

# Recurrent Herpes Simplex Encephalitis

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## Abstract

We describe a rare case of an immuno-competent patient who had been previously been treated for Herpes Simplex Encephalitis (HSE) and re-presented 5 years later with a recurrence of their HSE. Both clinical episodes were confirmed by a CSF Polymerase Chain Reaction (PCR) assay showing the presence of the Herpes Simplex Virus Type 1 (HSV - 1). While up to 26% of paediatric patients treated with acyclovir relapse, relapses in adults with PCR confirmation of HSV-1 in both original episode and the relapse are extremely rare.

## Key Words

Herpes Simplex Virus, Herpes Simplex Encephalitis, recurrence, relapse, latent

## Case presentation

In 2001, a 62-year-old previously well right-handed housewife was admitted with a one-week history of fever and diarrhoea with vomiting for one day.

Neurological examination revealed a Glasgow Coma Scale (GCS) of 14/15 with no neurological deficits. Soon after admission to the hospital she deteriorated and developed a left sided weakness.

CT scans were unremarkable, however MRI revealed high signal in both the temporal regions with white matter changes around the right lateral ventricle, occipital lobe, insulae and medial frontal lobe. (Figures 1 and 2). A SPECT scan showed increased perfusion in the right anterior/ medial and lateral temporal lobes with minimal reduction of the left side. CSF studies revealed lymphocytosis (65 cells / mm<sup>3</sup>), RBC's (235 cells / mm<sup>3</sup>) with normal glucose and protein.

CSF Polymerase chain reaction (PCR) analysis and type specific analysis were positive for HSV-1. She was successfully treated with Acyclovir 30mg / kg / day over a period of 10 days.

During her hospital stay she also developed temporal lobe seizures which was successfully managed with phenytoin 350 mg / day. At the time of her discharge she had made a good recovery with a GCS of 15 with a minimal left sided weakness associated with memory impairment, visual agnosia and cognitive impairment.

In 2006, five years after her original admission, she re-presented with fever, left sided hemiparesis and diarrhoea and vomiting. She had a GCS of 14 with no neck stiffness. There was a right sided conjugate deviation of the eyes and a left hemiparesis (MRC power Grade 2); reflexes were brisk with up going plantars bilaterally. She did not have papilloedema. She had no oral or genital lesions.

Her lymphocyte count, CD3 %, CD3 absolute numbers, CD4 %, CD4 absolute numbers, CD8 %, and CD8 absolute numbers were all within normal limits.

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CT scan of the brain showed low density lesion in the right temporal regions. MRI showed extensive high signal changes mainly in the right temporal lobe with mild signal change on the left temporal lobe suggestive of on going inflammation (Figures 3 & 4).

CSF studies revealed a lymphocytosis (52 cell / mm<sup>3</sup>), RBC's (26 cells / mm<sup>3</sup>) with normal glucose but a raised protein of 1.4 gms (0.12 – 0.6). CSF PCR analysis and type specific analysis confirmed the presence of HSV-1. (PCR was performed using the LightCycler system (Roche Molecular Biochemicals, Lewes, United Kingdom) as described by Read et al<sup>1</sup>).

The patient was treated with acyclovir 30 mg / kg / day for a period of 14 days and made a good recovery. However, at three years of follow-up, she has a mild residual left hemiparesis Grade 3-4 and she continues to have left sided visual neglect.

## Differential diagnosis

Encephalitis is an acute, often diffuse, inflammatory process affecting the brain. An infection by a virus is the most common cause of encephalitis, although other organisms may be responsible. An encephalitic illness can also be caused by alteration of normal immune function secondary to a previous viral infection or following vaccination (acute disseminated encephalomyelitis / ADEM). Infectious encephalitis may be difficult to distinguish from an encephalopathy associated with metabolic abnormalities.

