Glioblastoma multiforme masquerading as herpes simplex encephalitis

Introduction

Herpes simplex virus type 1 is the most commonly recognized cause of encephalitis in the UK (Granerod et al, 2010). It produces an acute necrotizing encephalitis of the orbitofrontal and temporal lobes, often strikingly unilateral, sometimes also involving insular and cingulate cortices, with an overlying meningitis. Typically the presentation is acute with fever and headache, sometimes with behavioural changes which may progress to clouding of consciousness and coma, sometimes complicated by focal or secondarily generalized seizures. Atypical presentations are also recognized.

CSF polymerase chain reaction for herpes simplex virus is a highly sensitive and specific test for confirmation of the diagnosis, although false negatives may be encountered early (<48 hours) or late (>10 days) in the disease process (Larner et al, 2011). Guidelines for management of suspected herpes simplex encephalitis have recently been published (Solomon et al, 2012). Empirical treatment for suspected herpes simplex encephalitis is often undertaken, since the diagnosis is more often suspected than proved (Bell et al, 2009), with a variety of recognized mimics. This article reports a case in which the initial presentation of an intraparenchymal brain tumour masqueraded as herpes simplex encephalitis.

Discussion

The clinical presentation of herpes simplex encephalitis has been described as protean, including isolated memory impairment (Young et al, 1992). Guidelines on the management of suspected viral encephalitis emphasize the importance of finding herpes simplex virus DNA in the CSF by polymerase chain reaction, or intrathecal production of herpes simplex virus-specific antibodies, to confirm a diagnosis of herpes simplex encephalitis. Herpes simplex encephalitis cannot be diagnosed on neuroimaging findings alone (Solomon et al, 2012).

In a series of suspected herpes simplex encephalitis cases, other diagnoses considered in the initial differential included stroke, meningitis, subarachnoid haemorrhage and sinus thrombosis, but not CNS tumour, although one patient was eventually diagnosed with an anaplastic astrocytoma (Bell et al, 2009). Occasional cases of temporal lobe glioblastoma masquerading as herpes simplex encephalitis have been reported (Whitley et al, 1989; Rees and Howard, 1999; Nam et al, 2011).

Treatment with aciclovir is appropriate if herpes simplex encephalitis is suspected clinically since it reduces morbidity and mortality. However, because the clinical and radiological features of herpes simplex encephalitis and temporal lobe glioblastoma may overlap, the possibility of an underlying tumour must be kept in mind, and continuing investigation is required when no diagnosis has been proved. Initial

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Case Report

A previously healthy 48-year-old man complained of light-headedness, nausea and headache shortly after a bout of moderate exercise. Over the next 2 hours he complained of tingling in his left hand and foot, then developed slurring of speech, increasingly severe headache and appeared vacant and confused. On admission to his local district general hospital he was apyrexial. He had a witnessed tonic-clonic seizure and was intubated. Collateral history indicated no drug use or family history of neurological disorder.

Initial brain imaging with computed tomography showed a swollen right temporal lobe with mass effect but no enhancement. Magnetic resonance brain imaging confirmed oedematous change confined to the right anterior and medial temporal lobes, appearances felt to be in keeping with herpes simplex encephalitis (*Figure 1a*). Neither diffusion-weighted magnetic resonance brain imaging nor electroencephalography was locally available. Basic CSF analysis (cell count, glucose; protein not recorded) was unremarkable. A diagnosis of herpes simplex encephalitis was suspected on the basis of the clinical history and neuroimaging findings. Antiviral treatment with intravenous aciclovir was started pending the result of CSF polymerase chain reaction for herpes simplex virus type 1, along with an antiepileptic drug in view of his witnessed seizure. Steroids were not administered since their place in the treatment of herpes simplex encephalitis remains uncertain (Kamei et al, 2005).

The patient improved rapidly and was deemed back to normal after 2 weeks of aciclovir (first week intravenous, second week oral). Because of the radiological appearance of brain swelling in a cognitively eloquent area, and the recognized cognitive sequelae of herpes simplex encephalitis (Utley et al, 1997; Noppeney et al, 2007), follow up was arranged in the local cognitive neurology clinic.

