Infection Association.
doi:10.1016/j.jinf.2011.11.014
Introduction

Although encephalitis is a relatively rare, its importance lies in that fact that for many forms treatment is effective if started promptly; in contrast, delays in treatment can be devastating. Encephalitis means inflammation of the brain parenchyma, and strictly speaking this is a pathological diagnosis. However, because of the obvious practical limitations of this, surrogate clinical markers of inflammation are used (Table 1. Definitions).

Classification of encephalitis

The causes of encephalitis can be defined as those due to direct infection of the central nervous system (CNS), para-, or post-infectious causes, and non-infectious causes. Infectious causes include numerous viruses, bacteria (especially intracellular bacteria such as *Mycoplasma pneumoniae*), parasites and fungi (Table 2. Causes of viral encephalitis; Table 3. Non-viral causes of encephalitis and encephalopathy). Acute disseminated encephalomyelitis (ADEM) after measles is an example of a post-infectious encephalitis. Non-infectious causes include antibody-associated encephalitis, which may or may not be paraneoplastic. Most viral encephalitis is acute, but sub-acute and chronic presentations are characteristic of particular pathogens, especially in the immunocompromised (Table 4. Sub-acute and chronic encephalitis).

Epidemiology

The global reported incidence of encephalitis varies according to the location, population studied, and differences in case definitions and research methods; however, the reported incidence in western settings ranges from 0.7 to 13.8 per 100,000 for all ages, being approximately 0.7–12.6 per 100,000 for adults and 10.5–13.8 per 100,000 children.

Herpes simplex virus (HSV) encephalitis is the most commonly diagnosed viral encephalitis in industrialised nations, with an annual incidence of 1 in 250,000 to 500,000. The age specific incidence is bimodal, with peaks in the young and the elderly. Most HSV encephalitis is due to HSV-1, but about 10% is caused by HSV-2. The latter typically occurs in immunocompromised individuals and neonates, in whom it can 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 causes, encephalitis associated with antibodies to the voltage-gated potassium channel complex, or N-methyl-D-aspartate antibody (NMDA) receptors are increasingly recognised.

Aims and scope of this guideline

In the 1980s the outcome of patients with HSV 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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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), supported by an evidence base, whose implementation 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, in an acute care setting such as acute medical unit or emergency department. They are thus intended as a ready reference for clinicians encountering the more common

<table>
<thead>
<tr>
<th>Groups</th>
<th>Viruses</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic causes (not geographically restricted) listed by group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes viruses (family Herpesviridae)</td>
<td>Herpes simplex virus type 1</td>
<td>Most commonly diagnosed sporadic encephalitis Causes meningitis in adults (esp. recurrent); Meningoencephalitis occurs typically in the immunocompromised. Also causes a radiculitis.</td>
</tr>
<tr>
<td></td>
<td>Herpes simplex virus type 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Varicella zoster virus</td>
<td>Post-infective cerebellitis, or acute infective encephalitis or vasculopathy</td>
</tr>
<tr>
<td></td>
<td>Epstein–Barr virus</td>
<td>Encephalitis in the immunocompromised</td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus</td>
<td>Encephalitis in the immunocompromised; also retinitis or radiculitis; often neutrophilic CSF with low glucose</td>
</tr>
<tr>
<td></td>
<td>Human herpes virus 6 &amp; 7</td>
<td>Febrile convulsions in children (after roseola); encephalitis in immunocompromised</td>
</tr>
<tr>
<td>Enteroviruses (family Picornaviridae)</td>
<td>Enterovirus 70</td>
<td>Epidemic haemorrhagic conjunctivitis, with CNS involvement</td>
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<tr>
<td></td>
<td>Enterovirus 71</td>
<td>Epidemic hand foot and mouth disease, with aseptic meningitis, brainstem encephalitis, myelitis</td>
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<tr>
<td></td>
<td>Poliovirus</td>
<td>Myelitis</td>
</tr>
<tr>
<td></td>
<td>Coxsackieviruses, Echoviruses, Parechovirus</td>
<td>Mostly aseptic meningitis</td>
</tr>
<tr>
<td>Paramyxoviruses (family Paramyxoviridae)</td>
<td>Measles virus</td>
<td>Causes acute post-infectious encephalitis, subacute encephalitis and subacute sclerosing panencephalitis</td>
</tr>
<tr>
<td></td>
<td>Mumps virus</td>
<td>Parotitis, orchitis or pancreatitis may occur before, during or after meningoencephalitis</td>
</tr>
<tr>
<td>Others (rarer causes)</td>
<td>Influenza viruses, adenovirus, Erythrovirus B19, lymphocytic choroemenigitis virus, rubella virus,</td>
<td></td>
</tr>
<tr>
<td>Arthropod-borne and zoonotic viruses</td>
<td>West Nile virus</td>
<td>North America, Southern Europe, Africa, Middle East, West and Central Asia associated with flaccid paralysis and Parkinsonian movement disorders</td>
</tr>
<tr>
<td></td>
<td>Japanese encephalitis virus</td>
<td>Asia, associated with flaccid paralysis and Parkinsonian movement disorders</td>
</tr>
<tr>
<td></td>
<td>Tick-borne encephalitis virus</td>
<td>Travel in Eastern Europe, Former USSR; tick bite; upper limb flaccid paralysis</td>
</tr>
<tr>
<td></td>
<td>Dengue viruses (types 1–4)</td>
<td>Causes fever, arthralgia, rash and haemorrhagic disease, occasional CNS disease</td>
</tr>
<tr>
<td>Alphaviruses (family Togaviridae)</td>
<td>Western, Eastern and Venezuelan encephalitis viruses</td>
<td>Found in the Americas; encephalitis of horses and humans</td>
</tr>
<tr>
<td></td>
<td>Chikungunya virus</td>
<td>Asia Pacific, Africa</td>
</tr>
<tr>
<td>Bunyaviruses</td>
<td>Lacrosse virus</td>
<td>Encephalitis in America</td>
</tr>
<tr>
<td>Coltiviruses</td>
<td>Colorado tick fever virus</td>
<td>North America</td>
</tr>
<tr>
<td>Rhabdoviruses</td>
<td>Rabies, virus other lyssaviruses</td>
<td>Non-arthropod-borne zoonitic viruses transmitted by dogs, cats, bats, depending on location</td>
</tr>
<tr>
<td>Henipah Viruses</td>
<td>Chandipura virus</td>
<td>Transmitted by sandflies, causing outbreaks in India</td>
</tr>
<tr>
<td></td>
<td>Nipah virus</td>
<td>Transmitted in faeces of fruit bats in Malaysia, Bangladesh</td>
</tr>
</tbody>
</table>

Most are zoonotic — ie animals rather than humans are the main natural hosts, the exceptions being dengue and chikungunya viruses.
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

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

<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><em>Mycoplasma pneumoniae</em></td>
<td><em>Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td><em>Chlamydia pneumoniae</em></td>
<td><em>Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td><em>Rickettsiae</em> (including scrub typhus, Rocky Mountain spotted fever)</td>
<td><em>Haemophilus influenzae</em></td>
</tr>
<tr>
<td>Ehrlichiosis (anaplasmosis)</td>
<td><em>Neisseria meningitidis</em></td>
</tr>
<tr>
<td><em>Coxiella burnetii</em> (Q fever)</td>
<td></td>
</tr>
<tr>
<td><em>Bartonella henselae</em> (cat scratch fever)</td>
<td></td>
</tr>
<tr>
<td><em>Tropheryma whippelii</em> (Whipple’s disease)</td>
<td></td>
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<tr>
<td><em>Brucella</em> (sp. brucellosis)</td>
<td></td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td></td>
</tr>
<tr>
<td><strong>Spirochetes</strong></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><strong>Other bacteria</strong></td>
<td></td>
</tr>
<tr>
<td>Nocardiosis</td>
<td>Infective endocarditis</td>
</tr>
<tr>
<td>Actinomycosis</td>
<td>Parameningeal infection</td>
</tr>
<tr>
<td>Abscess/empyema</td>
<td></td>
</tr>
<tr>
<td><strong>Parasites</strong></td>
<td></td>
</tr>
<tr>
<td><em>Trypanosoma brucei gambiense and rhodesiense</em> (African sleeping sickness)</td>
<td>Malaria</td>
</tr>
<tr>
<td><em>Naegleria fowleri,</em> <em>Balamuthia mandrillaris</em> (Amebic 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>
<td></td>
</tr>
<tr>
<td><em>Coccidioidomycosis</em></td>
<td>Cryptococcosis</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td></td>
</tr>
<tr>
<td>North American blastomycosis</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3 (continued)**

