The clinical approach to managing herpes simplex virus encephalitis

ABSTRACT

This article explains the approach to managing a patient with herpes simplex virus encephalitis. Acute encephalopathy is a common and often intimidating presentation in an acute general medical setting. Application of key principles will enable the generalist to take life-saving action before obtaining any specialist input. Viral infection is the most common cause (48.2%) of encephalitis; another large group is cases of autoimmune aetiology. Early diagnosis of encephalitis is crucial to ensure that the right treatment is given on time.

Guidelines on the management of viral encephalitis were published by the British Association of Neurologists and British Infection Association (Solomon et al, 2012), but adherence to these standards by clinicians has been found to be suboptimal (Han and Coebergh, 2017). This puts lives in danger, in the context of a treatable, serious, acute presentation. Although viral infection is the most common cause of encephalitis, an awareness of rarer forms of autoimmune encephalitis is necessary. The differential diagnosis of autoimmune encephalitis is important because the disease is potentially treatable with immunosuppressive agents. Paraneoplastic limbic encephalitis may present months or years before the detection of a tumour.

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Aetiology

A number of different viruses can cause acute encephalopathy, including herpes viruses, paramyxoviruses, enteroviruses and others. Herpes viruses include herpes simplex virus 1 and 2, varicella zoster virus, Epstein–Barr virus and cytomegalovirus. Herpes simplex virus encephalitis is the most commonly diagnosed viral encephalitis with an annual incidence of between 2 and 4 cases per million (Hjalmarsson et al, 2007). Among all of the forms of infective encephalitis, herpes simplex virus 1 and herpes simplex virus 2 are most predominant, accounting for 13.8% of hospitalizations and 21.8% of inpatient deaths in 2014 statistics from the USA (George et al, 2014). Enteroviruses include coxsackie viruses, echoviruses, enteroviruses 70 and 71, parechovirus and polioviruses. Other viruses are paramyxoviruses including measles and mumps, influenza viruses, adenovirus, parvovirus, and those which are arthropod borne such as Japanese encephalitis. Causes of chronic infection need to be excluded (*Table 1*).

Clinical features

Symptoms that should alert clinicians to the possibility of a patient having a viral encephalitis include a fever, headache, confusion, behavioural abnormalities, depressed level of consciousness, focal neurological deficits and new onset seizure activity.

Investigation

Investigations include a computed tomography scan of the brain, routine CSF analysis in addition to polymerase chain reaction assay for herpes simplex virus, varicella zoster virus, enteroviruses and parechoviruses. Further imaging should be arranged with magnetic resonance imaging of the brain. Electroencephalogram may also be diagnostic. In the immunocompromised patient CSF should also be tested for Epstein–Barr virus, cytomegalovirus, human herpes virus-6 and human herpes virus-7. Typical CSF findings include an increased number of white blood cells: 5–1000 x 10^6/litre (normal range <4 x 10^6/litre) (mainly lymphocytes). CSF and serum glucose ratio is

Table 1. Causes of infective encephalitis

Pathogen group		Pathogen
Viruses	Herpes viruses	Herpes simplex virus types 1 and 2, varicella zoster virus, Epstein–Barr virus, cytomegalovirus, human herpes virus 6/7
	Paramyxoviruses	Measles and mumps viruses
	Enteroviruses	Enteroviruses, poliovirus, parechoviruses coxsackieviruses, echoviruses
	Others	Influenza, viruses, adenoviruses, erythroviruses B19, rubella virus, choriomeningitis virus
	Zoonotic viruses	West Nile virus, Japanese encephalitis, dengue viruses, La Crosse virus, Western, Eastern and Venezuelan equine encephalitis viruses, chikungunya virus, Nipah virus, Chandipura virus, rabies, Colorado tick fever virus
Bacteria		*Mycoplasma pneumoniae*, Rickettsiae, Q fever (*Coxiella burnetii*), cat scratch fever (*Bartonella henselae*), Whipple's disease, brucellosis, listeria, syphilis
Parasites		African sleeping sickness (Trypanosoma), amoebic encephalitis, rat lung worm
Fungi		Histoplasmosis, coccidioidomycosis, North American blastomycosis

From Solomon et al (2012)

usually normal. CSF protein levels may be raised (0.5–1 g/litre; normal range >0.5 g/ litre). Herpes simplex virus polymerase chain reaction has a sensitivity of 75–85% and a specificity of 60–90% (Whitley et al, 1986). A moderate elevation in CSF opening pressure may be seen (>18 cmH_2O).

