Abstract:
Viral encephalitis can be caused by many types of viruses. Herpes simplex virus (HSV) type 1 is a sporadic cause of viral encephalitis with high mortality and morbidity. Relapse of encephalitis can occur in up to 10 of patients, manifested by recurrence of clinical symptoms, associated with abnormalities on M.R.I. In addition HSV DNA can be detected in cerebrospinal fluid. We describe a patient with clinical features, M.R.I. findings and CSF PCR of HSV encephalitis, who recovered completely later, had a recurrence at which time also CSF PCR HSV 1 is positive persisting even after 6 months of the second episode.

Keyword: HSV encephalitis, relapse, CSF PCR positivity

Introduction:
Viral encephalitis is a relatively rare CNS infection. However, mortality and morbidity in patients with viral encephalitis are relatively high. Herpes simplex virus encephalitis (HSE) is the most commonly seen viral encephalitis. HSV-1 is the etiologic agent of 85–95% of cases of HSE, and HSV-2 is the etiologic agent of the remainder. Herpes simplex encephalitis is diagnosed in 2–3 out of every 1 million adults per year in developed countries. The actual incidence is almost certainly higher and probably closer to 5 cases per million adults per year. Fever is present in about 90% and headache in about 80% of patients with biopsy or polymerase chain reaction (PCR) assay–proven HSE. Other common features include disorientation (70%), personality change (70%-85%), focal or generalized seizures (40%-67%), memory disturbance (25%-45%) motor deficit (30%-40%), and aphasia (33%).

However, this presentation is common among many forms of infectious encephalitis. Brain MRI and EEG can be helpful in distinguishing HSE from other forms of encephalitis, but again these studies are only suggestive, not diagnostic. Characteristic findings on an MRI would be hyper intensities in the temporal lobes and the inferior frontal lobes. An EEG may show periodic lateralized epileptiform discharges (PLEDs), presence...
of which may favour the diagnosis but the absence of PLEDS does not rule out HSE. CSF PCR for herpes simplex virus (HSV) is 95% specific & when performed between 48 h and 10 days after the onset of symptoms, is 95% sensitive. The sensitivity drops rapidly before and after that window. The data from this review are similar to data presented in other reviews of the literature. Despite the high overall sensitivity of CSF HSV PCR, false-negative results have been reported, most notably in patients in whom CSF was obtained within the first 72 hours of illness onset. However, delays in presentation to the hospital and delays in recognizing the diagnosis often lead to a delay in initiation of therapy. Delaying the treatment leads to worse outcomes even if treated with a full course of appropriate antiviral agents. Based on the review of the literature, an appropriate treatment for HSE was acyclovir 10 mg/kg every 8 h for at least 14 days. Some authors recommended extending treatment to 21 days in patients who are immunocompromised. Recommendation to treat for 21 days is based on a study showing that 20% of patients had a positive PCR result after 14 days of treatment and another study showing that 8% of patients who received 10–14 days of treatment required a second course for a suspected relapse. It is also recommended to treat patients with mannitol or steroids if there is evidence of edema on CT or MRI. However, these are recommendations based on experience without scientific evidence. Mortality from HSE at a large medical center is about 15%. The majority of patients who survive HSE have permanent sequelae with only about 15% of patients making a full recovery. When treated quickly and appropriately, mortality and morbidity can be reduced significantly. Relapse of HSV encephalitis is rare in adults and only limited to a few case reports in childhood.