<table>
<thead>
<tr>
<th>Encephalitis</th>
<th>Mimics</th>
</tr>
</thead>
<tbody>
<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>
</tr>
<tr>
<td>Acute necrotising encephalitis (ANE) in children</td>
<td></td>
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<tr>
<td>Bickerstaff’s encephalitis</td>
<td></td>
</tr>
<tr>
<td><strong>Toxic/Metabolic</strong></td>
<td></td>
</tr>
<tr>
<td>Reye’s syndrome</td>
<td></td>
</tr>
<tr>
<td><strong>Systemic infection</strong></td>
<td></td>
</tr>
<tr>
<td>Septic encephalopathy</td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td>Vasculitis</td>
<td>Primary brain tumour</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Metastases</td>
</tr>
<tr>
<td>Behçet’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></td>
</tr>
<tr>
<td>Primary brain tumour</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolic encephalopathy</strong></td>
<td></td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td></td>
</tr>
<tr>
<td>Renal encephalopathy</td>
<td>Epilepsy</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td></td>
</tr>
<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></td>
</tr>
<tr>
<td>Haemophagocytic Lymphohistiocytosis (HLH) syndrome (usually children)</td>
<td></td>
</tr>
<tr>
<td>Drug reactions</td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Functional disorder</td>
</tr>
</tbody>
</table>

Almost every infectious and non-infectious condition can occasionally present with an encephalitis-like illness. 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.
JC and BK viruses are named after the initials of the patients.

In immunocompromised patients
Measles virus (inclusion body encephalitis)
Varicella zoster virus (causes a multifocal leukoencephalopathy)
Cytomegalovirus
Herpes simplex virus (especially HSV-2)
Human herpes virus 6
Enteroviruses
JC/BKa virus (progressive multifocal leukoencephalopathy)
HIV (dementia)

In immunocompetent patients
JC/BKa virus (progressive multifocal leukoencephalopathy)
Measles virus (subacute sclerosing panencephalitis)

Mycobacterium tuberculosis
Treponema pallidum (syphilis)
Borrelia burgdorferi (Lyme neuroborreliosis)
Tropheryma whipplei (Whipple’s Disease)
Cryptococcus neoformans

Trypanosoma spp. brucei (African trypanosomiasis)
Toxoplasma gondii (toxoplasmosis)
Creutzfeldt-Jakob disease

*a* JC and BK viruses are named after the initials of the patients from whom they were first isolated.

HSV, VZV and enteroviruses. Encephalitis due to CMV is almost exclusively seen in the immunocompromised and is not covered in detail; its diagnosis and management is covered in HIV guidelines. At the end of the guidelines the special circumstances of returned travellers, immunocompromised patients and antibody-associated encephalitis 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 encephalitis patients 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 to 2008, to identify 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’; ‘Aciclovir’; ‘Steroids/Dexamethasone’) separately and in combination with the following MESH terms: (‘Herpes Simplex Virus’; ‘Varicella Zoster Virus’; ‘Enterovirus’; ‘Human Immunodeficiency Virus (HIV)’; ‘Immunocompromise’; ‘Arbovirus’). This yielded a total of 6948 citations, including many case series, which were grouped together in subject areas such as clinical presentation, diagnosis, imaging, treatment, outcome and immunocompromise. 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 Association of British Neurologists, 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.

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).

This document has been again internally peer-reviewed twice by the Guidelines Development Group and then by the wider Guidelines Stakeholders Group, which included representatives from the Royal College of Physicians and the British HIV Association. The document was then updated to include further comments from all contributing authors, incorporating references published in 2009–11. The guidelines are structured to answer common clinical questions posed during the work-up of a patient with possible encephalitis.

This guideline is for the management of patients over 16 years. National guidelines for the management of suspected viral encephalitis in children are also available as a separate document (Kneen, Michael, et al., 2012).

**Diagnosing encephalitis**

Which clinical features should lead to suspicion of encephalitis? How do they differ from other encephalopathies? And can they be used to diagnose the underlying cause?

**Recommendations**

- The constellation of a current or recent febrile illness with altered behaviour, cognition, personality or
Management of suspected viral encephalitis

Clinical features suspicious of encephalitis
- Assess ABCD and check glucose (+/- involve ICU)
- Clinical contraindication to immediate LP? *
- Urgent CT
- If delay (>6 hours) expected: Start IV aciclovir whilst results pending
- If no clue from CT scan, perform LP
- Review every 24 hours: ?LP
- Lumbar Puncture
  - Opening pressure: CSF and serum glucose; CSF protein; 2x MCV, virology PCR; lactate; consider paired oligoclonal bands
- CSF findings suggest encephalitis?****
  - Neuro-imaging if not yet performed (ideally MRI <24-48 hours)
  - HSV/VZV Encephalitis confirmed
  - Alternative diagnosis
    - Immunosuppressed? Or age 3 months-12 years?
      - Involve Neurology and Infectious Disease Teams
      - 14 days IV aciclovir
      - Repeat LP
      - PCR positive?
        - Stop aciclovir
        - 7 days IV aciclovir
    - 21 days IV aciclovir

Additional Investigations
- Consider swab
  - Throat
  - Rectal
  - Vaginal (if present)
- Sputum (if symptoms)
- Urine (if pyrexia)
  - If travel consider:
    - 3x thick/thin smears
    - Rapid malaria antigen test
    - CSF (flavivirus, GBV)
  - HIV (all patterns)
    - If positive:
      - CSF PCR for EBV + CMV
      - CSF TB staining + culture
      - CSF + blood culture for Listeria monocytogenes
      - CSF India ink staining for cryptococcal antigen
      - CSF PCR for toxoplasmosis, syphilis
      - CSF HSV PCR not sent (in first LP)
        - Repeat CSF PCR on 2nd LP
        - Consider HSV HSV IgG at 30-14 days
  - ECG indications
    - If subtle motor status epilepticus suspected
    - If unclue if psychiatric cause or encephalopathy
- Involve:
  - Microbiology
  - Virology
  - Infectious Diseases
  - Neurology

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

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.org)

Figure 1  Algorithm for the management of patients with suspected encephalitis.
consciousness, or new seizures, or new focal neurological signs, should raise the possibility of encephalitis, or another CNS infection; and should trigger appropriate investigations (A, II).

- Metabolic; toxic, autoimmune and non-CNS sources of sepsis as causes for encephalopathy should be considered early in patients presenting with encephalopathy (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, asterixis, lack of fever, acidosis, or unexplained negative base excess (B, III).
- Clinical features, such as a sub-acute presentation (weeks-months), orofacial dyskinesia, choreoathetosis, faciobrachial dystonia, intractable seizures or hyponatraemia, may suggest an antibody-mediated encephalitis, although these features are not all exclusive to antibody-mediated disease (B, II).
- The investigation priority shown in Table 9 is determined by the patient’s clinical presentation (C, III).

Evidence

Clinical features

The differential diagnosis of acute encephalitis 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).2,20

Fever and abnormal mental status, often with severe headache, nausea and vomiting, are the classical clinical features of infectious encephalitis. Eighty-five (91%) of 93 adults with HSV-1 encephalitis in one study were febrile on admission9; even those not febrile on admission will typically 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.9 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.2 Alterations in higher mental function include lethargy, drowsiness, confusion, disorientation and coma (Table 7. Examination).

With the advent of molecular diagnostic methods applied to CSF more subtle presentations of HSV encephalitis have been recognised.21 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. In one study, chronic alcohol abuse was one of several features associated with delays in initiating treatment.22 Seizures can sometimes be the initial presenting feature of a patient with encephalitis. Seizures are more common in patients presenting with encephalitic processes affecting the cortex. These are more often infectious in aetiology, as opposed to encephalitic processes predominantly affecting the sub-cortical white matter, such as ADEM. However, intractable seizures, often in the absence of fever, are also common in antibody-associated encephalitides.21

Distinction of HSV encephalitis from other encephalopathies

Several studies have documented the potential mimics of HSV encephalitis.13,24,25 Whitley et al. demonstrated that...
of 432 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. 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. Bell et al. and Michael et al. showed the broad range of final diagnoses in patients initially treated with aciclovir or undergoing an LP for possible encephalitis in secondary care hospitals in the UK.2,13

In clinical practice the most frequently encountered infection-associated encephalopathy is septic encephalopathy, which is found in 50–70% of septic patients. Clinically, the diagnosis is one of exclusion. It is the cause of encephalopathy in patients with an extracranial locus of sepsis, which cannot be attributed to other organ dysfunction. Neurologically, it is characterised by progression from a slowing of mentation and impaired attention, to delirium, then coma. Neurological examination findings are usually symmetrical and the finding of asterixis or multifocal myoclonus (typical of metabolic encephalopathies) is rare. Non-convulsive status epilepticus can mimic or result from acute encephalitis; it is found in up to 8% of comatose patients with no clinical evidence of seizure activity. The specific morbidity consequent on non-convulsive status epilepticus is difficult to dissect from that related to its underlying precipitant. Nevertheless, non-convulsive status epilepticus has specific treatments and access to electroencephalography (EEG) is essential to confirm the diagnosis.