Management

Aciclovir 10 mg/kg three times a day should be commenced if there is a strong clinical suspicion of herpes simplex virus encephalitis, supportive radiology or CSF findings. In particular, it should be started on a presumptive basis if such diagnostic tests will cause delays of many hours (*Figure 1*). Treatment should be given for 2–3 weeks if herpes simplex virus encephalitis is proven by polymerase chain reaction, followed by repeat polymerase chain reaction to ensure eradication of the virus (Solomon et al, 2012). If the polymerase chain reaction result is positive aciclovir should be continued until the virus is eradicated from the CSF. As most cases of sporadic viral encephalitis are caused by herpes simplex virus, treatment until confirmation of eradication in CSF is good clinical practice supported by biopsy-proven randomized controlled trials, and it reduces mortality (Whitley et al, 1986).

Aciclovir should be stopped earlier if there is a definite alternative diagnosis, or viral encephalitis seems unlikely based on clinical, imaging and CSF findings. If other clinical features suggest herpes simplex virus encephalitis, but initial tests are not diagnostic, treatment should be continued as polymerase chain reaction may be negative in the first few days of the illness. Viral polymerase chain reaction testing of the CSF should be repeated as it may be positive 24–48 hours later. If this is negative in addition to a normal magnetic resonance scan of the brain, then aciclovir treatment may be stopped (Solomon et al, 2012) (*Table 2*). If polymerase chain reaction is negative 72 hours after symptom onset, and after 72 hours the patient has no features of encephalopathy, a normal magnetic resonance scan of the brain, and a white cell count <5 x 10^6/litre, then aciclovir may be stopped. The role of steroids in herpes simplex virus encephalitis is currently under evaluation in a multicentre randomized controlled trial. The *case study* overleaf outlines the diagnosis and management of a typical case of herpes simplex virus encephalitis.

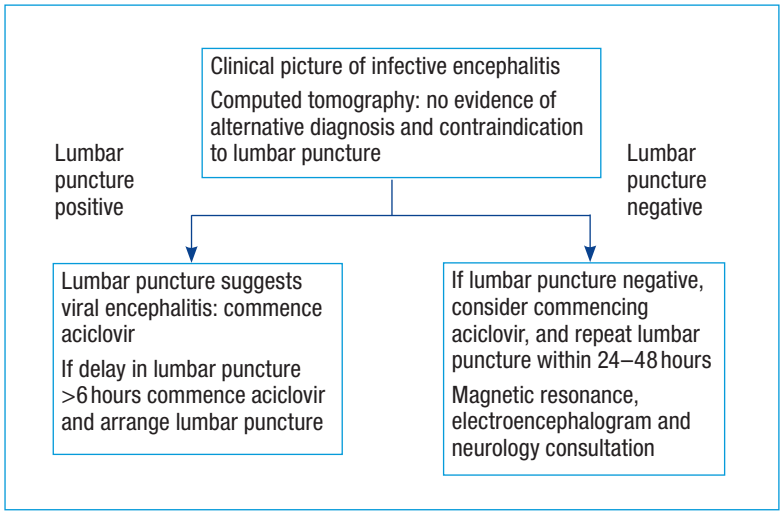

Figure 1. Tests for and treatment of suspected viral encephalitis in the acute window.

Table 2. When to stop aciclovir in the immunocompetent patient

Alternative diagnosis
Repeat polymerase chain reaction within 24–48 hours negative and negative magnetic resonance scan of the brain
Single polymerase chain reaction negative after 72 hours, and at 72 hours no features of ongoing encephalopathy and negative magnetic resonance scan of the brain

From Solomon et al (2012)

CASE STUDY

A 44-year-old woman presented with a 1-week history of worsening confusion, altered behaviour, recurrent vacant spells and generalized headache. On examination she had a raised temperature of 38°C and her Abbreviated Mental Test score was 4/10. Her fundi were normal. There were no signs of meningeal irritation, skin rashes and no focal neurology abnormality. Computed tomography of the head was normal. CSF showed a white cell count of 326x10^6/litre, >95% lymphocytes, protein = 2.71 g/litre, glucose in CSF = 3 mmol/litre, and paired CSF serum was not performed.

