Atypical herpes type 2 encephalitis associated with normal MRI imaging

N A Harrison, B K MacDonald, G Scott, R Kapoor

We describe a case of chronic atypical herpes simplex type 2 encephalitis in an immunocompromised 68 year old man presenting with headache and cognitive changes without focal neurological or MRI findings. To our knowledge this is the first described case of herpes simplex encephalitis associated with normal MRI brain imaging and non-focal neurological examination. This further expands the range of clinical presentations that may be associated with herpes simplex encephalitis and emphasises the value of PCR for herpes simplex virus in the investigation of encephalitis regardless of imaging findings.

Herpes simplex encephalitis is one of the most severe viral infections of the brain. Estimates of annual incidence vary but are in the order of 1.2 cases per million population per annum. The classical clinical presentation includes a syndrome of acute onset characterised by fever, headache, altered mentation, focal neurological signs, and seizures. Untreated, it is associated with mortality in excess of 70%.[2] Since DNA amplification has superseded brain biopsy as the diagnostic investigation of choice, many milder and more chronic forms have been reported in the literature and the spectrum of central nervous system disease broadened. We describe a case of atypical herpes simplex encephalitis in a 68 year old man with a particularly chronic course associated at presentation with a non-focal neurological examination and normal MRI imaging. To our knowledge this is the first described case of herpes simplex encephalitis presenting non-specifically and without abnormalities on MRI imaging. We believe that this further expands the range of clinical presentations associated with herpes simplex encephalitis.

A 68 year old businessman presented to his general practitioner with a three day history of frontal and vertex headache that had developed over a few hours. There were no meningitic symptoms. He was admitted to another hospital where neurological examination and MRI brain scan were recorded as normal. His symptoms resolved spontaneously and he was discharged after three days without diagnosis. A week later he re-presented to his general practitioner following a fall complaining of unsteadiness and worsening memory loss and was admitted to our hospital. On admission he was alert and orientated with normal speech. Apart from mild ataxia on heel/toe walking, neurological examination was unremarkable. General medical examination revealed hepatomegaly secondary to known B cell chronic lymphocytic leukaemia (CLL) diagnosed 12 years previously when a localised melanoma was excised. There were no oral or genital herpetic skin lesions. Other past medical history included atrial fibrillation and restrictive cardiomyopathy.

Blood film showed 141.8 x 10^9/l white cells (88% lymphocytes) with frequent smear cells. Erythrocyte and platelet counts were normal. Electrolytes, liver, bone, and thyroid function tests were normal. MRI brain showed only minor atrophic changes (fig 1).

Electroencephalogram showed widespread theta activity with intermittent excesses of 2–3 Hz slow activity suggestive of a moderately severe encephalopathy. Cerebrospinal fluid (CSF) contained 540 leucocytes/µl (>90% lymphocytes) a raised protein of 1.58g and a reduced CSF:serum glucose ratio 2.1:5.9 (36%) (table 1, day 0). Neuropsychometry revealed mild intellectual underfunctioning on tests of sustained attention and concentration, impairment of memory functions, and evidence of visual perceptual and frontal executive difficulties indicative of mild widespread cognitive dysfunction. Extensive investigation for infective agents including serology for borrellosis, brucellosis, mycoplasma, cryptococcus, chlamydia, listeria,
and bartonella, and throat and rectal swabs for enterovirus were negative. Autoantibodies including anti-neuronal antibodies were negative.

In view of the above negative results, its non-focal presentation and the inflammatory CSF a differential diagnosis of tuberculous meningoencephalitis and leukoaeamic/lymphomatous infiltration was made and he was started on anti-tuberculous therapy and a reducing course of oral prednisolone. CSF lymphocyte subset analysis subsequently identified the cells as T cells positive for the markers CD3 and UCLH1. Herpes simplex virus encephalitis (HSVE) was initially considered unlikely in view of his non-focal presentation and normal MRI and DNA amplification for herpes simplex virus (HSV) was not performed. He was discharged after two weeks feeling generally better with stable findings on neurological examination.

