CASE REPORT

# Herpes simplex encephalitis

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## Abstract

Herpes simplex encephalitis (HSE) is a condition that may follow herpes simplex virus (HSV) infection with high mortality and serious morbidity among survivors. We report the case of a 2-year-old boy who presented to us with features of a central nervous system infection associated with visual and auditory impairments. Serology for HSV was positive and cerebro-spinal fluid culture yielded the virus. He was commenced on intravenous acyclovir and eventually responded to treatment after 21 days of therapy. Neurological deficits observed at discharge resolved by the third month. This case highlights the challenges of early recognition, accurate diagnosis, appropriate treatment and follow-up of such patients. In addition, there is a need for urgent documentation of the prevalence and associated factors of HSE in Nigeria.

**Key words:** Acyclovir, children, herpes simplex encephalitis

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## Introduction

Herpes simplex encephalitis (HSE) is a life-threatening consequence of herpes simplex virus (HSV) of the central nervous system. Mortality rates reach 70% in the absence of treatment and only a minority of patient's return to normal function.[1,2] Effective antiviral therapy, however, significantly improves outcome.[3,4] Early diagnosis leading to prompt treatment can be a challenge due to its similarity in presentation to other central nervous system infections, atypical presentations as well as limited diagnostic facilities in resource-poor settings like ours. Thus, a high index of suspicion is required to prevent significant morbidity and mortality. We present this case to raise the awareness among health practitioners of the need to have a high index of suspicion for this potentially fatal but fortunately treatable condition.

## Case Report

A 2-year-old boy of social middle class was first seen in the children's emergency room of the Lagos University Teaching Hospital (LUTH), Lagos, Nigeria in September 2006 with complaints of focal seizures and low-grade fever of 1 week. Three days prior to presentation, he developed an unsteady gait with inability to see, hear or speak and had subsequently become extremely restless with abnormal body movements. He was referred to us from a private hospital where he had been treated for meningitis with intravenous ceftriaxone. Essential findings were impaired consciousness (Glasgow coma score of 11/15), extreme restlessness and no response to auditory or visual stimuli. There were no signs of meningeal irritation but tone was increased in all limbs. He had polymorphonuclear leucocytosis and normal serum electrolytes and urea levels. Cerebrospinal fluid (CSF) biochemistry was essentially normal but he had red blood cells in the CSF.

We made an initial assessment of complicated bacterial meningitis to rule out a viral encephalitis and commenced him on parenteral cefotaxime at 200 mg/kg/day. Oral carbamazepine and diazepam were administered to control the seizures and restlessness, respectively. Chlorpromazine was later added to his treatment when the diazepam did not effectively control his restlessness which subsequently resolved.

There was, however, a history of peri-oral blisters at the

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onset of his illness on account of which serology for HSV was done which yielded HSV-specific IgM. He was then commenced on intravenous (IV) acyclovir at 10 mg/kg/ doses every 8 hrs and had a total of 28 doses. Viral culture of the CSF grew HSV Type 1 while EEG revealed generalized slow waves compatible with HSV encephalitis. After the 28 doses of IV acyclovir, repeat HSV serology was still weakly positive for IgM so his acyclovir was converted to oral which he had for another 2 weeks.

He commenced physiotherapy while on admission and was co-managed with the ophthalmologists and ear, nose and throat surgeons on account of his visual and hearing impairments. Following discharge, he gradually regained sight and hearing and muscle tone improved. Three months after onset of illness, he was fully ambulant and is being followed up in the out-patient clinic.