Polymerase chain reaction was positive for herpes simplex virus 1 DNA. Electroencephalogram showed non-specific slowing in keeping with a generalized encephalopathy, with no diagnostic features reflective of aetiology.

Magnetic resonance imaging showed features suggestive of herpes simplex encephalitis with bilateral mesial temporal lobe hyperintensity (greater right than left), with asymmetric swelling, diffusion restriction and patchy enhancement seen (*Figure 2*).

Aciclovir 10 mg/kg was commenced and continued for 2 weeks before repeat lumbar puncture which confirmed eradication of the herpes simplex 1 virus. She was commenced on levetiracetam for suspected subclinical seizures, and this antiepileptic was weaned down gradually on discharge.

On follow up 3 months after discharge she reported some problems with her short-term memory. Otherwise, there were no deficits in the domains of cognition, language, spatial orientation or praxis. She has returned to her normal work.

Prognosis

The mortality of patients with untreated herpes simplex virus encephalitis is 70% (Whitley et al, 1977). However, the 6-month mortality of treated patients in randomized controlled trials was 20%, and minor or no neurological sequelae were seen in between 37.5 and 55.5% of treated patients (Sköldenberg et al, 1984). In other multicentre studies, severe disability has been found in 13% of treated patients (Raschilas et al, 2002).

Differential diagnosis

It is important to consider other treatable causes of acute encephalopathy. Many of these are of an inflammatory aetiology and are distinguished primarily by their more subacute onset. Nonetheless there may considerable overlap clinically. These include acute disseminated encephalomyelitis, voltage-gated potassium channel related encephalitis, N-methyl-D-aspartate (NMDA) receptor-associated encephalitis, and anti-AMPA (GluR1/2), anti-GABA(b), anti-GAD, anti-glycine and anti-thyroid peroxidase antibodies. Encephalitis specific to malignancy may also be seen secondary to anti Hu (small cell lung cancer), anti Ma2 (testicular tumours), anti CV2/CRMP5 (thymoma, small cell lung cancer), anti Ri (small cell lung cancer, breast cancer) or anti amphiphysin (small cell lung cancer).

Acute disseminated encephalomyelitis is a para-infectious or post-infectious autoimmune demyelinating disease of the CNS. It follows a monophasic course and is usually precipitated by a viral or bacterial infection or vaccination.

An autoimmune limbic encephalitis associated with antibodies to voltage-gated potassium channels may be considered. Hyponatraemia is a feature of encephalitis associated with anti-voltage-gated potassium channel complex antibodies and can be associated with a syndrome of inappropriate anti-diuretic hormone picture (Lai et al, 2010). Lung carcinoma, thymoma and haematological cancers were the malignancies seen most frequently in patients with voltage-gated potassium channel encephalitis (Paterson et al, 2014). Most cases do not have a tumour. The frequency of anti-voltage-gated potassium channel antibodies in patients with appropriate clinical syndromes without evidence of cancer is high: 90% (Plantone et al, 2016).

