Demystifying encephalitis: guidelines for an emergency not to miss

The clinical presentation of encephalitis is often non-specific, complicating the immediate diagnosis and management. This article highlights key messages from recently published guidelines, identifies common pitfalls and discusses how these lessons can be applied to routine clinical practice.

Physicians on the acute medical take often encounter patients with acute encephalopathy and fever. The differential diagnosis in this setting is broad, but a minority of patients may have encephalitis: a potentially fatal inflammatory disorder of the CNS.

Encephalitis is a relatively rare but important condition; left untreated it can be devastating, with a mortality rate over 50% (Sköldenberg et al, 1984; Whitley et al, 1986). A prospective study of 203 patients with encephalitis showed that nearly half of patients (45%) had moderate to severe disability when assessed using the Glasgow outcome scale (Granerod et al, 2010). Early intervention can be life-saving.

Identifying which patients require investigation and treatment for encephalitis is challenging. Are there any pathognomic symptoms and signs? What investigations should be arranged and how sensitive are they? How can the diagnosis be confidently confirmed or excluded? For how long should treatment be continued?

Guidelines by Solomon et al (2012) recognize that the management of suspected encephalitis can be improved by increasing awareness among clinicians encountering the more common forms of encephalitis. Building on the success of the emergency management of meningitis by using a simple algorithm, the authors have taken a similar approach with acute encephalitis (*Figure 1*), thus filling an important gap in national guidelines.

Encephalitis is defined by inflammation of the brain parenchyma. Causes of encephalitis are broadly classified as infectious or immune-mediated (*Table 1*). The latter include para- or post-infectious, and the more recently recognized antibody-associated encephalitides. The incidence of all forms across all ages in the UK is estimated at 5.23–8.66/100 000/year (Granerod et al, 2013).

Herpes simplex encephalitis, the most commonly diagnosed viral encephalitis in resource-rich settings, has an estimated incidence of 1 per 250 000–500 000 (Solomon et al, 2012). In over a third of cases, no cause is identified (Granerod et al, 2010). Most generalists are unlikely to encounter the rarer causes of encephalitis, but should be aware of when to refer for specialist assessment.

Symptoms and signs of encephalitis are non-specific and non-discriminatory. Most patients present with fever (72%). Other features include headache (60%), personality or behavioural change (64%), lethargy (55%) or seizures (52%) (Granerod et al, 2010). Prospective studies have shown a high incidence of gastrointestinal (48%), respiratory (20%) and urinary (10%) symptoms in adults with encephalitis (Granerod et al, 2010). Many conditions can mimic encephalitis and patients with suspected encephalitis are frequently found to have alternative diagnoses – septic encephalopathy secondary to non-CNS infection being particularly common. Encephalitis may be missed in the setting of alcohol abuse or withdrawal, delaying initiation of treatment (Poissy et al, 2009).