## Discussion

HSE, the most important treatable viral encephalitis has an estimated incidence of about one case per million per year worldwide.[3] In this environment, the true incidence is unknown presumably as a result of inadequate diagnostic facilities and even when this is available, a low index of suspicion, both resulting in under-reporting. It is caused by primary HSV infection of the brain in one-third of cases while the rest are thought to be due to reactivation of a latent HSV infection or reinfection by a second HSV.[1,2]

The pathogenesis of HSE is poorly understood but it is known to have a predilection for the temporal and to a lesser extent parietal region of the brain. Brain involvement is diffuse and petechial hemorrhage and necrosis are distributed in an asymmetric fashion throughout the medial temporal and inferior frontal lobes.[1-3]

In a retrospective review of 20 patients with HSE, Wasay *et al*,[5] reported temporal lobe involvement in 60% of them on brain imaging. Fifty-five percent of the patients demonstrated both extratemporal and temporal pathology while 15% demonstrated extratemporal pathology exclusively. They therefore concluded that extratemporal involvement is not as uncommon as previously thought in patients with HSE. Only one patient was, however, in the pediatric age-group hence further studies in children are needed to verify this.

In concordance with the distribution of brain lesions, HSE is specifically associated with a constellation of frontotemporal features such as aphasia, personality changes and mutism as in our patient.[1-4,7] Progression is usually rapid resulting in death in 10-14 days if untreated.[2]

We were first alerted to the possibility of HSE in our patient by the history of cold sores which he had at about the time of onset of the illness. This is of particular interest as it conflicts with previous reports that such lesions have no relationship to HSE and are not relevant in making a diagnosis.[1,6] The significance of cold sores in patients with HSE may therefore remain yet to be determined. Clinical diagnosis may, however, be a challenge as symptoms may be mild or atypical.[6,7] In a recent report by Xavier *et al*,[7] the patient presented with only mild clinical symptoms and had a normal CSF but was IgM positive for HSV hence treatment was commenced early.

Presentations as only aphasia and apparent psychiatric syndromes have also been reported as posing a diagnostic challenge.[8,9] This underscores the need for a high index of suspicion for diagnosis especially in poor resource settings where much reliance may have to be placed on clinical parameters to initiate treatment. Some have even recommended commencement of treatment before obtaining laboratory results if HSE is suspected in view of the attendant morbidity and mortality.[6] The CSF analysis of this patient was normal but this is not unusual[6] as it was done early in the disease. Typically, however, it may show pleocytosis with lymphocytic predominance though polymorphonuclear predominance has been reported.[4,6] Neuroimaging study of choice is magnetic resonance imaging which typically shows areas of focal edema in the temporal lobes and orbital surface of the frontal lobes as well as the insular cortex and angular gyrus.[2,3,6] Computed tomography scan is also useful but may be normal early in the disease[3,6,7] while various EEG abnormalities have also been described.[1,2,6]

The gold standard for the diagnosis of HSE is DNA polymerase chain reaction of the CSF having a sensitivity of 94-98% and a specificity of 98-100%.[2,6,10] Viral culture which was positive in this patient is equally conclusive though reported as rarely positive.[2,10] Alternatively, confirmation may be made by a four-fold rise in serum or CSF antibody titer or by detection of viral antigen in the CSF or brain tissue[2,3,6,10]

Early administration of acyclovir, an effective antiviral agent, is the only parameter that can be modified to improve HSE diagnosis. This was the conclusion of a multicenter study by a group of French workers who found that a delay of more than 2 days initiation of therapy was associated with poor outcome.[3] There was, however, a delay of about 2 weeks before initiation of treatment in our patient yet outcome was excellent implying that other factors may play a role in response to treatment. Relapse following treatment has been described, the risk of which is inversely proportional to the duration of acyclovir therapy as observed by Hiroshi *et al*.[10]

Data about morbidity following HSE is provided in a 5-year follow-up study of 28 children in Israel.[6] Neurological

sequelae described include cognitive dysfunction, personality changes, speech abnormalities, motor skill disturbances and epileptic seizures all within the first year.

## Conclusion

HSE is a fatal but fortunately treatable condition. A high index of suspicion is a pre-requisite for early diagnosis and treatment. Further studies are needed in this environment to document its true burden and epidemiology. This will go a long way in formulating effective case management protocols.

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