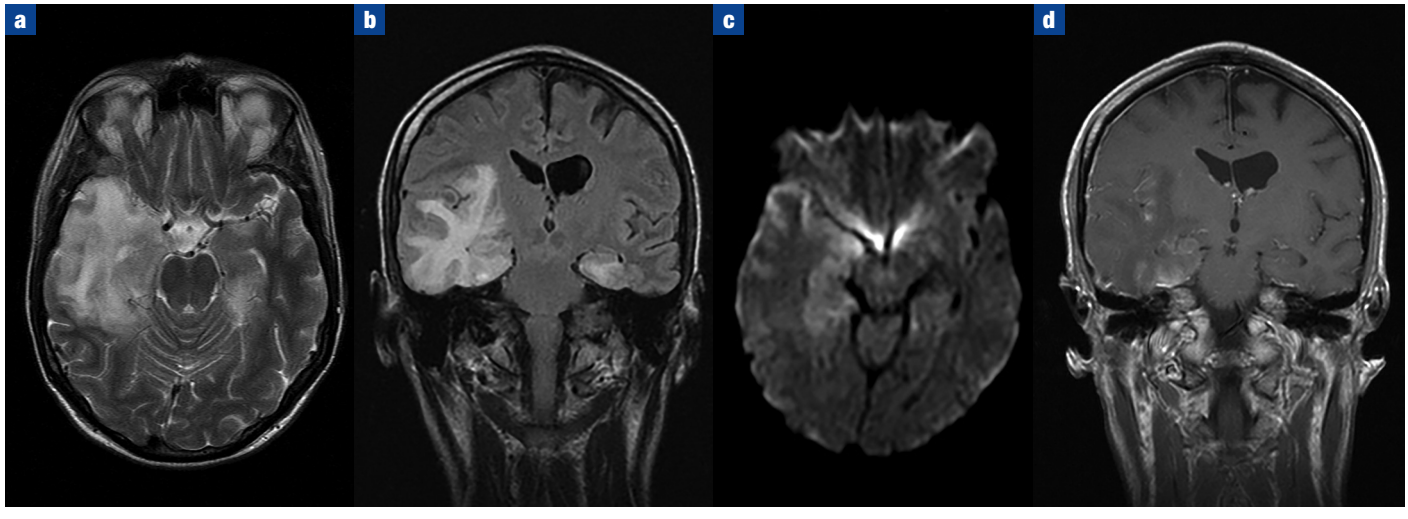

Figure 2. **a.** Axial T2: T2 hyperintense change with swelling in the right temporal lobe. A lesser degree of involvement is seen on the left side. **b.** Coronal flair: bilateral T2 hyperintensities extending into the mesial temporal lobes. Mass effect is seen in the right frontal and temporal lobes with partial effacement of the right lateral ventricle and midline shift towards the left. **c.** Diffusion weighted imaging: cortical areas of restricted diffusion in the anterior and medical temporal lobe. **d.** Coronal T1 post-gadolinium: patchy enhancement identified in the medial and anterior inferior temporal lobe and also within the insula.

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N-methyl-D-aspartate (NMDA) receptor-associated encephalitis is a cause of subacute encephalitis. It is strongly associated with ovarian teratoma, found in 56% of women >18 years of age presenting with this form of encephalitis (Dalmau et al, 2008). Other tumours are uncommon, including Hodgkin's lymphoma and neuroblastoma. Overall there is a 75% recovery rate (Dalmau et al, 2011). The risk of relapse is 12% within 2 years (Titulaer et al, 2013).

Other causes of non-paraneoplastic autoimmune limbic encephalitis (directed against cell surface antigens, may respond to immunomodulation) include anti-AMPA (GluR1/2), anti-GABA(b), anti-GAD, anti-glycine and anti-thyroid peroxidase antibodies.

Paraneoplastic neuronal antibodies directed against intracellular antigens may cause encephalitis, and are usually unresponsive to immune modulation. Examples include anti Hu (small cell lung cancer), anti Ma2 (testicular tumours), anti CV2/CRMP5 (thymoma, small cell lung cancer), anti Ri (small cell lung cancer, breast cancer) and anti amphiphysin (small cell lung cancer).

Other cases of acute or subacute encephalopathy can have a systemic, non-primary neurological cause, which are beyond the scope of this article. Examples include secondary metabolic disorders such as uraemia, hepatic failure, hypothyroidism, nutritional deficiencies causing low levels of vitamin B_{12} and folate, drugs and toxins including alcohol, Wernicke–Korsakoff syndrome, and further infective aetiologies including HIV and syphilis.

Conclusions

Early diagnosis of encephalitis is crucial to ensure that the right treatment is given on time. The key features of history and examination can be used quickly and effectively to identify a strong suspicion of either infective or autoimmune aetiology. Following supportive investigation, antimicrobial or anti-inflammatory treatment can massively decrease mortality and morbidity. Encephalitis is a fascinating and important topic for any clinician working in acute medicine. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Symptoms that should alert clinicians to the possibility of a patient having a viral encephalitis include a fever, headache, confusion, behavioural abnormalities, depressed level of consciousness, focal neurological deficits and new onset seizure activity.
- Aciclovir 10 mg/kg three times a day should be commenced before tests if there is clinical suspicion of herpes simplex encephalitis.
- If CSF is positive for herpes simplex virus, aciclovir should not be stopped until a 14–21-day course has been given, and it has been proved to be eradicated from the CSF.
- If the presentation is subacute, consider the possibility of the patient having autoimmune encephalitis.

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