## Herpes Simplex encephalitis

HSE is one of the commonest acute cause of viral encephalitis<sup>2</sup> with a bimodal age distribution. One third of cases occur in those less than 20 years of age and up to one half of cases occur in patients aged 50 years or more.<sup>3</sup> There is a peak incidence between 60-64 years of age accounting for nearly 37.5% of cases.<sup>4</sup> It is thought that the bimodal distribution of cases may be due to a primary HSV infection in the younger patients and a reactivation of a latent HSV in the older group.<sup>4</sup>

There are no specific signs or symptoms for HSE, but it is usually associated with an abrupt onset and a rapidly progressive clinical course over several days. Reported symptomatology include prodromal influenza like symptoms (48%), sudden onset of headache, confusion and altered consciousness (52%), meningism (65%), aphasia / mutism (46%), coma (35%), raised ICP (33%), focal neurological signs (89%), and seizures in 61% of cases.<sup>5</sup> Seizures are common and are usually complex partial with secondary generalisation.<sup>6</sup>



Figure 1: T1 coronal image (2001) – Subtle areas of low signal are seen in the subcortical region of the right temporal lobe.

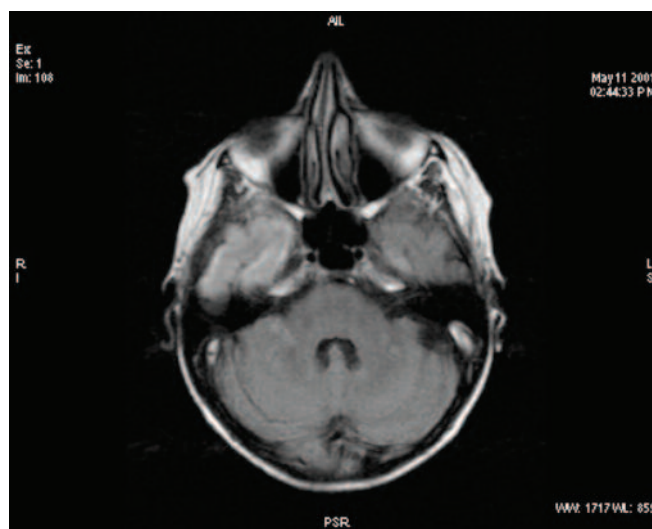


Figure 2: Axial FLAIR (2001) showing high signal in the right temporal lobe and a smaller area of high signal in the medial aspect of the left temporal lobe.

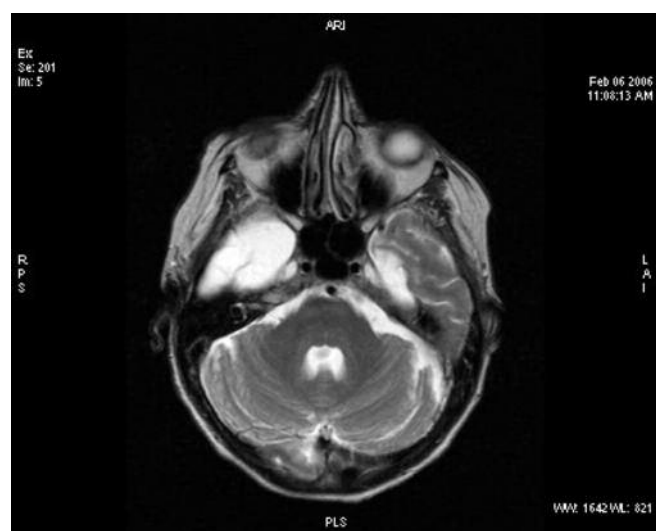


Figure 3: T2 Axial scan (2006) showing high signal in the right temporal region with high signal also in the medial aspect of the left temporal lobe.