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 the features for HSV are non-specific, most patients with suspected HSV encephalitis prove to have a different diagnosis.2,13,24 Although olfactory hallucinations are described in HSV encephalitis, they are not a reliable predictor. The finding of labial herpes has no diagnostic specificity for HSV encephalitis and is merely a marker of critical illness. Encephalitis caused by VZV at the time of primary infection (chickenpox) may follow the rash at an interval of days or weeks, though it occasionally occurs before the rash, or even in patients with no rash.29,30 Adults over 20 years old, the immunocompromised, or those with cranial dermatome involvement, disseminated skin disease, or immune compromise are at increased risk of encephalitis following chickenpox. The presentation may be acute or subacute with fever, headache, altered consciousness, ataxia and seizures. An acute cerebellar ataxia is also seen in association with chickenpox; typically this is seen in children, but adults are occasionally affected.

Reactivation of VZV may also lead to encephalitis, especially in the elderly or the immunocompromised. The onset is typically insidious, and there may be no zoster rash, fever, or CSF pleocytosis; sometimes there is a brainstem encephalitis associated with Ramsay Hunt syndrome.32 The primary cause is thought to be immune-mediated reaction to virus replicating at low levels, rather than viral cytopathology itself. A small-vessel vasculitic, or large-vessel stroke syndrome may also be seen.33

Rashes are seen in other encephalitides; for example a maculopapular or vesicular rash may be present in some rickettsial infections. Lesions on the hands, feet and mouth are seen in enteroviral infections, such as that caused by Enterovirus 71.

Sometimes the pattern of neurological deficit can provide clues to the possible aetiology. Autonomic dysfunction, myoclonus and cranial neuropathies can indicate a brainstem encephalitis, which is seen in listeriosis, brucellosis, tuberculosis (TB), and some viral CNS infections (Table 8. Brainstem encephalitis). Tremors or other movement disorders occur with thalamic or other basal ganglia involvement. This is seen in some flavivirus infections, such as West Nile virus and Japanese encephalitis, and alphavirus infection such as Eastern equine encephalitis virus and chikungunya.34,35 For other movement disorders found in antibody-associated encephalitis, please see the ‘special circumstances’ subsection. An encephalitis with an acute flaccid paralysis is characteristic of polio, and other enteroviruses, such as Enterovirus 71, as well as flaviviruses.

Recognising encephalitis in the elderly can be especially difficult because they are more likely than younger people to have other causes of neurological disorder, such as stroke. Additionally, they are at increased risk of systemic causes for altered cerebral function, such as systemic sepsis. However, as HSV encephalitis is more common in the elderly than younger adults, it is especially important that the diagnosis is considered promptly in such patients.

<table>
<thead>
<tr>
<th>Table 8</th>
<th>Brainstem encephalitis (rhombencephalitis) – clues and causes, modified from (Solomon, Hart et al. 2007).36</th>
</tr>
</thead>
</table>
| **Suggestive clinical features** | • Lower cranial nerve involvement  
• Myoclonus  
• Respiratory drive disturbance  
• Autonomic dysfunction  
• Locked-in syndrome  
• MRI changes in the brainstem, with gadolinium enhancement of basal meninges |
| **Causes** | • Enteroviruses (especially EV-71)  
• Flaviviruses, e.g. West Nile virus, Japanese encephalitis virus  
• Alphaviruses, e.g. Eastern equine encephalitis virus  
• Rabies  
• Listeriosis  
• Brucellosis  
• Lyme borreliosis  
• Tuberculosis  
• Toxoplasmosis  
• Lymphoma  
• Paraneoplastic syndromes |
Which patients with suspected encephalitis should have a lumbar puncture? And in whom should this be preceded by a computed tomography scan?

Recommendations

- All patients with suspected encephalitis should have an LP as soon as possible after hospital admission, unless there is a clinical contraindication (Table 10. Contraindications to an immediate 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 patient’s clinical condition changes (B, III)
  - If a CT is not needed before an LP, imaging (CT or MRI) should be performed as soon as possible afterwards (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 LP (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)
  - In situations where an LP is not possible at first, the situation should be reviewed every 24 h, and an LP performed when it is safe to do so (B, II)
  - Lumbar punctures should be performed with needles that meet the standards set out by the National Patient Safety Agency (A, III)

<table>
<thead>
<tr>
<th>Table 9</th>
<th>Additional investigations to consider to in the differential diagnosis of encephalitis.</th>
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</thead>
<tbody>
<tr>
<td>Differential diagnosis</td>
<td>Investigations to consider</td>
</tr>
<tr>
<td>Para-infectious immune mediated encephalitis</td>
<td>MRI brain and spine, AntiDNAse B and ASO titre, influenza A and B PCR and/or antibody in CSF and serum, CSF examination, Brain and meningeal biopsy</td>
</tr>
<tr>
<td>Autoimmune/Inflammatory encephalitis</td>
<td>FBC, ESR, CRP, ANA, ENA, dsDNA, ANCA, C3, C4, lupus anticoagulant, cardiolipin, thyroglobulin, thyroperoxidase antibodies, ferritin, fibrinogen, triglycerides, Voltage-gated potassium channel complex and NMDA receptor antibodies, Serum and CSF ACE, Serum 25OH Vitamin D, 24hr urinary calcium, Whole body CT</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Biopsy: Brain, meninges, skin, lymph node, peripheral nerve/muscle, Renal, liver, bone &amp; thyroid profiles</td>
</tr>
<tr>
<td>Vascular</td>
<td>CT or MRI head with venogram and/or angiogram</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>MRI brain and MR spectroscopy, CSF cytological analysis, Brain and meningeal biopsy, CT chest/abdomen/pelvis, LDH, IgG/A/M, protein electrophoresis, urinary Bence-Jones protein (in adults), bone marrow trephine</td>
</tr>
<tr>
<td>Paraneoplastic</td>
<td>Anti-neuronal and onconeural antibodies, CT or PET chest, abdomen and pelvis, Biopsy of non CNS viscera</td>
</tr>
<tr>
<td>Toxic</td>
<td>Blood film; blood or urine levels of alcohol, paracetamol, salicylate, tricyclic, heavy metals, Urinary illicit drug screen</td>
</tr>
<tr>
<td>Septic Encephalopathy</td>
<td>Serum microbiological cultures, serology and PCR</td>
</tr>
</tbody>
</table>

Abbreviations: MRI magnetic resonance imaging; ASO antistreptolysin; PCR polymerase chain reaction; CSF cerebrospinal fluid; FBC full blood count; ESR erythrocyte sedimentation rate; CRP C-reactive protein; ANA antinuclear antibodies; ENA extraneuclear antibodies; dsDNA double stranded deoxyribonucleic acid antibodies; C3/4 complement; ACE angiotensin converting enzyme; CT computed tomography; LDH lactate dehydrogenase; IgG/M/A immunoglobulin; PET positron emission tomography; CNS central nervous system.
There is no agreement on the depth of coma that necessitated swelling, or space occupying lesion. In 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.

Note:
- Patients on anticoagulant therapy 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.
- Systemic shock
- Coagulation abnormalities:
  - Coagulation results (if obtained) outside the normal range
  - Platelet count <100 × 10^9/L
  - Anticoagulant therapy
- Local infection at the lumbar puncture site
- Respiratory insufficiency
- Suspected meningococcal septicaemia (extensive or spreading purpura)

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

**Other contraindications**
- Systemic shock
- Coagulation abnormalities:
  - Coagulation results (if obtained) outside the normal range
  - Platelet count <100 × 10^9/L
  - Anticoagulant therapy
- Local infection at the lumbar puncture site
- Respiratory insufficiency
- Suspected meningococcal septicaemia (extensive or spreading purpura)

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

**Evidence**

*Lumbar puncture and computed tomography discussion*

A lumbar puncture (LP) is an essential investigation in the management of patients with suspected encephalitis both to confirm the diagnosis and to rule out other causes. There has been considerable controversy over the role of computed tomography (CT) and LP in patients with suspected CNS infection, in particular whether a CT is needed before an LP.37–39 Few studies specifically address this issue in patients with suspected encephalitis, but much of the literature about suspected bacterial meningitis is pertinent because of overlap in the clinical presentations.