**Case vignette:**
Seven year old girl was admitted, following five day duration of fever, headache and vomiting without any history of seizure. Her birth and developmental history was normal. Past history of febrile seizures at age of 3 years was present. On examination she was found to have hepatosplenomegaly without focal neurological deficits. No seizures during hospital stay. CSF examination showed normal sugar and protein levels without cells but HSV IgM was positive. EEG showed right hemispherical epileptiform activity. Mantoux test was negative. MRI showed diffuse cortical swelling with obliteration of sulci and white matter edema over right temporo occipital region with gyriform enhancement on contrast administration. She was treated with parental acyclovir for 14 days, recovered completely. Her MRI taken one year later showed mild atrophic changes in the right parieto occipital region, suggestive of post encephalitic sequelae. Three years later she developed persistent headache for 15 days duration, not associated with fever. Neurological examination was normal and her brain MRI showed region of hyper intensity seen involving the right parietal occipital region in a linear manner in FLAIR images which enhanced with contrast. CSF studies showed normal protein, sugar without cells. CSF HSV -1 PCR is positive but HSV IgM was negative. Serum anti ds DNA was negative. She was treated with parental acyclovir for 3 weeks and symptoms subsided. Six months later her MRI and CSF analysis are repeated ,CSF showed HSV PCR positive ,IgM negative and with contrast enhancement in the same regions. But she is asymptomatic, with normal neuropsychological assessment for her age.
Discussion:
Relapses due to HSV encephalitis are rare and limited to a small number of cases reported in the literature. Persistence of HSV, detection of high viral load or detection of HSV by polymerase chain reaction, prior corticosteroid therapy, low total dosage of acyclovir (especially for children under 2 years of age) and short duration of therapy increases risk of relapse. The mechanism of the relapse is not exactly clear, but detection of viral DNA and persistent immuno histo chemical activity of HSV type 1 in the brain suggest persistence of HSV replication following the recovery from encephalitis. The most commonly suspected mechanism of reactivation of HSV in relapsing HSV encephalitis is supported by recurrence of attack within 2-4 weeks after treatment. In our patient relapse occurred after 3 years of initial episode and has persistence of CSF HSV PCR positivity even after 6 month of recovery. In relapsing cases, there is clinical deterioration, neuropsychological deficits, expansion of the lesions in MRI. However these were not observed in our patient who was neurologically normal. In children, there are reports describing progressive mental and behavioural deterioration for many years following herpes simplex encephalitis. Neuro pathological studies of these patients showed chronic active encephalitis, consisting of meningeal and perivascular infiltration of lymphocytes with severe gliosis and mineralisation. In those brain tissues, herpes simplex virus expression could not be detected by immune histo chemical methods, though specific viral DNA was demonstrated by PCR. These observations suggested that persistence of the virus after herpes simplex encephalitis may be associated with chronic inflammation, resulting in neurological problems in paediatric patients.

Presumptive cases of chronic HSV encephalitis have been described in children with remote clinical histories of acute HSV encephalitis who subsequently develop neurological disorders lasting for many years. When the brains of these patients were examined years after disease onset, they demonstrated tissue destruction, lymphocytic inflammation, and severe gliosis. PCR has detected HSV-1 DNA up to 12 and 17 years after encephalitis. However, since HSV DNA can also be found in normal human brains, detection of HSV DNA in these children does not prove persistent, productive viral infection. MRI study of HSV-1 encephalitis in infants aged 4 to 13 months demonstrated enhancing, thickened cortical lesions throughout all lobes of the cerebral hemispheres, as well as the insulae and thalami. Our patient had temporal, occipital and parietal lobe involvement on the right side. Mollaret in 1944 described, recurring aseptic meningitis episodes presenting with no identifiable infecting agent. In 1962, Bruyn et al outlined the criteria for diagnosis of Mollaret meningitis as follows: 1. Recurring episodes presenting with severe headache, meningismus and fever. 2. Pleocytosis in the CSF composed of endothelial cells, neutrophils and lymphocytes. 3. Development of episodes after symptom-free periods of weeks to months. 4. Spontaneous remission of symptoms and signs observed during the episodes. 5. Absence of a detectable etiological agent. Our patient did not have CSF pleocytosis and also had an etiological agent detected by positive CSF HSV PCR. In a study of CSF PCR testing for herpesvirus, Herpesvirus DNA was amplified in 86 of 1,387 (6.2%) CSF samples. These samples originated from 76 patients. Of the 76 patients, 66 showed clinical findings typically caused by the respective herpesvirus.
Though our patient had first episode suggestive of HSE, the second episode was manifested as headache but CSF PCR was positive for HSV indicating relapse.

**Conclusions:**

HSV PCR positivity has to be correlated with clinical features. Children with CSF HSV PCR positivity may be benefited with 3 weeks duration of acyclovir therapy to prevent relapse of infection.

**Fig 1 - First episode - T 1 sagittal**

**Fig 2 - First episode T 2 axial**

**Fig 3 - First episode - T2 flair coronal images showing hyperintensities in right parieto occipital region**

**Fig 4 - First episode - T1 contrast sagittal showing contrast enhancement in right parieto occipital region**

**Fig 5 - First episode - T 1 contrast coronal images showing enhancement in occipital region**

**Fig 6 - First episode - T 1 contrast axial images showing enhancement in parieto occipital region**
Fig 7 - one year after first episode - T1 sagittal images showing right occipital atrophy Fig 8 - one year after first episode - T2 Flair

Fig 9 - second episode - T2 axial images showing right occipital lobe atrophy

References:


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