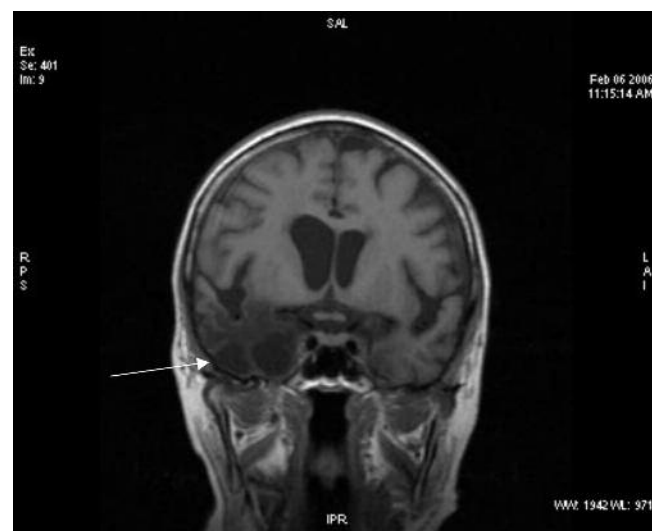


Figure 4: T1 coronal scan (2006) showing low signal in the right temporal lobe with a smaller area of low signal in the medial aspect of the left temporal lobe corresponding with the T2 scan. Asymmetrical enlargement of the right lateral ventricle has developed.

It has recently been recognised that about 20% of HSE cases may be relatively mild and atypical without the typical focal features.<sup>7</sup> Raised intracranial pressure may be evident but does not necessarily occur.

CT scans may be normal in the first five days<sup>8</sup> but later on a non contrast scan will show reduced attenuation in one or both temporal and/or frontal regions in 50% of patients.<sup>5</sup> MRI is the investigation of choice which typically shows focal oedema in the medial aspect of the temporal lobe, orbital surfaces of the frontal lobe, insular cortex and cingular gyrus.<sup>5</sup> SPECT (single photon emission computed tomography) may yield additional useful information in cases of viral encephalitis – temporal lobe hyperperfusion may be a marker of HSE.<sup>5</sup>

EEG is abnormal in almost all patients<sup>5</sup> showing either early non-specific slowing or later 'PLEDS' (periodic lateralising epileptiform discharges), although these are not themselves diagnostic of HSE.

CSF analysis typically shows a normal or raised pressure, lymphocytic pleocytosis (10-200 cells / mm<sup>3</sup>) normal glucose, raised protein (0.6-6 g / l). It is not uncommon to have red cells within the CSF (<500 cells / mm<sup>3</sup>). Absence of CSF lymphocytosis in a non immunocompromised patient should alert the physician to an alternative diagnosis.<sup>6</sup> PCR analysis of the CSF for HSE is virtually 100% specific with > 90% specificity.<sup>9</sup>

Atypical HSE has been described presenting with a febrile encephalopathy in the absence of focal neurological deficits / initial CSF lymphocytosis / abnormal CT.<sup>10</sup> These cases are usually associated with immunocompromised states or involvement of the non dominant temporal lobe.

Pathologically, HSE is an acute necrotising encephalitis with preferential involvement of the fronto-temporal, cingular and insular cortex.

In immuno-competent adults > 90% of cases of HSE are due to HSV-1 with the remainder due to HSV-2.<sup>7</sup> Over two thirds of de novo HSE due to HSV-1 are due to reactivation of latent virus.<sup>11</sup> In contrast cases of HSV-2 are probably primary infections.<sup>7</sup> An association between HSV-2 and AIDS has also been reported.<sup>12</sup>

Primary oropharyngeal HSV-1 infection results in axoplasmic movement of the virus to the trigeminal ganglion where it becomes latent.<sup>13</sup> The virus on reactivation normally has a retrograde transport with resultant herpes labialis. However on rare occasions this may get altered and the virus may spread via the temporal nerves to the anterior and medial cranial fossa.<sup>8</sup> Alternatively, an oropharyngeal infection could spread via the olfactory bulbs to the orbito-frontal and medial temporal lobes.<sup>2</sup> This is confirmed by typical MRI findings of a necrotising encephalitis involving the orbital surface of the frontal lobe and infero-medial temporal lobe with high T2 signal lesions.<sup>15</sup>

