

PRACTICE

EASILY MISSED?

Herpes simplex encephalitis

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This is one of a series of occasional articles highlighting conditions that may be more common than many doctors realise or may be missed at first presentation. The series advisers are Anthony Harnden, university lecturer in general practice, Department of Primary Health Care, University of Oxford, and Richard Lehman, general practitioner, Banbury. To suggest a topic for this series, please email us at easilymissed@bmj.com

The wife of a previously healthy 40 year old man requested a domiciliary visit from their general practitioner for her husband, who had been in bed for a few days with “bad flu,” fever, and headache. She was worried that he was becoming quite confused and unable to recall recent events. The GP finds the patient is febrile, agitated, and disoriented in time and place. Concerned about encephalitis, he sends the patient immediately to hospital. There a CT scan shows an area of decreased attenuation in the right temporal lobe and a lumbar puncture a raised lymphocyte count, both suggesting herpes simplex encephalitis. Aciclovir treatment is immediately started.

What is herpes simplex encephalitis?

Herpes simplex encephalitis is a severe viral infection of the central nervous system that is usually localised to the temporal and frontal lobes in adults. Typically, it causes a flu-like illness with headache and fever followed by seizures, cognitive impairment, behavioural changes, and focal neurological signs, but its presentation is variable.

Why is it missed?

The clinical presentations of herpes simplex encephalitis are varied. The viral prodrome may be absent, and the cognitive impairment may be subtle. Focal neurological features can be mistaken for stroke, seizures for primary epilepsy, cognitive impairment for non-specific delirium, and behavioural changes for a primary psychiatric disorder. Clinicians may be reluctant to perform invasive testing unless viral encephalitis is strongly suspected. A recent analysis of 16 cases presenting between 1993 and 2005 showed that there were often substantial delays

in performing examinations of cerebrospinal fluid.⁵ Even when investigations are performed early in the course of the disease, results may be misleadingly negative: cerebrospinal fluid cell count is normal in 5–10% of patients, particularly in children; computed tomography results are normal in the first week of illness in up to a third of patients; magnetic resonance images are normal in 10%; and detection of viral DNA by the polymerase chain reaction can be negative initially.^{6, 3}

Why does this matter?

Herpes simplex encephalitis is uncommon but has high mortality and morbidity if treatment with aciclovir is not given or delayed. Aciclovir inhibits viral replication and prevents extension of the disease within the brain, thereby reducing mortality from more than 70% in untreated patients to 19%.⁴ The most common result of delayed treatment is neuropsychological impairment, with amnesia because of selective involvement of the limbic system.

In the well known case of the celebrated pianist and conductor Clive Wearing, diagnosis was delayed for five days, and he survived with permanent and profound anterograde amnesia.⁷ Several costly medicolegal claims have resulted from similar delays in diagnosis.⁵

How is herpes simplex encephalitis diagnosed?

Clinical features

There is usually a prodrome of malaise, fever (90%), headache (81%), and nausea and vomiting (46%) lasting for a few days, consistent with a viral infection.⁸ On this background, features raising suspicion of encephalitis include the concurrent onset of⁸:

- Progressive alterations of behaviour (71%)
- Features suggestive of focal epilepsy (67%), such as olfactory hallucinations or periods of altered awareness

How common is herpes simplex encephalitis?

- Herpes simplex was the most commonly identified cause of infectious encephalitis in a large prospective UK study¹
- It accounts for 5–10% of all cases of encephalitis worldwide²
- The annual incidence of herpes simplex encephalitis is 0.2–0.4/100 000 in the general population³
- It affects either sex, with no seasonal variation¹
- It affects all age groups but is most common and severe in children and elderly people.⁴ About 33% of patients are aged less than 20 years, and 50% are over 50 years at presentation
- Of the two types of herpes simplex virus (HSV-1 and HSV-2), HSV-1 encephalitis is more common in adults, and HSV-2 infection is more common in neonates⁵
- Other herpes viruses that cause encephalitis include varicella zoster virus, Epstein-Barr virus, cytomegalovirus, and human herpes viruses 6 and 7

- Focal neurological signs (33%), such as unilateral weakness
- Cognitive problems (24%), such as difficulty in word finding, memory impairment, or confusion.