After 2 months, the patient reported no problems but his partner thought he was occasionally confused; no further seizures had occurred. On cognitive testing the patient scored 29/30 on the Mini-Mental State Examination (MMSE), but on the Mini-Mental Parkinson, a variant of the MMSE which has greater emphasis on testing of visuoperceptual function (Larner, 2012), he scored 27/32 with impairment on a test of visual recall. On the Montreal Cognitive Assessment, a more sensitive test of cognitive function, he scored 26/30 with impairment on the alternating trail test. The CSF polymerase chain reaction result was pursued and proved to have been negative.

Because of the subtle cognitive deficits, and the failure to confirm a diagnosis of herpes simplex encephalitis on CSF polymerase chain reaction, repeat magnetic resonance brain imaging was arranged (*Figure 1b*). This showed some resolution of the previous right temporal lobe swelling but revealed an underlying mass lesion, not evident on review of the original images. Subsequent stereotactic biopsy of the mass showed histological evidence of a glioblastoma multiforme.

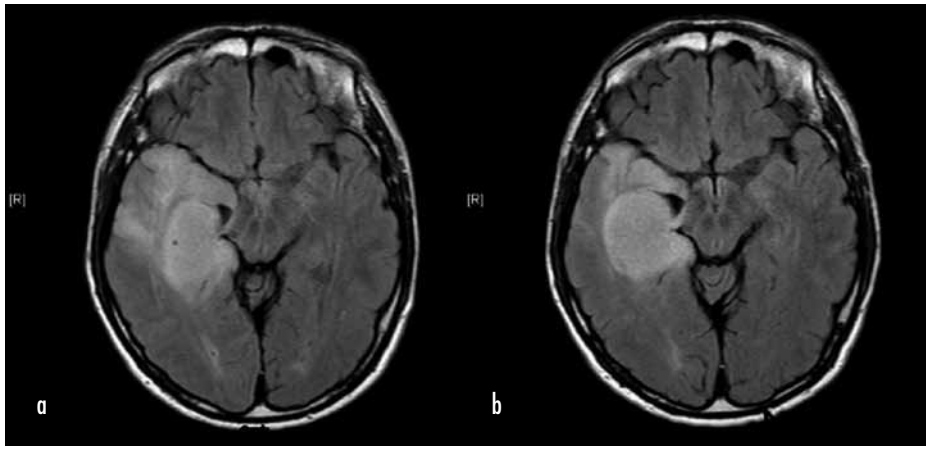

Figure 1. a. Acute imaging (T2 FLAIR) shows swelling and signal change in right anterior and medial temporal lobe. b. Three months later there is partial resolution of oedema and the underlying mass lesion is now evident.

clues to the non-herpes simplex encephalitis diagnosis in the current case included the apyrexia and normal CSF. Pyrexia is present in around 90% of herpes simplex encephalitis cases (Granerod et al, 2010), and although CSF pleocytosis may be absent in early cases of herpes simplex encephalitis this would be rare in a patient with widespread parenchymal involvement. As previously mentioned, false negative herpes simplex virus polymerase chain reaction is recognized to occur on occasion in herpes simplex encephalitis.

Repeat brain imaging to document the evolution of temporal lobe changes in suspected herpes simplex encephalitis has been advocated in order to ensure that space-occupying lesions which mimic herpes simplex encephalitis are not missed (Nam et al, 2011), a recommendation endorsed by the findings in the current case. Diffusion-weighted magnetic resonance imaging is another imaging modality which may be helpful in diagnosis of suspected herpes simplex encephalitis since changes occur early, sometimes when standard magnetic resonance imaging is normal (Küker et al, 2004).

Conclusions

CNS mass lesions including glioblastoma should be considered in the differential diagnosis of suspected herpes simplex encephalitis. Follow-up brain imaging should be considered in patients with suspected herpes simplex encephalitis, particularly if the diagnosis is not confirmed by typical CSF findings. BJHM

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LEARNING POINTS

- High-grade brain tumours, including glioblastome multiforme, may on occasion present acutely in a manner which mimics herpes simplex encephalitis.
- Serial brain imaging may be indicated in cases of suspected herpes simplex encephalitis if the diagnosis is not confirmed by typical CSF findings, even if clinical improvement has occurred following treatment with aciclovir.