While some reports suggest that up to 5-26% of paediatric patients treated with acyclovir, relapse, relapses in adults with PCR confirmation of HSV-1 in both the original episode and the relapse is much rarer.<sup>16</sup>

A variety of mechanisms to explain the aetiology of the relapse have been put forward. One mechanism is the reactivation of the latent HSV. The HSV virus is known to lie dormant in neuronal cells and re-activation of the latent virus can occur following physical and emotional stress,

fever, and trauma. Our patient was febrile on both admissions. HSV DNA can be found in over a third of asymptomatic but sero positive patients at post mortem from diverse parts of the brain such as the olfactory bulbs, brain-stem, and gyrus rectus.<sup>13</sup> Reactivation of the latent virus resulting in encephalitis could explain the apparent involvement of the same anatomical areas of the brain as in the previous episode. The increased neurological symptoms and residual disability could be explained as a heightened immune response to the reactivation of the latent virus resulting in increased neurological damage. Neuro-radiology confirms an increased inflammatory response in the same anatomical region as the previous insult.<sup>17</sup>

A further mechanism could be a delayed pro-inflammatory immunological response in the CSF.<sup>3</sup> This is most likely the cause, especially if associated with a lack of demonstrable HSV DNA in the CSF associated with demyelination on neuroimaging. Dennett et al<sup>18</sup> reported five cases of apparent 'relapse' of HSE. PCR detection of the HSV was possible during the initial infection, but could be detected at the subsequent 'relapse'. There was no increase in intrathecal antibody synthesis during the second episode. Skoldenberg B et al<sup>19</sup> have also reported five episodes of 'relapse' in three patients, all except one of which occurred within the first four months of the initial episode. However, HSV DNA could not be demonstrated in any of the patients during the 'relapse'. This data suggests that the relapse may not have been due to active viral infection but a delayed immunological response

Another mechanism for the development of relapsing HSE could be of inadequate treatment at the time of the original infection with some debate on the dose of acyclovir and duration of course. Inadequate treatment could leave a latent organism in the CNS with an opportunity for the virus to re-activate itself at a later date. Van Landingham et al<sup>20</sup> reported a patient who relapsed four days after completing a 10-day course. Acyclovir is a synthetic purine analogue which selectively inhibits the HSV replication. Thus, a virus that is not in the viral replication cycle may survive especially when the patient is treated with a short (10-day) course of medication.

### Treatment

Antiviral therapy with acyclovir is the treatment of choice in HSV. Acyclovir selectively inhibits viral replication after being metabolised to acyclovir triphosphate. It has a relatively short half life in plasma with more than 80% of the drug being excreted via the urine (a fact which has a bearing on patients with renal problems). The standard adult dose of acyclovir is 30 mg/kg/day in divided doses for 14 days. However acyclovir is not without complications and can precipitate a toxic encephalopathy. Supportive therapy should include management of seizures, management of raised ICP and careful management of respiratory, cardiac functions

### Outcome

Mortality in untreated HSE is around 70% with less than 3% having a normal function following recovery.<sup>2,21</sup> Following acyclovir

treatment the survival improves to 81% with serious neurological deficits seen in nearly half the patients.<sup>21</sup> Persistent unilateral hyperperfusion in the cerebral SPECT scan is a poor prognostic marker.<sup>22</sup>

Neurological complications following HSE include cerebral infarction, cerebral venous thrombosis, and SIADH. Other complications include epilepsy, persistent anosmia, aphasia, and motor deficits.

### Conclusion

The case described here demonstrates the diagnostic dilemma of a patient presenting with an apparently 'relapsing' HSE. The ability to detect viral DNA suggested re-infection which may have potentially led to a more aggressive neurological clinical course secondary to an increased immune response.

Another possibility is that inadequate treatment following the first infection may have led to the virus developing latency for later re-activation. This can be avoided by demonstration of a negative PCR at the end of the initial course of treatment at first admission. Early management with antiviral and anti-inflammatory drugs may help in improving the clinical outcome in these patients by limiting the neurological deficit.

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