Two weeks later he was readmitted complaining of worsening concentration, alertness, and memory loss. Neurological examination was unchanged. There was no clear evidence of intellectual decline. Repeat lumbar puncture showed an improved leucocyte count of 183 cells/µl (table 1, day 27). He was discharged continuing anti-tuberculous medication and a reducing course of oral steroids. CSF was sent for HSV specific DNA amplification. Isoelectric focussing of CSF and serum showed more bands in the CSF.

He was readmitted two days later following a positive PCR of recurrent HSV brain stem encephalitis with an upwards period.

Repeat CSF continued to show a high leucocyte count (153 cells/µl, day 69). PCR for HSV was repeated and was again positive and he was treated with a ten day course of oral aciclovir.

At reassessment one month later he continued to complain of residual balance and memory difficulties. Examination findings were considerably improved with minor gait ataxia and slight gaze evoked nystagmus bilaterally. EEG showed a near normal picture. CSF continued to show a high lymphocyte count (day 103), which were shown to be polyclonal.

The causative agent in our case was herpes simplex type 2, a relatively rare cause of encephalitis outside the neonatal period.

A number of studies from the UK, United States, and Sweden have looked at the relative incidence of HSE caused by type 1 and type 2 virus. Relative incidences for HSV type 2 range from 1.6% to 6.5%.

Although associated with a more aggressive course and worse outcome in neonates, it is unclear how virulent type-2 HSV is in adults. Our case demonstrates that persistent infection with a low-grade encephalopathy can occur in immunocompromised adults.

Our case was highly resistant to therapy and required prolonged oral therapy with valaciclovir before the CSF leukocytes resolved and PCR for HSV became negative. Although classical HSVE is effectively treated with a single ten-day course of aciclovir, atypical cases requiring repeat or prolonged treatment courses are well described in the literature even in the absence of immunodeficiency.

<table>
<thead>
<tr>
<th>Table 1 Cerebrospinal fluid analysis</th>
<th>Protein g/l</th>
<th>White cells cells/µl</th>
<th>CSF:serum glucose ratio</th>
<th>HSV-2 PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.58</td>
<td>540</td>
<td>0.36</td>
<td>Not tested</td>
</tr>
<tr>
<td>27</td>
<td>1.73</td>
<td>183</td>
<td>0.45 +</td>
<td>+</td>
</tr>
<tr>
<td>69</td>
<td>1.24</td>
<td>153</td>
<td>0.59 +</td>
<td>+</td>
</tr>
<tr>
<td>103</td>
<td>1.25</td>
<td>240</td>
<td>0.38 +</td>
<td></td>
</tr>
<tr>
<td>195</td>
<td>1.26</td>
<td>&lt;1</td>
<td>0.82 +</td>
<td>+</td>
</tr>
<tr>
<td>228</td>
<td>1.05</td>
<td>&lt;1</td>
<td>0.57 –</td>
<td>–</td>
</tr>
<tr>
<td>456</td>
<td>3.1</td>
<td>200</td>
<td>0.69 +</td>
<td>+</td>
</tr>
<tr>
<td>510</td>
<td>1.0</td>
<td>15</td>
<td>0.71 –</td>
<td>–</td>
</tr>
</tbody>
</table>

with valaciclovir was stopped. Seven months later he re-presented with deterioration of his gait and memory (day 240). Repeat CSF examination revealed that PCR for HSV was once again positive, and that the CSF was again active (200 leucocytes/µl –day 456). Valaciclovir was restarted, on day 510 the CSF leucocyte count had fallen to 15/µl and the HSV PCR was once again negative. At the last follow up his gait and cognitive abilities were stable.

**DISCUSSION**

The classical clinical syndrome of HSVE has been defined almost exclusively on the basis of clinical and laboratory features of patients diagnosed by brain biopsy or autopsy. Enrolment in clinical trials of aciclovir required that patients had: an acute febrile encephalopathy with disordered mentation, focal cerebral signs, evidence of localisation by diagnostic procedures, and CSF findings compatible with viral infection. This inevitably led to case ascertainment bias and the under recognition of atypical or mild cases. Atypical cases have long been recognised, especially in immunocompromised patients, since the introduction of HSV PCR for diagnosis of HSVE the number of case reports and spectrum of clinical presentations described in the literature has increased. A recent study identified 17% of PCR diagnosed HSVE as atypical or having mild disease, defined as PCR proven HSVE in the absence of focal neurological findings and a slow progression in the absence of antiviral therapy.