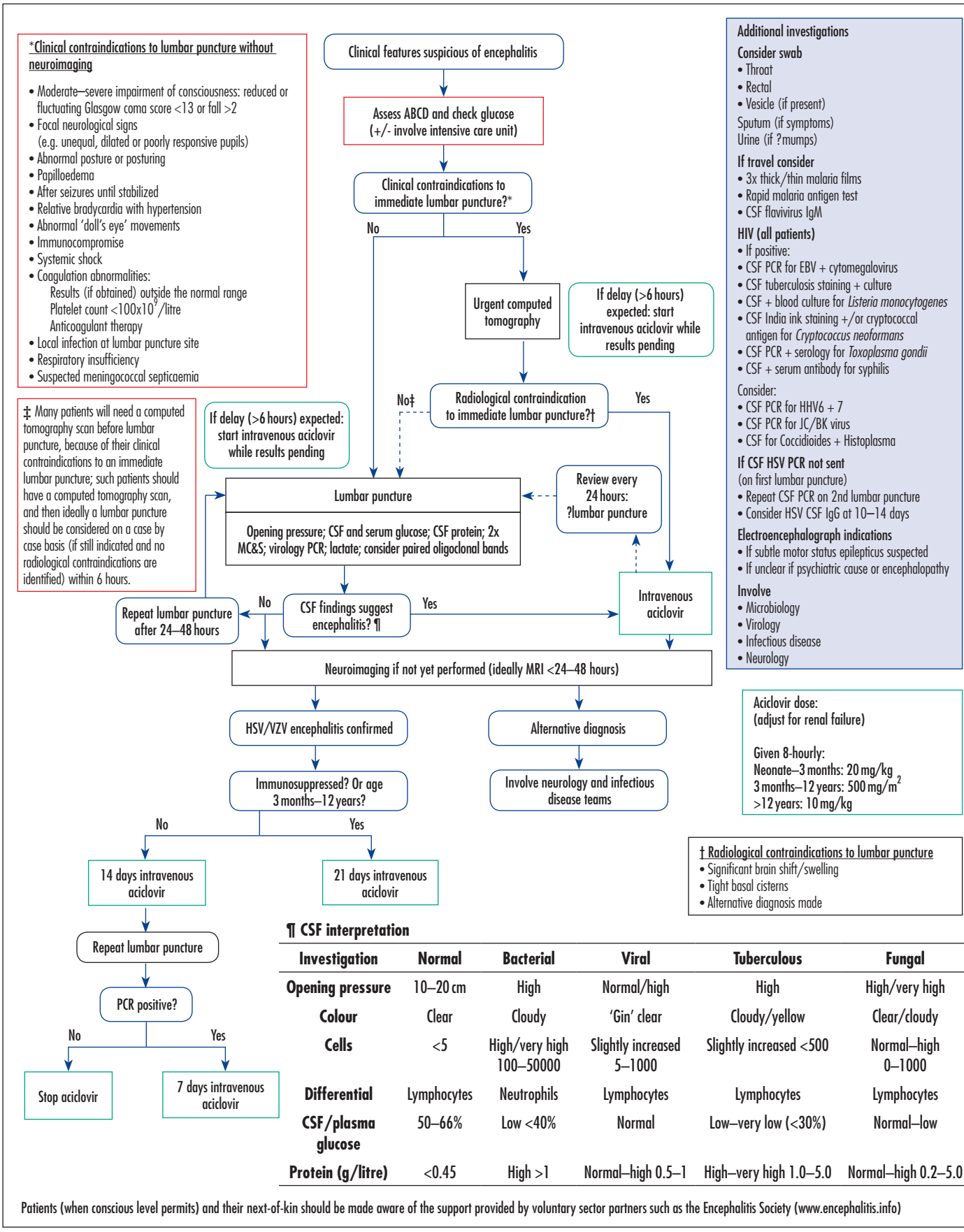
Encephalitis affects people of all ages, but has a bimodal peak age distribution in the very young and the elderly. Recognizing encephalitis in the elderly can be challenging, particularly as elderly patients are more likely to have other neurological disorders. Patients with acute focal neurological deficits or speech disturbance may present to hospital as a suspected stroke. They are also more likely to present with fever and behavioural change in the context of infections such as pneumonia or urinary tract infection. It is important that the diagnosis is considered promptly to ensure appropriate treatment is commenced.

A parallel guideline has been published for children aged between 28 days and 16 years with suspected encephalitis (Kneen et al, 2012). As in adults, the initial presentation of encephalitis can be confusingly non-specific, especially in infants and younger children who might have difficulty communicating their symptoms. Presentation may include respiratory or gastrointestinal symptoms.

Presentation can differ in children and adults. In children, herpes simplex encephalitis is more often associated with primary herpes infection than in adults. Varicella zoster infection in children is more commonly associated with post-infectious cerebellitis than encephalitis, and can cause ischaemic stroke. Enteroviral encephalitis typically affects children under 5 years of age, whereas Epstein–Barr virus encephalitis more commonly affects teenagers.