In patients with suspected encephalitis, an early CT scan has two clear 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 25–80% of patients with herpes simplex virus (HSV) encephalitis, though it is not, on its own, diagnostic.9,40 Almost all those with proven HSV encephalitis and a negative initial scan will have abnormalities on a second scan.9,40

An important role of CT, in some patients, is to exclude shift of brain compartments, due to mass lesions and/or oedema, which might make a subsequent LP dangerous. In patients with brain shift, a reduction of the CSF pressure below the lesion following an LP could precipitate herniation of the brainstem or cerebellar tonsils.37,41 This may occur in patients with brain abscess, subdural empyema, tumour, or a necrotic swollen lobe in encephalitis. Thus in selected patients, with appropriate clinical features, a scan is performed to see if there is significant brain swelling and shift, or whether there is space around the basal cisterns. However, unselected CT scanning of all patients before an LP can cause unnecessary delays for the majority of patients, in whom there are no contraindications to an immediate LP.2,13 For example, in one recent study of 21 patients with suspected encephalitis, 17 had an LP, which was preceded by 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.13 Furthermore, in a larger study of 217 patients with suspected CNS infections the median (range) time to LP was significantly longer if the patient had a CT scan first (18.5 [2–384] versus 6 [1–72] hours respectively, p < 0.0001).2 The increasing availability of CT scans in emergency units since this work was published (developments to implement national guidelines for acute stroke thrombolysis and acute head injury) will undoubtedly result in easier access to imaging for patients with suspected encephalitis.

Clinical assessment rather than CT scanning should be used to determine the safety of performing an LP. A series of studies has examined which clinical signs can be used to determine which patients with suspected bacterial meningitis need a CT scan before LP.38,41,42 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 seizures, focal neurological signs (excluding cranial neuropathies), signs suggestive of a space occupying lesion or moderate to severe impairment of consciousness, as indicated by a Glasgow coma score of 10 or less.42 Papilloedema, a direct indicator of raised intracranial pressure, is also an indication for imaging before an LP. Given the potential for overlap of clinical features in patients with suspected meningitis and suspected encephalitis, this approach can also be applied to patients with suspected encephalitis. Although there is good agreement about most of the indications for a CT scan before an LP, there is disagreement about the precise level of consciousness that should be taken as a contraindication to an immediate LP. Among seven commentaries, reviewed by Joffe,39 three suggested “deterioration in consciousness level”, two suggested a GCS < 8, and one a GCS < 13.37,43–48 There is also lack of clarity about whether an LP should then be performed at all in such patients, if the scan is normal, or whether a low coma score is an absolute contraindication, whatever the scan shows. Deterioration after LP has been occasionally reported in patients with bacterial meningitis and an apparently normal CT; but we are not aware of similar cases in patients with viral encephalitis. In one retrospective series of 222 adults with suspected encephalitis less than 5% of patients had imaging changes suggestive of raised intracranial pressure.25 Most clinicians would argue that the information from the LP is essential to make a diagnosis and guide treatment.
Recommendations

What information should be gathered from the LP?

**Recommendations**

- CSF investigations should include:
  - Opening pressure (A, II)
  - Total and differential white cell count, red cell count, microscopy, culture and sensitivities for bacteria (2 × 2.5 ml) (A, II)
  - If necessary, the white cell count and protein should be corrected for a bloody tap
  - Protein and glucose (1–2 ml), which should be compared with a plasma glucose taken just before the LP (A, II)
  - A sample should be sent and stored for virological investigations or other future investigation as indicated in the next section (2 ml) (A, II)
  - *Mycobacterium tuberculosis* (6 ml) when clinically indicated (A, II)
  - If an initial LP is non-diagnostic, a second LP should be performed 24–48 h later (B, II)

Evidence

In adults with HSV encephalitis the CSF opening pressure is typically moderately elevated; there is a moderate CSF pleocytosis (tens to hundreds of cells × 10^6/L), a mildly elevated CSF protein, and normal CSF:plasma glucose ratio. Occasionally, polymorphonuclear cells predominate or the CSF may even be normal, especially early in the illness. In approximately 5–10% of adults with proven HSV encephalitis initial CSF findings may be normal with no pleocytosis and a negative HSV polymerase chain reaction (PCR). The figure is even higher in the immunocompromised and in children, especially infants. However, if the first CSF is normal in patients with HSV encephalitis, a second CSF examination 24–48 h is likely to be abnormal with a positive HSV PCR.

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 in encephalitis caused by other viruses, including VZV, EBV, and CMV; it occurs more frequently in the immunocompromised.

Although a lymphocytic CSF pleocytosis is typical of viral CNS infections, bacterial infection can give a similar picture particularly in tuberculosis, listeriosis, brucellosis and partially treated acute bacterial meningitis. 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.

Following a traumatic tap white blood cells and protein from the blood can contaminate the CSF. The white cell count and protein can be approximately corrected for the number of red cells in the CSF by subtracting 1 white cell for every 7000 × 10^6/L red blood cells in the CSF, and 0.1 g/dl protein for every 100 red blood cells. This approximation will suffice in most circumstances, though more complicated formulae allowing for anaemia etc are available.

What virological investigations should be performed?

**Recommendations**

- 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 cases due to known viral pathogens (B, II)
- Further testing should be directed towards specific pathogens as guided by the clinical features, such as occupation, travel history and animal or insect contact (B, III)

Evidence

Although the list of viral causes of encephalitis is long, HSV 1 & 2, VZV and enteroviruses are the most commonly identified 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 developments in PCR methods. CSF PCR for HSV between day 2 and 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 3–7 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, insect, and sexual contacts; immune status; occupation; recreational activities; geography and a 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.

What antibody testing should be done on serum and CSF?

Recommendations

- Guidance from a specialist in microbiology, virology or infectious diseases should be sought in deciding on these investigations (B, III)
- For patients with suspected encephalitis where PCR of the CSF was not performed acutely, a later CSF and serum sample (taken 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, brucellosis, rickettsioses, ehrlichiosis or mycoplasma are suspected (B, II)

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

| CSF PCR | 1. All patients | HSV-1, HSV-2, VZV |
| 2. If indicated | Enterovirus, parechovirus |
| | EBV/CYM (especially if immunocompromised) |
| | HHV 6,7 (especially if immunocompromised, or children) |
| | Adenovirus, Influenza A & B, rotavirus (children) |
| | Measles, mumps |
| | Erythrovirus B19 |
| | Chlamydia |
| 3. Special circumstances | Rabies, West Nile virus, tick-borne encephalitis virus (if appropriate exposure) |
| Antibody testing (when indicated — see text) | IgM and IgG in CSF and serum (acute and convalescent), for antibodies against |
| 1. Viruses | 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 |
| | Chlamyphilia serology |
| Ancillary investigations (when indicated — These establish carriage or systemic infection, but not necessarily the cause of the CNS disease) | PCR/culture of throat swab, rectal swab, faeces for enteroviruses |
| | PCR of throat swab for mycoplasma, chlamyphilia |
| | 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 |
| | Patients with herpetic lesions (for HSV, VZV) |
| | Children with hand foot and mouth disease (for enteroviruses) |

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.
Evidence
Antibody testing discussion
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.63 The detection of intrathecal synthesis of HSV IgG antibodies may help to establish the diagnosis of HSV encephalitis in patients when the CSF sampled 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 CSF antibody study sampled 10–14 days after symptom onset effectively ruled out the disease.28 However, intrathecal immune responses may be delayed or absent when antiviral therapy is started early.64 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.25,28 In one series two of 10 patients with HSV encephalitis were diagnosed by detection of intrathecal HSV-specific antibodies.25 Antibody detection can also be particularly useful in VZV encephalitis.65

The detection of virus specific IgM in CSF indicates an intrathecal antiviral immune response. This is especially useful for flaviviruses and other RNA viruses that are usually primary infections, rather than DNA viruses, which typically cause encephalitis following reactivation of latent virus.25

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.12 Examples of infectious causes of encephalitis that can be diagnosed from serological investigations of blood include: Epstein–Barr virus (EBV), arthropod-borne viruses (arboviruses), Borrelia burgdorferi (Lyme disease), brucellosis, rickettsioses and ehrlichioses, and mycoplasma.66

