Clinical Manifestations, Laboratory Findings and Outcomes of Children with Herpetic Encephalitis in Amirkola Children Hospital, Northern Iran

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Abstract

Background: Herpes simplex encephalitis (HSE) is a fatal infection of the central nervous system. The early diagnosis of HSE is crucial because the early introduction of antiviral therapy can significantly decrease mortality and morbidity associated with this disease. This study was carried out to determine the clinical manifestations, laboratory findings and the outcome of the children admitted due to a presumptive diagnosis of HSE to Amirkola Children Hospital; a referral hospital in the north of Iran, during 2006-2007.

Methods: This cross-sectional study was performed on patients with diagnosis of HSE in Amirkola Hospital, affiliated to the Babol University of Medical Sciences in the north of Iran. All of the children with a diagnosis of encephalitis were enrolled in this study. After admission, a special investigation including CSF analysis, electro-encephalogram (EEG), Computerized tomography (CT scan) and/or magnetic resonance imaging (MRI) were performed. PCR (Polymerase Chain Reaction) analysis for herpes virus DNA was done on CSF sample in all patients. All the patients with a clinical diagnosis of herpetic encephalitis were treated with acyclovir at the time of admission but every patient with a positive PCR was assumed as a definite diagnosis of HSE. Clinical manifestations, laboratory findings and outcome of patients were collected. At the end of the study, frequency of HSE was reported according to the PCR for HSV DNA among the children admitted due to encephalitis.

Results: The mean age of the patients was 5.58±3.46 years. The most common clinical manifestations were fever (70%), nausea, vomiting (54%) and headache (44%). Seizure was more common among girls, and was significantly more prevalent in younger patients. Abnormal EEG was presents in 42%, abnormal CT-scan in 38% and abnormal MRI in 48% of subjects. PCR was positive in 34% of our patients. All patients were discharged from the hospital after treatment with acyclovir.

Conclusion: Herpetic encephalitis should be considered in each patient admitted with sudden change in the level of consciousness in a previously healthy child with fever and antecedent viral infection.

Keywords: Herpes simplex; Encephalitis; PCR; Mortality; Children; Iran

Introduction

Herpes Simplex virus (HSV) is a sporadic and most important cause of encephalitis in the world. It is an uncommon but grave central nervous system infection in children, with high rate of morbidity and mortality.¹ HSV infection can be localized to skin, eye and mouth (SEM disease), involve the central nervous system (CNS) or manifest as disseminated infection involving multiple organs.²

Non-specific symptoms are cough, sore throat, fever, headache and abdominal complaints, which are followed by characteristic symptoms of progressive lethargy, behavioral changes and neurological deficits. Seizures are common at presentation. Children with encephalitis also may have a maculopapular rash and severe complications.³ Cerebrospinal fluid (CSF) should be submitted for polymerase chain reaction (PCR) detection of HSV DNA that can rapidly and
specifically diagnose HSE, and has been regarded as the best method for its detection. Special investigations included CSF analysis (cytology, biochemistry and serology), electroencephalogram (EEG), computed tomography (CT-scan) and magnetic resonance imaging (MRI). Virus can be cultured from the CSF in 25-40% of all cases. When the brain is involved, pleocytosis (50-700 WBC/mm³ that are predominantly mononuclear) and proteinosis and elevated pressure of the CSF, are generally present. Also some patients with CNS infection have no CSF abnormalities. Cutaneous vesicles are absent at presentation in about 40% of cases. Some specimens contain RBCs.

Patients with suspected HSV infection should be treated with IV acyclovir. Brain biopsy may be necessary for definitive diagnosis of the cause of encephalitis. The aim of this study was to assess the clinical manifestations, laboratory findings and outcomes of the treatment in children admitted due to encephalitis to Amirkola Children Hospital; a referral hospital in the north of Iran.

**Materials and Methods**

This cross-sectional study was performed on 50 patients with primary diagnosis of herpetic encephalitis who were hospitalized during 2006-2007 in Amirkola Children Hospital; a referral hospital in the north of Iran.

A detailed history was taken and a complete physical examination was done. Clinical diagnosis of herpetic encephalitis is based on symptoms such as fever, headache, nausea, vomiting, seizure, lethargy and acute altered consciousness without any other possible etiology in a febrile child. Additionally, CT-Scan or MRI was done for all patients and EEG was performed in enrolled subjects. CSF analysis was done in all patients and normal CSF values were defined according to the criteria adjusted for age.

All CSF samples were sent for PCR. A positive PCR for HSV from CSF sample was considered as evidence for Herpes encephalitis. Although a negative PCR did not reject the diagnosis of HSE but in our facility brain biopsy was not done. We considered these patients as having encephalitis according to the clinical, EEG, CT, MRI and laboratory findings. All the patients were treated with acyclovir, but every patient with a positive PCR was assumed a definite diagnosis of HSE. Clinical manifestations, laboratory findings and outcome of patients were collected. At the end of the study period, the frequency of HSE on the base of HSV-PCR was reported among children admitted due to encephalitis.