Dr Malick MM Gibani *is Core Medical Trainee in the Department of Infectious Diseases and Tropical Medicine, Northwick Park Hospital, London,* **Dr Rachel L Brown** *is Core Medical Trainee, National Hospital for Neurology and Neurosurgery, Queen Square, London, and* **Dr Nicholas WS Davies** *is Consultant in the Department of Neurology, Chelsea and Westminster Hospital and Imperial College Healthcare NHS Trust, London SW10 9NH*

Correspondence to: Dr NWS Davies (Nicholas.davies@chelwest.nhs.uk)



¶ CSF interpretation

Investigation	Normal	Bacterial	Viral	Tuberculous	Fungal
Opening pressure	10–20 cm	High	Normal/high	High	High/very high
Colour	Clear	Cloudy	'Gin' clear	Cloudy/yellow	Clear/cloudy
Cells	<5	High/very high 100–50000	Slightly increased 5–1000	Slightly increased <500	Normal–high 0–1000
Differential	Lymphocytes	Neutrophils	Lymphocytes	Lymphocytes	Lymphocytes
CSF/plasma glucose	50–66%	Low <40%	Normal	Low–very low (<30%)	Normal–low
Protein (g/litre)	<0.45	High >1	Normal–high 0.5–1	High–very high 1.0–5.0	Normal–high 0.2–5.0

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)

Figure 1. Algorithm for diagnosis and management of suspected encephalitis. Adapted from Solomon et al (2012). ABCD = airway, breathing, circulation and disability; CT = computed tomography; EBV = Epstein–Barr virus; HHV = human herpes virus; HIV = human immunodeficiency virus; MC+S = microscopy culture and sensitivity; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; VZV = varicella zoster virus.

Investigations

When encephalitis is suspected, what investigations should be requested and how promptly? Lumbar puncture is a key investigation and should be performed in all patients as soon as encephalitis is suspected, provided there are no contraindications. The guidelines suggest that a lumbar puncture should be performed within 6 hours of hospital admission (Solomon et al, 2012).

Table 1. Causes of encephalitis and potential mimics

Infectious	Viruses	Sporadic	Herpes viruses (e.g. herpes simplex virus-1, herpes simplex virus-2, varicella zoster virus, cytomegalovirus, Epstein–Barr virus, human herpes virus-6/7)
			Enteroviruses (e.g. enterovirus, poliovirus, echovirus, coxsackievirus)
			Paramyxovirus (e.g. measles, mumps)
		Arthropod-borne/ zoonotic viruses	Flaviviruses (e.g. West Nile virus, Japanese encephalitis, dengue 1–4)
			Alphaviruses (e.g. Western, Eastern and Venezualan equine encephalitis viruses, Chikungunya)
			Bunyaviruses (e.g. La Crosse virus)
			Rhabdiviruses (e.g. rabies)
		Others	HIV, influenza, adenovirus, rubella, lymphocytic choreomeningitis virus
	Bacteria	Small bacteria, mostly intracellular (e.g. *Mycoplasma pneumonia*, Rickettsiae, *Tropheryma whipplei*, Brucella spp., *Listeria monocytogenes*)	
		Spirochetes (e.g. *Trepenoma pallidum, Borrelia burgdorferi*)	
		Mycobacterium tuberculosis	
	Parasites	e.g. *Trypansoma brucei gambiense* and *rhodesiense, Toxoplasma gondii*	
	Fungi	e.g. *Cryptococcus neoformans*, coccidiomycosis, histoplasmosis	
Immune mediated	Acute disseminated encephalomyelitis		
	Acute haemorrhagic leukoencephalopathy		
	Bickerstaff's encephalitis		
	Paraneoplastic encephalitis		
	Encephalitis secondary to systemic vasculitis		
	Antibody-associated encephalitis, e.g. anti NMDA receptor, anti VGKC complex		
	Encephalitis lethargica		
Encephalitis mimics	Infection (e.g. septic encephalopathy, meningitis)		
	Vascular (ischaemic stroke, intracranial haemorrhage, vasculitis)		
	Neoplasia (e.g. primary brain tumour, cerebral metastases)		
	Metabolic encephalopathy (e.g. hepatic encephalopathy, renal encephalopathy, hypoglycaemia, toxic encephalopathy including and alcohol and drugs)		
	Epilepsy		
	Functional disorders		

Adapted from Solomon et al (2012). The above list is non-exhaustive. NMDA = N-methyl-D-aspartic acid, VGKC = voltage-gated potassium channel