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

Recommendations
- Investigation should be undertaken through close collaboration between a laboratory specialist in microbiology or virology and the clinical team (B, III)
- In all patients with suspected viral encephalitis throat and rectal swabs for enterovirus investigations should be considered (B, II); and swabs should also be sent from vesicles, if present (B, II)
- When there is a recent or concomitant respiratory tract infection, sputum (bacteria) or bronchial lavage or nose and throat swab/nasopharyngeal wash or aspirate (viruses) should be sent (B, III)
- 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, III)

Evidence
Investigation of other samples discussion
Investigation of sites outside the CNS can provide clues to possible aetiology (Table 11. Microbiological investigations). However, such infection might be co-incidental rather than causal. This is especially true for non-sterile sites, or sites from which long-term shedding of virus occurs (e.g. in faeces). In enterovirus encephalitis, the virus may be isolated from faeces or from swabs of the throat and rectum, or, if present, vesicles.11 Vesicular fluid is the most useful because positive results indicate acute and systemic infection, whereas carriage in the faeces, and to some extent the throat, may be long-term.67 Vesicles, if present, suggest enterovirus or VZV infection, but 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 useful. 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. Nevertheless, mumps encephalitis is most accurately confirmed by PCR of the CSF.

Viral infection may be demonstrated by culture, detection of viral antigens (by direct immunofluorescence), viral genomes (by PCR), or, if available, viral particles (by electron microscopy).10,12

Which patients with encephalitis should have a HIV test?

Recommendation
- A HIV test should be performed on all patients with encephalitis or with suspected encephalitis irrespective of interpretation of possible risk factors (A, II)

Evidence
HIV discussion
HIV should be considered in patients with suspected encephalitis for three reasons. First, the most common neurological manifestation of primary HIV-1 infection is acute, self-limiting meningoencephalitis as part of a seroconversion illness.68,69 Secondly, patients with undiagnosed advanced HIV disease can present with CNS infections caused by less common infections, such as toxoplasma, CMV, pneumocystis, cryptococcus and JC virus.70 Thirdly...
In immunocompetent adults with VZV-related CNS disease the most common pathological finding is a large vessel vasculopathy. Clinically it presents as stroke; ischaemic or haemorrhagic infarcts and intracranial arterial abnormalities are seen on cranial imaging.\textsuperscript{33,85,86}

Although MRI is the imaging modality of choice in acute encephalitis, in acutely ill, comatose or confused patients it may not be practical without general anaesthesia. In such cases, CT head scan may be the only urgent imaging available, particularly outside routine working hours. MRI is not usually performed in pregnant women, especially in the first trimester, unless there is no clear alternative. However, there is no evidence of harm or otherwise to the unborn baby, and in a pregnant woman with suspected encephalitis the benefits are likely to outweigh the risks.

**Other modalities**

MR spectroscopy can identify and quantify various brain metabolites. It may help distinguish normal from diseased brain tissue; characterise the nature of the damage and potentially distinguish inflammatory from neoplastic processes. However, there are no prospective studies assessing its diagnostic role in encephalitis. Single photon emission computed tomography (SPECT) can show focal hypoperfusion persisting after recovery from acute viral encephalitis.\textsuperscript{87} Its principle use is as a research tool; it has little application to the management of suspected acute encephalitis. Brain fluorodeoxyglucose positron emission tomography (FDG-PET) shows abnormalities in acute viral encephalitis.\textsuperscript{88} Regions of FDG-PET hypermetabolism are seen most frequently in the medial temporal lobes in HSV encephalitis, and may reflect seizure activity. Brain FDG-PET is not yet sufficiently informative, or widely available, for routine use in patients with suspected acute viral encephalitis.

### Recommendations

- An EEG need not be performed routinely in all patients with suspected encephalitis (A, II). However, for patients with mildly altered behaviour and uncertainty whether there is a psychiatric or organic cause, an EEG should be performed to seek encephalopathic changes (B, II)
- EEG should also be performed if subtle motor, or non-convulsive seizures are suspected (B, II)

### Evidence

**MRI and advanced imaging discussion**

MRI is significantly more sensitive than CT in detecting the early cerebral changes of viral encephalitis.\textsuperscript{12} In HSV encephalitis a CT obtained early may be normal, or have only subtle abnormalities; in one small series only a quarter of patients with HSV encephalitis had an abnormality on initial CT scan.\textsuperscript{43} In contrast, MRI obtained within 48 h of hospital admission is abnormal in approximately 90% of patients.\textsuperscript{76–78}

Early MRI changes occur in the cingulate gyrus and medial temporal lobe. These include gyral oedema on T-1 weighted images and high signal intensity on T2-weighted and T2 fluid attenuated inversion recovery (FLAIR) images.\textsuperscript{79} Later there may be haemorrhage. Diffusion-weighted MRI may be especially sensitive for early changes.\textsuperscript{80–82}

The changes seen on MRI are reported to be highly specific (87.5%) for PCR-confirmed HSV encephalitis.\textsuperscript{77} MRI also identifies alternative, often treatable, diagnoses in patients with conditions mimicking HSV encephalitis.\textsuperscript{77} Therefore, it is important that an MRI scan is performed urgently. In small studies, the extent of MRI abnormality seen in acute HSV encephalitis did not correlate with the clinical evolution of the disease or with subsequent depression.\textsuperscript{77,83}

Although a correlation is reported between the number of seizures in acute HSV encephalitis and subsequent brain atrophy on MRI.\textsuperscript{84}

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

### Recommendations

- MRI (including diffusion weighted imaging), is the preferred imaging modality and should be performed as soon as possible on all patients with suspected encephalitis for whom the diagnosis is uncertain; ideally this should be within 24 h of hospital admission, but certainly within 48 h (B, II)
- If the patient’s condition precludes an MRI, urgent CT scanning may exclude structural causes of raised intracranial pressure, or reveal alternative diagnoses (A, II)
- The role of MR spectroscopy is uncertain; SPECT and PET are not indicated in the assessment of suspected acute viral encephalitis (B, II)

### Evidence

MRI is significantly more sensitive than CT in detecting the early cerebral changes of viral encephalitis.\textsuperscript{12} In HSV encephalitis a CT obtained early may be normal, or have only subtle abnormalities; in one small series only a quarter of patients with HSV encephalitis had an abnormality on initial CT scan.\textsuperscript{43} In contrast, MRI obtained within 48 h of hospital admission is abnormal in approximately 90% of patients.\textsuperscript{76–78}

Early MRI changes occur in the cingulate gyrus and medial temporal lobe. These include gyral oedema on T-1 weighted images and high signal intensity on T2-weighted and T2 fluid attenuated inversion recovery (FLAIR) images.\textsuperscript{79} Later there may be haemorrhage. Diffusion-weighted MRI may be especially sensitive for early changes.\textsuperscript{80–82}

The changes seen on MRI are reported to be highly specific (87.5%) for PCR-confirmed HSV encephalitis.\textsuperscript{77} MRI also identifies alternative, often treatable, diagnoses in patients with conditions mimicking HSV encephalitis.\textsuperscript{77} Therefore, it is important that an MRI scan is performed urgently. In small studies, the extent of MRI abnormality seen in acute HSV encephalitis did not correlate with the clinical evolution of the disease or with subsequent depression.\textsuperscript{77,83}

Although a correlation is reported between the number of seizures in acute HSV encephalitis and subsequent brain atrophy on MRI.\textsuperscript{84}
PLEDs occur in many cases of HSV encephalitis and were at one stage considered pathognomonic, they also occur in other viral encephalitides and non-infectious conditions, and it is accepted that there are no EEG changes diagnostic of HSV encephalitis. 24

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

Recommendations

- Brain biopsy has no place in the initial assessment of suspected acute viral encephalitis. Stereotactic biopsy should be considered in patients with suspected encephalitis in whom no diagnosis has been made after the first week, especially if there are focal abnormalities on imaging (B, II)
- If imaging shows nothing focal, an open biopsy, usually from the non-dominant frontal lobe, may be preferable (B, II)
- The biopsy should be performed by an experienced 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. Subsequently CSF PCR for HSV DNA was developed, and proved a rapid and reliable diagnostic test largely replacing biopsy in diagnosing HSV encephalitis. However, biopsy still has a role in the investigation of other patients. Until recently, it was considered highly invasive with a significant mortality and morbidity from intracranial haemorrhage or biopsy site oedema. Using modern stereotactic approaches the incidence of serious adverse events is low, and it is now considered to be a relatively safe investigation.94,95

There is no role for a brain biopsy in the initial assessment of patients with suspected HSV encephalitis. However, it may be useful in patients with suspected HSV encephalitis who are PCR negative and deteriorate despite aciclovir, or to identify alternative causes, such as vasculitis.96 Biopsy is especially helpful if there is a focal lesion on imaging.94 In one series, an alternative diagnosis was made by biopsy in one fifth of patients with suspected HSV encephalitis, and was treatable in half of such patients.24

Treatment of viral encephalitis

For which patients should aciclovir treatment be started empirically?