Investigations

If herpes simplex encephalitis is suspected, brain imaging (magnetic resonance imaging if possible, otherwise computed tomography) and cerebrospinal fluid analysis (if lumbar puncture is not contraindicated, such as by mass effect or coagulopathy) should be performed urgently.³ Magnetic resonance imaging is the imaging modality of choice, and is abnormal in 90% of patients (figure 1).² Brain imaging both helps to support the diagnosis of herpes simplex encephalitis and to exclude contraindications to lumbar puncture. It typically shows unilateral or asymmetric bilateral high signal in the medial temporal lobes, insular cortex, and orbital surface of the frontal lobes (best seen with fluid attenuated inversion recovery (FLAIR) and diffusion weighted imaging (DWI)). These changes are not specific for herpes simplex. The differential diagnosis includes other causes of limbic encephalitis (such as paraneoplastic or autoimmune limbic encephalitis),⁹ gliomatosis cerebri (a rare primary brain tumour), middle cerebral artery ischaemia, and possibly the effects of status epilepticus.

The cerebrospinal fluid typically shows a raised lymphocyte count (10–500×10⁶/L, average 100×10⁶/L), sometimes with red blood cells with or without xanthochromia, reflecting the haemorrhagic nature of the encephalitis, mildly raised protein levels, and normal or mildly decreased glucose. Definitive diagnosis of herpes simplex encephalitis is made by the detection of viral nucleic acid in the cerebrospinal fluid by the polymerase chain reaction. This test has a sensitivity of 96–98% and specificity of 95–99% and has removed the need for brain biopsy.² It remains positive for at least five to seven days after starting antiviral therapy.⁶ Viral DNA may be undetectable in early disease, but, if so, a repeat examination by polymerase chain reaction on cerebrospinal fluid three to seven days later can clinch the diagnosis.²

Electroencephalography has a high sensitivity (84%) but low specificity (32%) for the diagnosis of herpes simplex encephalitis.⁹ However, it can be helpful in identifying non-convulsive seizure activity, which will benefit from anticonvulsant treatment.

How is herpes simplex encephalitis managed?

Pending the confirmation of the diagnosis of herpes simplex encephalitis, all adults with suspected encephalitis should be given aciclovir empirically, at a dose of 10 mg/kg, administered as intravenous infusions over one hour and repeated every eight hours for 14–21 days if renal function is normal.^{2,3} Higher doses are recommended for immunocompromised patients. If bacterial meningitis is considered a possibility, appropriate antibacterial therapy should also be given.² Should seizures occur, they are treated with anticonvulsants along standard lines. Raised intracranial pressure will occasionally require treatment. The role of adjunctive corticosteroids is not yet established.

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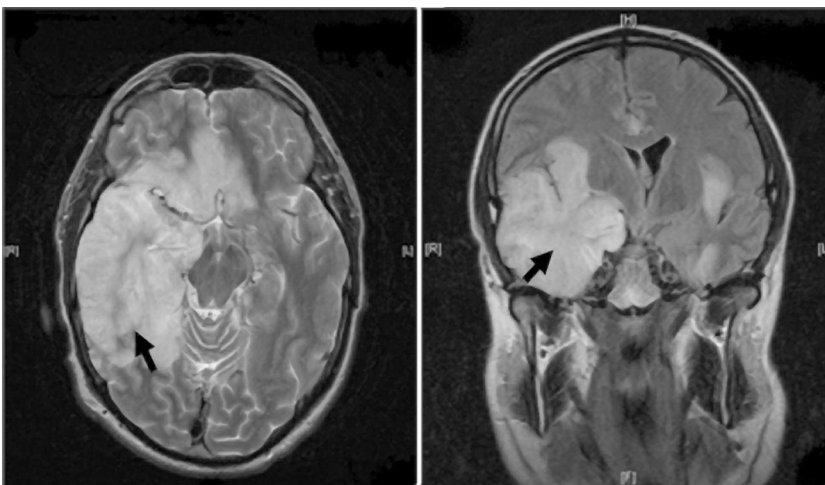
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Key points

- Herpes simplex encephalitis is highly treatable, but can cause death or severe neuropsychological impairment if untreated
- The diagnosis is suggested by acute or subacute onset of
 - Alterations of behaviour
 - Focal or generalised seizures
 - Focal neurological signs
 - Cognitive difficulties
 - Usually on a background of fever and headache
- If it is suspected perform urgent brain imaging (preferably magnetic resonance imaging) and cerebrospinal fluid analysis for microscopy and DNA testing (if lumbar puncture is not contraindicated), bearing in mind that these may be normal early in the course of the disease
- Start intravenous aciclovir immediately if the diagnosis is suspected

Figure

Axial and coronal T2 weighted magnetic resonance images showing areas of hyperintensity (arrowed) corresponding to oedematous changes in the temporal lobes and inferior frontal lobes with mass-like effect due to herpes simplex virus encephalitis. Reproduced with permission of Southampton General Hospital's picture library