Patients usually undergo a computed tomography head scan to exclude alternative diagnoses, but the need for computed tomography before lumbar puncture is controversial. Published studies suggest that time to lumbar puncture is significantly prolonged if preceded by computed tomography (Michael et al, 2010). The guidelines state that: 'unselected computed tomography scanning of all patients before a lumbar puncture may lead to unnecessary delays for the majority of patients, for whom there are no contraindications to an immediate lumbar puncture' (Solomon et al, 2012). Clinical contraindications to lumbar puncture are highlighted in *Figure 1* and many patients will have at least one. However, if computed tomography is not immediately available and there are no contraindications, 'prompt lumbar puncture may be the most useful approach to diagnosis' (Solomon et al, 2012).

CSF analysis typically shows moderate pleocytosis and moderately elevated protein levels. Polymerase chain reaction is crucial for diagnosis of encephalitis; a recommended panel (herpes simplex virus, varicella zoster virus and enterovirus polymerase chain reaction) will identify 90% of cases caused by known viral pathogens. An extended panel may be required in immunocompromised patients or in the setting of recent travel. Herpes simplex virus polymerase chain reaction confirms the diagnosis of herpes simplex encephalitis and has a high sensitivity (>95%) when taken between day 2–10 of illness. In approximately 5–10% patients, particularly the immunocompromised, initial CSF analysis is normal when taken early in the course of the illness. If clinical suspicion of herpes simplex encephalitis remains high, lumbar puncture should be repeated after a further 24–48 hours (Davison et al, 2003; Solomon et al, 2012). The central role of CSF analysis in diagnosing and managing encephalitis emphasizes the need for trainees of all grades to be competent in performing lumbar punctures.

Magnetic resonance imaging is the preferred imaging modality in suspected encephalitis and should be performed within 48 hours of hospital admission. This is a welcome target: having a national audit standard may help radiology departments when triaging scan requests. In herpes simplex encephalitis, magnetic resonance imaging demonstrates abnormalities in approximately 90% of patients, which are often highly specific (Solomon et al, 2012).

HIV testing should be offered to all patients with suspected encephalitis. HIV seroconversion can present with a self-limiting meningoencephalitis; immunosuppression increases the spectrum of potential responsible infective agents.

Treatment

Fortunately, many forms of encephalitis have effective treatments. The prognosis of herpes simplex encephalitis is dramatically improved by treatment with aciclovir (adult dose 10 mg/kg three times a day). Evidence from randomized controlled trials suggest improvement in

untreated mortality from >50% to less than 20% with treatment (Sköldenberg et al, 1984; Whitley et al, 1986). Delays in initiating treatment, particularly >48 hours, are associated with worse prognosis (Raschilas et al, 2002). Given the wide differential, the authors take a pragmatic approach, advocating starting aciclovir as soon as the initial CSF or imaging findings suggest encephalitis or within 6 hours, whichever is sooner.

Treatment for herpes simplex encephalitis should be continued for 14–21 days, and successful treatment confirmed by a negative CSF herpes simplex virus polymerase chain reaction (Solomon et al, 2012). Many patients are commenced on aciclovir empirically when herpes simplex encephalitis is suspected but knowing when it is safe to stop can be challenging. As outlined above, the negative predictive value of CSF polymerase chain reaction and magnetic resonance imaging varies depending on the time of testing. The guidelines state that aciclovir can be stopped in an immunocompetent patient if 'an alternative diagnosis has been made' (e.g bacterial infection) or 'if herpes simplex virus polymerase chain reaction in the CSF is negative on two occasions 24–48 hours apart and magnetic resonance imaging is not characteristic for herpes simplex virus'. Alternatively, aciclovir can also be stopped if 'a negative herpes simplex virus polymerase chain reaction result is obtained from CSF >72 hours into the disease process and that the patient has a low clinical probability of herpes simplex virus encephalitis (i.e. normal neuroimaging, CSF <5 white cells 10^6/litre, and unaltered consciousness)' (Solomon et al, 2012).

Effective management requires multidisciplinary input from several specialties, including neurology, infectious diseases, microbiology and virology, especially when the presentation is atypical or in special circumstances such as recent travel. Services such as the Imported Fever Service offer round the clock access to expert clinical and microbiological advice, when not available locally (Public Health England, 2013).