Recommendations

- Intravenous aciclovir (10 mg/kg three times daily) should be started if the initial CSF and/or imaging findings suggest viral encephalitis, or within 6 h of admission if these results will not be available, or if the patient is very unwell or deteriorating (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 h of admission whilst further diagnostic investigations (as outlined) are awaited (A, II)
- If meningitis is suspected, patients should be treated in accordance with the British Infection Society (now British Infection Association) guideline (A, II)
- 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 (A, III)

Evidence

Aciclovir is a nucleoside analogue with strong antiviral activity against HSV and related herpesviruses including VZV. Two randomised trials have shown that aciclovir (10 mg/kg three times a day) improves the outcome in adults with HSV encephalitis reducing mortality to less than 20–30%; whereas patients who receive no antiviral medication have a mortality rate in excess of 70%.6,7,97 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.8,9 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, in contrast to patients with meningococcal septicaemia, where a delay of minutes in initiation of treatment may be fatal, for patients with encephalopathy and only mild confusion, investigation with a lumbar puncture before considering treatment is pragmatic, especially given the very wide differential diagnosis and relative the rarity of HSV encephalitis.98 Moreover, empirical use of antimicrobial agents can prematurely halt the diagnostic pathway because clinicians feel falsely reassured; this delays the identification of other aetiologies for which different treatments might be appropriate.

Experience from paediatric practice has shown that the use of presumptive antiviral treatment for all patients with encephalopathy, without regard to the likely diagnosis, is not beneficial.14 However, if there is a strong clinical suspicion of encephalitis and potential delay in performing an LP, or the patient is rapidly deteriorating, then aciclovir should be started sooner, together with antibiotic treatment for acute bacterial meningitis.99 In HSV encephalitis the CSF usually remains PCR positive for several days after starting aciclovir treatment; therefore when an LP is delayed, later CSF sampling can still confirm the diagnosis.12

Although aciclovir is a relatively safe drug it has important side effects. It is predominantly excreted by the kidneys, where it can cause renal impairment through crystalluria resulting in obstructive nephropathy.100 This reversible nephropathy usually manifests after 4 days of intravenous therapy and can affect up to 20% of patients.73,101 It is only rarely seen after oral valaciclovir, usually as an overdosage.102 The risks of nephropathy...
can be reduced by maintaining adequate hydration and monitoring renal function. The dose of aciclovir should be reduced in patients with pre-existing renal impairment. 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?**

**Recommendations**

- In patients with proven HSV encephalitis, intravenous aciclovir treatment should be continued for 14–21 days (A, II), and a repeat LP performed at this time to confirm the CSF is negative for HSV by PCR (B, II); if the CSF is still positive, aciclovir should continue intravenously, with weekly PCR until it is negative (B, II)

**Evidence**

Duration of treatment in the original randomised trials of aciclovir for HSV encephalitis was 10 days. However, reports of clinical relapse after 10 days treatment were published subsequently.\(^{103,104}\) Although an ongoing immune-mediated and inflammatory reaction to the infection is now thought by many to be the major pathogenic process of relapse,\(^{5,103,104}\) there is evidence for continuing viral replication in some cases.\(^{9,103,105}\) As a consequence, most clinicians now use at least 14–21 days intravenous treatment in confirmed cases, though later relapses can occur.\(^{9}\) Some advocate repeating a CSF examination at 14–21 days, and continuing treatment until the CSF is negative of virus by PCR,\(^{36}\) which is supported by a European Consensus Statement.\(^{28}\)

Given orally, aciclovir does not achieve adequate levels in the CSF; however its valine ester valaciclovir has good oral bioavailability, and is converted to aciclovir after absorption.\(^{106}\) Valaciclovir has been used in paediatric practice, especially when maintaining intravenous access has proved difficult.\(^{107}\) In adults it may have a role in ongoing treatment, particularly in patients with HSV detectable in the CSF after 2–3 weeks. The American NIAID Collaborative Antiviral Study Group is assessing the role of high dose valaciclovir (2 g three times daily) for three months.\(^{108}\)

**In patients who are HSV PCR negative when can presumptive treatment with aciclovir be safely stopped?**

**Recommendations**

- Aciclovir can be stopped in immunocompetent patients, if:
  - An alternative diagnosis has been made, or
  - HSV PCR in the CSF is negative on two occasions 24–48 h apart, and MRI is not characteristic for HSV encephalitis, or
  - HSV PCR in the CSF is negative once >72 h after neurological symptom onset, with unaltered consciousness, normal MRI (performed >72 h 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.\(^{26}\) When the initial CSF reveals an alternative diagnosis, such as bacterial infection, the aciclovir can be safely stopped. However, 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 late in the illness after virus has been cleared. Similar findings have been reported for other CNS viral infections.\(^{109}\) Thus aciclovir treatment should not be stopped on the basis of a single negative CSF PCR only, when HSV encephalitis is still suspected clinically.

A European consensus statement recommended the combined approach to diagnosis of testing CSF for HSV DNA (by PCR) and HSV antibody; such that a negative HSV PCR result early in the disease process coupled with a negative HSV CSF antibody study sampled 10–14 days after symptom onset effectively ruled out the disease.\(^{28}\) Given that CSF HSV antibody studies 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.\(^{59}\) It proposes that if a negative HSV PCR result is obtained from CSF sampled >72 h into the disease process and that the patient has a low clinical probability of HSV encephalitis (i.e. normal neuroimaging, CSF <5 white cells \(\times 10^6\)/L, and unaltered 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 after 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?**

**Recommendations**

- 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.\(^{110}\) Even before antiviral drugs became available, many clinicians considered that corticosteroids were beneficial in HSV encephalitis, though others disagreed.\(^{111,112}\) Since the advent of aciclovir, corticosteroids have often been 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. Although, a retrospective analysis of 45 patients with HSV encephalitis showed that older age, lower Glasgow coma score on admission, and lack of administration of corticosteroids were significant independent predictors of a poor outcome. An accompanying editorial made a strong case for a randomised placebo-controlled trial, which is now being carried out across several European countries including the UK.

What should be the specific management of VZV encephalitis?

Recommendations

- No specific treatment is needed for VZV cerebellitis (B, II)
- For VZV encephalitis, whether due to primary infection or reactivation, intravenous aciclovir 10–15 mg/kg three times daily is recommended, with or without a short course of corticosteroids (B, II)
- If there is a vasculitic component, there is a stronger case for using corticosteroids (B, II)

Evidence

In cerebellitis caused by VZV, antiviral treatments are not normally used because the disease is usually self-limiting, resolving in one to three weeks. The primary pathogenic process is thought to be immune mediated demyelination, rather than viral cytopathology. Although there are no good studies in primary VZV encephalitis, this condition is usually treated with antiviral drugs and corticosteroids. Intravenous aciclovir (10 mg/kg three times daily) is often recommended, 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, but renal function must be reviewed frequently and most clinicians use the 10 mg/kg dose.

For encephalitis and other CNS disease associated with reactivation of VZV, although the evidence is limited, most would recommend treatment with aciclovir (10 mg/kg three times daily intravenously) for up to 14 days, especially if it can be started within a few days of symptom onset. The dose of aciclovir should be adjusted for patients with impaired renal function. A course of steroids (for example 60–80 mg of prednisolone daily for 3 to 5 days) is also often given, because of the inflammatory nature of the lesion. 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 mcg/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. The drug has also been used in patients with chronic enterovirus infection due to agammaglobulinemia, enterovirus myocarditis, poliovirus vaccine-associated paralysis and neonatal infection. However, there have been no trials assessing its role in enterovirus encephalitis. It is not easily available.

Intravenous immunoglobulin has been used in patients with chronic enterovirus meningitis, and may also be useful in patients with severe enterovirus 71 infection, though no randomised trials have been conducted.

