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RESEARCH LETTER

Herpes simplex encephalitis: A Case series

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Abstract:
The prognosis of Herpes simplex encephalitis (HSE) depends on the early and appropriate administration of specific antiviral therapy. We retrospectively reviewed 42 children with acute CNS infection, over a period of 18 months, of which 4 were positive for HSV antibodies. All four showed CSF pleocytosis, with mildly elevated protein and rising titers of antibodies to HSV in the CSF. All the 4 cases were started on i.v. acyclovir on day 1 and continued for a total duration of 14 days. The patients responded well to the treatment and on follow up did not show any significant CNS morbidity. The point of presenting this case series is to emphasize the fact that HSE is very fatal encephalitis if left untreated. There are a very few viral encephalitis which have a definite treatment and HSE is one of them.

Keywords: Herpes *simplex encephalitis (HSE), Herpes simplex virus (HSV), Cerebrospinal fluid CSF*
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Introduction

Herpes simplex encephalitis (HSE) remains one of the most devastating infections of the central nervous system despite available antiviral therapy. Children and adolescents account for approximately one third of all the HSE. It is estimated to affect at least 1 in 500.000 individuals per year [1].

The majority of the cases of herpes encephalitis are caused by herpes simplex virus type 1(HSV-1). 90% of the individuals are infected with HSV-1, which is spread through droplets and casual contacts. 10% of the cases of herpes encephalitis are caused by HSV-2, which is spread through sexual contact.

HSV in older children and adults is caused by both primary and recurrent HSV infections. Two thirds of the cases are caused by virus reactivation. The route of access of the virus to the CNS in primary infections is under exploration. It has been documented to occur via the trigeminal nerve after tooth pulp inoculation, and by olfactory bulb involvement [2]. Such infectious path are consistent with the temporal and orbit frontal localization of the resulting encephalitis.

The exact path physiology of HSE encephalitis is unclear. It is characterized by intense meningitis and destructive changes in the brain parenchyma. Inflammation with accompanying necrosis and hemorrhage occur, often maximally involving frontal and temporal lobes. Temporal brain regions are most involved quantitatively in autopsy studies [3].

Case Reports

We retrospectively reviewed 42 cases of acute CNS infections, over a period of 18months in children above 1month of age. Clinically all the 42 cases presented with fever and convulsions. All the 42 cases had CSF pleocytosis, with mildly elevated proteins. The CSF was sent for HSV antibody titers on day 1. Four cases had positive HSV antibody titers more than 1:625. These 4 children were in the age ranging from 7 months to 15 yrs with male: female ratio being 1:1. Acyclovir was started on day1 in 27 of the 42 cases of acute CNS infection. It was stopped after retrieving the negative CSF reports for HSV antibodies. CT scan done in the 4 cases of proven HSE did not show any significant change (temporal enhancement). PCR for HSV could not be sent due to financial constraints. However a repeat CSF done on day 10 showed a significant fall in the cell count and protein levels. The CSF sent for HSV antibody titers also showed a significant fall.

Clinically all the four children improved, fever spikes reduced, convulsions stopped and there was improvement in their sensorium over a period of two weeks. The patients were discharged after 14 days of intra venous acyclovir. On follow up the children fared well. There was no significant CNS morbidity.

Discussion

HSE is an acute or sub acute illness that causes both general and focal signs of cerebral dysfunction. It is

sporadic and occurs without a seasonal pattern. Although the presence of fever, headache, behavioral changes, confusion, focal neurologic findings, and abnormal CSF findings are suggestive of HSE, no pathognomonic clinical findings reliably distinguish HSE from other neurologic disorders with similar presentations [4].

The CSF of patients with HSE usually exhibits a pleocytosis containing predominantly lymphocytes and moderately elevated protein levels. However samples drawn within the first few hours of the disease may be normal or reveal a predominance of polymorphonuclear cells [5,6]. In the present study, all the 42 cases showed CSF pleocytosis including the 4 cases which were positive for HSV antibody titres.

During the past 10 years, techniques based on the amplification of viral genomes by PCR have provided the most sensitive tools for the diagnosis of viral encephalitis. In our study, out of the 42 cases screened HSV PCR was negative for the 4 cases which showed rising antibody titres for HSV in CSF. Early negative HSV PCR results during HSE have been recorded repeatedly [5, 7]. However, the proportion of negative PCR results obtained in children is surprisingly higher than that observed in an adult population tested during the same period of time [5].

Negative results of HSV PCR could theoretically be due to a lack of sensitivity of the method. Another hypothesis is that HSV probably was in the brain and caused symptoms of encephalitis, although it was not in the CSF at the time of the first lumbar puncture. Experimental data have suggested that HSV may be absent from the CSF during the earliest phase of the disease [8]. The negative result from one CSF sample that contained mostly polymorphonuclear cells, which might indicate an early stage of the disease [6,8], supports this hypothesis.

In the present case series, neither initial biological nor radiological testing was suggestive of HSE. The CSF leukocyte count was elevated in all the 4 patients and contained predominantly polymorphonuclear cells. Whatever the mechanism that explains the negativity of PCR at onset of HSE in children, we want to draw attention to the fact that a careful interpretation of initial negative HSV PCR results is warranted in the context of clinical, EEG, and/or radiological features suggestive of encephalitis. In the pediatric setting, acyclovir is most often administered as soon as HSE is suspected. Antiviral therapy should not be interrupted solely on the basis of the results of PCR done on the CSF.

The biological diagnosis of HSE is confirmed by a delayed intrathecal synthesis of specific antibodies, because this synthesis is constant and represents the hallmark of a previous infection of the CNS by HSV [9]. This marker should be sought in all undiagnosed encephalitis cases. Several studies have shown that the prognosis of HSE is significantly improved by acyclovir treatment, provided that the delay between the onset of symptoms and the administration of the drug is brief. This is of particular importance in infants and children, in whom lesions of the developing brain due to HSV may have devastating consequences. HSV PCR is presently considered to be the reference standard for an early diagnosis of HSE.[10]

Conclusion

We want to insist on the possibility of negative biological data that may lead to the interruption of appropriate therapy. In these cases antiviral therapy should be administered as long as the diagnosis has not been excluded. The point of presenting this case series is to emphasize the fact that HSE is very fatal encephalitis if left untreated. There are a very few viral encephalitis which have a definite treatment and HSE is one of them.

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