Sequelae of encephalitis may persist for years, requiring long-term rehabilitation and post-hospital care. Patients should be made aware of voluntary sector support, from organizations such as The Encephalitis Society (www.encephalitis.info). Their stated aim is to ensure that 'those affected and their families, have access to early diagnosis, excellent management of their condition, timely access to rehabilitation and other forms of social support.' The guidelines represent an important step achieving these aims.

Conclusions

The diagnosis of encephalitis should be considered in patients presenting with a fever with altered behaviour, altered consciousness, new seizures or new focal neurology. Studies suggest that the incidence of encephalitis is considerably higher than previously estimated (Granerod et al, 2013). The guidelines by Solomon et al (2012) are a valuable tool for clinicians encountering the more common forms of encephalitis. It is hoped that these guidelines will lead to improved diagnosis and management of encephalitis and will also provide a benchmark for clinical audit, through which practice can continue to improve. **BJHM**

Conflict of interest: Dr NWS Davies assisted in the development and writing of the guidelines; other authors: none.

Davison KL, Crowcroft NS, Ramsay ME, Brown DWG, Andrews NJ (2003) Viral encephalitis in England, 1989-1998: what did we miss? *Emerg Infect Dis* **9**: 234–40

Granerod J, Ambrose HE, Davies NWS et al; UK Health Protection Agency (HPA) Aetiology of Encephalitis Study Group (2010) Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis* **10**: 835–44

Granerod J, Cousens S, Davies NWS, Crowcroft NS, Thomas SL (2013) New estimates of incidence of encephalitis in England. *Emerg Infect Dis* **19**(9): 1455–62

Kneen R, Michael BD, Menson E et al; National Encephalitis Guidelines Development and Stakeholder Groups (2012) Management of suspected viral encephalitis in children - Association of British Neurologists and British Paediatric Allergy, Immunology and Infection Group national guidelines. *J Infect* **64**: 449–77

Michael BD, Sidhu M, Stoeter D et al; North West Neurological Infections Network (2010) Acute central nervous system infections in adults--a retrospective cohort study in the NHS North West region. *QJM* **103**: 749–58

Poissy J, Wolff M, Dewilde A et al (2009) Factors associated with delay to acyclovir administration in 184 patients with herpes simplex virus encephalitis. *Clin Microbiol Infect* **15**(6): 560–4

Public Health England (2013) Imported Fever Service. www.hpa.org.uk/webw/HPAweb&Page&HPAwebAutoListName/Page/1317133839448 (accessed 13 December 2013)

Raschilas F, Wolff M, Delatour F et al (2002) Outcome of and prognostic factors for herpes simplex encephalitis in adult patients: results of a multicenter study. *Clin Infect Dis* **35**: 254–60

Sköldenberg B, Forsgren M, Alestig K et al (1984) Acyclovir versus vidarabine in herpes simplex encephalitis. Randomised multicentre study in consecutive Swedish patients. *Lancet* **ii**: 707–11

Solomon T, Michael BD, Smith PE et al; National Encephalitis Guidelines Development and Stakeholder Groups (2012) Management of suspected viral encephalitis in adults--Association of British Neurologists and British Infection Association National Guidelines. *J Infect* **64**: 347–73

Whitley RJ, Alford CA, Hirsch MS et al (1986) Vidarabine versus acyclovir therapy in herpes simplex encephalitis. *N Engl J Med* **314**: 144–9

KEY POINTS

- Encephalitis is defined as inflammation of the brain parenchyma, which may be infectious, para-infectious or non-infectious. Herpes simplex encephalitis is the commonest cause in the UK.
- A lumbar puncture is crucial in the diagnosis of encephalitis, and ideally should be performed within 6 hours of presentation, provided there are no contraindications.
- Magnetic resonance imaging is the preferred imaging modality in suspected encephalitis and should be performed within 48 hours of hospital admission.
- Early administration of aciclovir is associated with improved survival in confirmed. Aciclovir should be continued for 14–21 days, and successful treatment confirmed by a negative CSF herpes simplex virus polymerase chain reaction.
- Specialist advice should be sought promptly, including remotely if local advice is not available.