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

Recommendations

- Patients with falling level of consciousness require urgent assessment by 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 an immediate neurological specialist opinion and should be managed in a setting where clinical neurological review can be obtained as soon as possible and definitely within 24 h of referral (B, III)
- There should be access to neuroimaging (MRI and CT), under general anaesthetic if needed, and neurophysiology (EEG), which may mean transfer to a specialist neurosciences unit (B, III)
- As CSF diagnostic assays are critical to confirming diagnosis, the results of CSF PCR assays should be available within 24–48 h 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 neurological unit is recommended. The transfer should occur as soon as possible and definitely within 24 h of being requested (B, III)

Evidence

Currently in the UK there is sparse evidence and little guidance for the in-patient 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.

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 with the condition. Patients require close monitoring in a quiet environment but do not routinely require isolation. Unlike stroke, where clear evidence exists to support patient management in specialist units, no such studies have been undertaken for encephalitis. Appropriate environments for managing patients with encephalitis include neurological wards, high dependency units, or intensive care units.

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

What rehabilitation and support services should be available for adults affected by encephalitis and their carers?

Recommendations

- 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) (B, II)
- Patients should not be discharged from hospital without either a definite or suspected diagnosis. Arrangements for outpatient follow-up and plans for on-going therapy and rehabilitation should be formulated at a discharge meeting, and should include at least one follow-up appointment (A, II)
- All patients irrespective of age should have access to assessment for rehabilitation (A, III)

Evidence

The sequelae and consequences of encephalitis may not be immediately apparent when a patient is discharged from hospital following the acute illness. However, anxiety, depression and obsessive behaviours often become evident subsequently, and may be more frequently encountered after encephalitis than other causes of acute brain injury. A charity-commissioned study of encephalitis patients found that 33% were discharged without outpatient follow-up although 96% reported ongoing complications from their illness.

A broad and comprehensive approach to both assessment and rehabilitation is necessary, with input from specialists in neuropsychology and neuropsychiatry as central components, in addition to speech and language therapy, neuro-physiotherapy, and occupational therapy. Access to specialist brain injury rehabilitation services is key to recovery in many cases, and patients and their families greatly value the support provided by voluntary sector organisations such as the Encephalitis Society (www.encephalitis.info).

Patients affected by encephalitis and those supporting them require information on the condition and its consequences, and directions on how to access this information. In one survey one-third of patients were discharged from hospital without they or their families recalling being informed of the diagnosis. Information and support reduces isolation, helps family adjustment and can provide useful signposting to other services as appropriate. Older patients should not immediately be referred to elderly person’s service, unless local services have a specific interest in neurological rehabilitation, if this will preclude them receiving brain injury specific assessment and rehabilitation.

Special circumstances

How does the management of suspected encephalitis in the returning traveller differ?

Recommendations

- 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 regional and national tropical and infectious disease units should be sought regarding appropriate investigations and treatment for the other possible causes of encephalitis in a returning traveller (Table 2) (A, III)

Evidence

Individuals 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, 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 and rapid antigen tests for malaria antigens in blood. Rapid antigen tests are slightly less sensitive than thick blood film examination in a specialist laboratory, but are more readily available in most British hospitals. 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 from previous residents in 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 early treatment should be considered. Patients with tuberculous meningitis (TBM) have often visited or been visited by people from tuberculosis endemic areas, or often originate from an area with a high incidence of TB. The initial CSF white cell count may be normal in patients with TBM, especially in the
immunocompromised. British guidelines on the management of TBM have recently been produced.\textsuperscript{130,131}

In addition occasional cases have been reported of dengue encephalopathy, rabies, Japanese encephalitis, Eastern equine encephalitis, West Nile virus encephalitis, and tick-borne encephalitis.\textsuperscript{34,132} Table 2 gives an indication of the geographical risk factors associated with these viral CNS infections. Close liaison with regional and national tropical and infectious diseases units, and national specialist diagnostic laboratories is needed when deciding on appropriate investigations.

Other relatively rare non-viral causes of encephalopathy in returning travellers include eosinophilic meningitis, African trypanosomiasis (sleeping sickness) and typhoid encephalopathy.\textsuperscript{125,126,133} Cysticercosis and schistosomiasis typically present with focal or multiple space occupying lesions often causing seizures especially in the case of cysticercosis, rather than an encephalitis. Because some people may place themselves at risk of HIV infection when travelling, HIV seroconversion illness should always be considered.

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, there is no febrile element, or the CSF white cell count is normal (A, III)
- A CT head scan before LP should be considered in patients with known severe immunocompromise (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 an LP
- MRI should be performed as soon as possible in all immunocompromised patients with suspected encephalitis (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 \textit{M. tuberculosis}
  - CSF and blood culture for \textit{Listeria monocytogenes}
  - Indian ink staining and/or cryptococcal antigen (CRAG) testing for \textit{Cryptococcus neoformans},
  - Antibody testing and if positive CSF PCR for \textit{Toxoplasma gondii},
  - Antibody testing of serum and if positive CSF for syphilis
- Other investigations to consider, depending on the circumstances, include (C, III):
  - CSF PCR for HHV6 and 7
  - CSF PCR for JC/BK virus
  - CSF examination for \textit{Coccidioides} \textit{sp and Histoplasma} \textit{sp}
- Patients with HIV should be treated in an HIV centre (A, II)
- Immunocompromised patients with encephalitis caused by HSV-1 or 2, should be treated with intravenous aciclovir (10 mg/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 CD4 cell count is $>200 \times 10^6$/L (A, II)
- Acute concomitant VZV infection causing encephalitis should be treated with intravenous aciclovir (A, II)
- CNS CMV infections should be treated with ganciclovir, valganciclovir, forcarnet or cidovifor (A, II)

Evidence

\textbf{Immunocompromise}

Immunocompromise presents specific challenges in all aspects of the management of patients with suspected encephalitis, including the range of causative pathogens, presenting clinical features, and differences in the investigations, and treatment.\textsuperscript{75} 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.

\textbf{Causes}

Whilst many of the following pathogens may also uncommonly affect the immunocompetent, in immunocompromised patients there is a wider range of pathogens that may cause an encephalitic presentation; these include bacterial diseases such as tuberculous meningitis, listeria and syphilis, fungi, such as cryptococcus, parasitic infections such as toxoplasmosis, and viruses. The viruses implicated include CMV, particularly in advanced HIV (i.e. patients with CD4 counts less than $50 \times 10^6$/L) and EBV,\textsuperscript{10,12,16,50,61} Progressive multifocal leukoencephalopathy (PML) is caused by JC virus, but 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 herpesviruses in 180 non-selected CSF samples from 141 patients, 23 patients were HIV positive.\textsuperscript{134} 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 \textit{Coccidioides} \textit{species}, \textit{Histoplasma capsulatum} and West Nile virus.\textsuperscript{62,79}

\textbf{History}

Immunocompromised patients are more likely to have subtle and sub-acute presentations of viruses that cause an acute encephalitis in the immunocompetent, such as HSV\textsuperscript{135} and enterovirus, as well as for viruses specific to the immunocompromised, such as HHV-6 (Table 4. Sub-acute and chronic infections).

\textbf{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 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, from a broader range of pathogens. 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 patients with HIV suffering from a neurological disease should be treated in an HIV 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
- The diagnosis of antibody-mediated encephalitis should be considered in all patients with suspected encephalitis as they have a poor outcome if untreated. Moreover, the clinical phenotypes of these recently described disorders are still expanding (B, II)
- Clinical features, such as a sub-acute presentation, orofacial dyskinesia, choreoathetosis, faciobrachial dystonia, intractable seizures or hyponatraemia, may suggest an antibody-mediated encephalitis, although these features are not exclusive to antibody-mediated disease (B, II)
- All patients with proven VGKC complex or NMDA receptor antibody-associated encephalitis should have screening for neoplasm (B, II)
- Early immune suppression and tumour removal results in improved outcomes (B, II)

Evidence
In patients with an acute or more commonly sub-acute onset of encephalitis, immune-mediated encephalitis should be considered as the treatment is very different and early intervention may significantly improve outcome.

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

**History**
The median age at presentation is 65 years and the male to female ratio is 2:1, although children are now beginning to be identified. It is uncommon for adult patients to have fever or headache. Instead they usually have profound disorientation and confusion with seizures and anterograde and retrograde amnesia. Low plasma sodium is found in about 60%. A newly described faciobrachial dystonic seizure syndrome may precede the onset of the encephalitis by a few weeks and appears to be pathognomonic for this condition.