Our case is unusual in three aspects. Clinical examination revealed no focal abnormalities until late in the disease course when cerebellar signs consistent with a rhombencephalitis became prominent. Brain MRI scans at presentation and late in the course of the encephalopathy were unremarkable. All previously described cases of HSVE in the literature with this picture have been associated with an abnormal MRI brain if one was performed. The typical MRI abnormalities reported are high T2 signal intensities in the temporal and frontal regions due to underlying oedema. Tyler et al described a case of recurrent HSV brain stem encephalitis with an upwards gaze palsy, facial numbness, and prominent cerebellar signs which was associated with a normal MRI brain scan. However, we believe that the prominent cognitive features in our patient associated with widespread marked EEG changes suggest a more diffuse encephalitis than that described by Tyler where EEG and mental status were reported as normal.

In patients with AIDS the virus does not appear to have the same predilection for the temporal lobes and imaging findings are more diffuse. One case reported mild changes on MRI 72 hours after presentation though the coronal sections published clearly show high T2 signal in the cingu late gyrus and at the ninth day of illness the MRI was grossly abnormal. In their study of atypical HSVE, Fodor et al identified two cases due to HSV type 2, interestingly both patients had normal CT scans but unfortunately did not have MRI scanning.

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patients with AIDS, the resistance to therapy is due to the development of thymidine kinase negative mutants. The majority of cases however, such as ours, appear to be due to other mechanisms with the infection finally being cleared with prolonged courses of aciclovir based therapies.

CONCLUSIONS
Herpes simplex encephalitis should be considered in all cases of encephalopathy even in the presence of a non-focal neurological examination and normal imaging studies. Treatment with aciclovir should be started promptly even if results of PCR for HSV are still pending. This extends the recommendations of Fodor et al. who recommended checking PCR in cases where examination was non-focal and CT negative. Therapy for atypical cases in immunocompromised hosts may need to be prolonged when as in this patient, the long term outcome may be good.

Authors' affiliations
N A Harrison, Psychiatry, Maidstone Hospital, Denmark Hill, London, UK
B K MacDonald, Neurology, Mayday Hospital, Croyden, Surrey, UK
G Scott, Microbiology, University College London Hospitals, UK
R Kapoor, Neurology, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

Competing interests: none declared

Correspondence to Dr Kapoor, Neurology, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK; r.kapoor@ion.ucl.ac.uk

REFERENCES

NEURONLINE
Telemicine Information Exchange: http://tie.telemed.org

Doctors often feel a bit threatened by the technobabble and management speak that can be associated with telemedicine. Happily these are absent from the Telemicine Information Exchange, which is run by the Telemedicine Research Center in Portland, Oregon. The site has a number of useful features including a searchable bibliography of 12 877 references on telemedicine (200 hits for “psychiatry”, 47 for “neurosurgery”, and a paltry 42 for “neurology”). A good proportion of these do not show up on Pubmed.

The rather cryptically named Telemed 101 section aims to be a beginner’s guide to starting a telemedicine service and contains some useful overviews of what telemedicine actually is. There is a list of established telemedicine programmes worldwide that, because it relies on self-notification, is probably incomplete.

The Meetings section allows you to see if the programme for that idyllic sounding meeting on the Ligurian coast in June can possibly justify your attendance. Other sections deal with legal aspects, equipment vendors, and jobs vacant—true a global marketplace. There are good links to the telemedicine journals, and to other telemedicine related sites. My personal favourite is the What’s New section, which provides twice monthly news updates from around the world and is an eclectic mix of cutting edge and gossip. And you can receive it free by email.

This is a well kept and regularly updated website with the human touch of Nancy Brown, librarian, enthusiast, and telemedicine pioneer. It provides as good an overview of telemedicine as you will get anywhere, and is well worth a look.

V Patterson
Royal Victoria Hospital
Belfast BT12 6BA, UK;
tele.neuro@royalhospitals.n-i.nhs.uk

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