**Investigation findings**
In a patient with suspected encephalitis, the presence of a subacute history or hyponatraemia, or a history of brief arm and face (less frequently leg) dystonic seizures, should trigger the request for serum VGKC-complex antibodies. The MRI will show characteristic abnormalities in about 60% of patients with discrete hippocampal high signal, often with associated swelling. In the majority this is bilateral but in 15% it is unilateral. The EEG shows generalised slowing with or without an ictal focus. Significant CSF abnormalities are uncommon and antibodies are not always detectable in the CSF. All patients should have appropriate imaging to identify an associated tumour which is present in <10% and is usually a thymoma or a small cell lung cancer.

**Treatment**
With high dose oral steroids (0.5 mg/kg/day) the antibody levels will normalise within 3–6 months. The dose can then be tapered over the next 12 months. If the patient is acutely unwell then intravenous immunoglobulin (IVig) (0.4 g/kg/day) or plasma exchange can be used in conjunction with steroids, to accelerate improvement. Regular IVlg alone, without steroids, may be less effective at reducing antibody levels with associated poorer clinical outcomes (Buckley and Vincent unpublished observations). In the majority, the confusion and seizures improve rapidly with immunosuppression, and the serum sodium normalises. The improvement in memory may take several months to years after the initial presentation.

This is usually a monophasic illness and once the antibodies become undetectable with treatment, they remain undetectable and relapse is uncommon, but it can occur.

Encephalitis associated with antibodies to N-methy-o-Aspartic acid (NMDA) receptor

**Presentation**
The median age at presentation is 25 years and the male to female ratio is 1:2. These patients often have headache, and sometimes fever, as one of the earliest symptoms and there may be evidence of a prodromal viral infection. The subsequent illness then appears to have two phases. The first phase is characterised by seizures, confusion, amnesia and psychosis. Days to a few weeks later, the patients develop involuntary movements, classically choreoathetosis and orofacial dyskinesia, fluctuations in conscious level, dysautonomia and, in some, episodes of central hypoventilation. As a result, despite current best therapy, the median length of hospital stay is 160 days (range 16–850) and many patients require admission to the ICU for assisted ventilation.
**Investigation findings**

The CSF is frequently abnormal especially in the first phase with lymphocytosis (up to 500 cells $\times 10^6/L$ has been reported) and detectable NMDA antibodies. CSF is not essential to make the diagnosis as the antibodies are also present in the serum, but paired samples are informative. The MRI is initially normal in approximately 90% and remains normal in many (approximately 77%), but some may show areas of high signal in hippocampus or white matter. The EEG shows epileptiform activity early in approximately 50% and generalised slowing, in approximately 80%, later in the illness. All patients need investigation for an associated tumour, which in women, is almost always an ovarian teratoma. Of female patients, 20–50%, will have a tumour whereas in men and children the rate of associated tumours is lower.

**Treatment**

Optimal treatment regimens are still being developed for these patients. There is some evidence that two immunosuppressive agents in combination are important and so current practice is to prescribe corticosteroids and either plasma exchange or IVIg. In patients who have not responded well to this combination, further immune suppression, such as with rituximab or cyclophosphamide, has been used with some success. In contrast to patients with VGKC-complex antibody associated encephalitis, patients with NMDA receptor antibody-associated encephalitis can relapse in approximately 30%, despite there being no evidence of tumour presence. Therefore, long-term immunosuppression with agents such as azathioprine may be helpful. 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 (Appendix. Audit parameters for national encephalitis guideline). This audit and guidelines will be reviewed every 5 years, through the national guidelines development group.

**Acknowledgements**

In addition to the authors, the following are members of the National Encephalitis Development Group: Solomon Almond, Enitan Carrol, Mehrengise Cooper, Cheryl Hemmingway, Paul Klapper, Ming Lim, Jean-Pierre Lin, Hermione Lyall, Kevin Mackway-Jones, Nick Makwana, Anthony Marson, Bimal Mehta, Esse Merson, Isam Osman, Andrew Riordan, Delane Shingadja, Aman Sohal, David Stoeter, Ed Wilkins

This article presents independent work funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (Grant Reference Number RP-PG-0108-10048). Additional funding was provided by the Association of British Neurologists, the British Infection Association, the Encephalitis Society and University of Liverpool; these organisations contributed members to the guideline development team, but have no conflicts of interests to declare.

**Appendix A. Supplementary data**

Supplementary data associated with this article (summary document and patient information leaflet) can be found in the online version at doi:10.1016/j.jinf.2011.11.014.
### National encephalitis guideline audit tool

<table>
<thead>
<tr>
<th>Question</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is the time from presentation to suspicion of encephalitis recorded?</td>
<td>Y/N</td>
</tr>
<tr>
<td>If Y what was it? (hours)</td>
<td></td>
</tr>
<tr>
<td>If Y was it &lt;6 h?</td>
<td>Y/N</td>
</tr>
<tr>
<td>2. Is the time from admission to LP recorded?</td>
<td>Y/N</td>
</tr>
<tr>
<td>If Y what was it? (hours)</td>
<td></td>
</tr>
<tr>
<td>If Y was it &lt;6 h?</td>
<td>Y/N</td>
</tr>
<tr>
<td>Were there any clinical contraindications to an LP?</td>
<td>Y/N</td>
</tr>
<tr>
<td>If Y what was it? (please tick all that apply)</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
</tr>
<tr>
<td>Focal neurological signs</td>
<td></td>
</tr>
<tr>
<td>Abnormal posturing;</td>
<td></td>
</tr>
<tr>
<td>Respiratory insufficiency;</td>
<td></td>
</tr>
<tr>
<td>Bradycardia and hypertension;</td>
<td></td>
</tr>
<tr>
<td>GCS &lt;13 or fall &gt;2</td>
<td></td>
</tr>
<tr>
<td>Systemic shock</td>
<td></td>
</tr>
<tr>
<td>Infection at LP site</td>
<td></td>
</tr>
<tr>
<td>Coagulation disorder</td>
<td></td>
</tr>
<tr>
<td>Immune compromise</td>
<td></td>
</tr>
<tr>
<td>Papilloedema</td>
<td></td>
</tr>
<tr>
<td>If N was imaging performed before LP?</td>
<td>Y/N</td>
</tr>
<tr>
<td>What was the time to LP? (hours)</td>
<td></td>
</tr>
<tr>
<td>If Y was imaging performed before LP?</td>
<td>Y/N</td>
</tr>
<tr>
<td>What was the time to LP? (hours)</td>
<td></td>
</tr>
<tr>
<td>3. Were the following CSF tests sent?</td>
<td>Y/N</td>
</tr>
<tr>
<td>Protein</td>
<td></td>
</tr>
<tr>
<td>Total WCC</td>
<td></td>
</tr>
<tr>
<td>Differential WCC</td>
<td></td>
</tr>
<tr>
<td>Microscopy and Gram stain</td>
<td></td>
</tr>
<tr>
<td>Bacterial culture</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
</tr>
<tr>
<td>Blood glucose</td>
<td></td>
</tr>
<tr>
<td>PCR for viruses</td>
<td></td>
</tr>
<tr>
<td>HSV</td>
<td>Y/N</td>
</tr>
<tr>
<td>VSV</td>
<td>Y/N</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>Y/N</td>
</tr>
<tr>
<td>Other (please specify)</td>
<td></td>
</tr>
<tr>
<td>ZN stain for TB</td>
<td>Y/N</td>
</tr>
<tr>
<td>Culture for TB</td>
<td>Y/N</td>
</tr>
<tr>
<td>4. Was CSF diagnostic?</td>
<td>Y/N</td>
</tr>
<tr>
<td>If Y what was it?</td>
<td>HSV</td>
</tr>
<tr>
<td>If Y what was it?</td>
<td>VZV</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>Y/N</td>
</tr>
<tr>
<td>Other (please specify)</td>
<td>Y/N</td>
</tr>
<tr>
<td>5. Was a HIV test offered?</td>
<td>Y/N</td>
</tr>
<tr>
<td>Was it accepted?</td>
<td>Y/N</td>
</tr>
<tr>
<td>6. Was an MRI brain performed?</td>
<td>Y/N</td>
</tr>
<tr>
<td>What was the time to it? (hours)</td>
<td></td>
</tr>
<tr>
<td>Was this &lt;48 h?</td>
<td>Y/N</td>
</tr>
<tr>
<td>7. Was specialist advice sought?</td>
<td>Y/N</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td></td>
</tr>
<tr>
<td>Microbiology</td>
<td></td>
</tr>
<tr>
<td>Virology</td>
<td></td>
</tr>
<tr>
<td>Neurology</td>
<td></td>
</tr>
</tbody>
</table>
References


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