**Results**

Fifty patients with primary diagnosis of Herpetic encephalitis diagnosis were enrolled. Among them, 17 patients had positive results for HSV DNA in the PCR of CSF samples. So totally HSV PCR was performed on all patients and positive detection rate was 34%. MRI showed lesions compatible to HSV encephalitis in 24 cases (48%) and CT-scan in 14 cases (28%).

Male to female ratio was 0.66. Fever was the most common compliant at the time of admission (80%) and other symptoms were nausea and vomiting (54%), headache (50%), seizure (34%) and altered consciousness (28%). The mean age of patients was 5.58±3.46 years. Clinical manifestations, laboratory findings, neuroimaging, EEG findings and abnormal CSF-PCR for Herpes DNA in children admitted with HSE are shown in Table 1.

According to our findings, lymphocytes had the most count variation. WBC, PMN, lymphocyte and RBC counts were high in the majority of the patients. The CSF culture was negative for any bacterial agent in all cases. All the patients received acyclovir intravenously for 14 days and discharged from hospital with a good general condition.

Table 1: Frequencies of clinical manifestations and laboratory findings of patients admitted due to HSV encephalitis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical manifestation</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>40 (80)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>27 (54)</td>
</tr>
<tr>
<td>Headache</td>
<td>25 (50)</td>
</tr>
<tr>
<td>Seizure</td>
<td>17 (34)</td>
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<tr>
<td>Altered level of consciousness</td>
<td>14 (28)</td>
</tr>
<tr>
<td>Abnormal CSF profile</td>
<td></td>
</tr>
<tr>
<td>PMN</td>
<td>17 (34)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>32 (64)</td>
</tr>
<tr>
<td>RBC</td>
<td>20 (40)</td>
</tr>
<tr>
<td>Protein</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Glucose</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Positive PCR for HSV DNA in CSF</td>
<td>17 (34)</td>
</tr>
<tr>
<td>Abnormal brain CT</td>
<td>14 (28)</td>
</tr>
<tr>
<td>Abnormal brain MRI</td>
<td>24 (48)</td>
</tr>
<tr>
<td>Abnormal EEG</td>
<td>21 (42)</td>
</tr>
</tbody>
</table>

PMN: Polymorphonuclear, RBC: Red blood cells
Discussion

In this study, we assessed the prevalence of Herpetic encephalitis, the clinical presentation and the outcome of the children with a diagnosis of HSE. HSE is an important cause of acute necrotizing encephalitis, with an incidence of 1 in 250,000 to 1 in 500,000. In this study, the male to female ratio was 2/3. Prodromal phase of 4-10 days with nonspecific symptoms was common in HSV and were characterized by fever and constitutional symptoms which was observed in 80% of our patients. Among the patients, 54% of cases had nausea and vomiting and 50% had headache, 34% had seizures and 28% had altered consciousness level. Patients were between 2 months and 12 years of age and the mean age was 5.58±3.46 years.

Routine CSF examination is important in establishing the diagnosis of encephalitis but does not identify the causative viral agents. This study revealed increased lymphocyte count in 64%, mononuclear pleocytosis (50-200/mm³) in 34% and raised CSF proteins in 12% of the patients. Because of hemorrhagic nature of the disease, RBCs were present in up to 40% of cases. However, normal CSF findings can be seen early in the course of the disease. CSF culture was negative in all cases. The EEG is usually abnormal in HSE but no specific EEG pattern is pathognomonic for HSE. The typical patterns of findings are unilateral or bilateral periodic focal spikes against a background of slow activity, but this constellation of findings is not specific for diagnosis. In our study abnormal EEG was seen in 42% of cases.

Whereas in the past brain biopsy was the gold standard for diagnosis of HSE, PCR is now the preferred diagnostic test despite the possibility of false negative results. False negative PCR may be encountered if the CSF is collected too early (first 24-48 hours) or too late (after 10-14 days). It has sensitivity rate as high as 98-99% and specificity of 100%. HSV-PCR in our study produced a positive result in 34% of our patients. In suspected cases with the initial negative HSV DNA in CSF, this test should be repeated again from 48-72 hours to confirm the diagnosis; but we did not do this. Instead, we recruited other modalities like MRI to confirm the diagnosis in highly suspected cases.

MRI appears to be the most sensitive and specific neuroimaging method for HSE. It shows hypertense signals on T2W1 in medial temporal and inferior frontal areas bilaterally. MRI findings showed abnormalities in 48% of cases. CT-Scan is less sensitive and showed delayed positivity in the form of frontotemporal hypodensities. With or without hemorrhage, 30-40% of patients may have normal CT-scan. CT scan was abnormal in 28% of cases in our study.

The limitations of this study were lack of brain biopsy due to non-availability. This is an attempt to highlight the value of high index of suspicion on clinical grounds, systematically, excluding those cases with different etiologies resembling HSE.

We can conclude that Herpetic encephalitis should be considered in each patient admitted with a sudden change in level of consciousness in a previously healthy child with fever and antecedent viral infection.

Acknowledgement

The authors would like to thank Dr. M.R. Salehiomran; pediatric neurologist in our center for his kindly co-operation at the time of consult and also to Dr. Pournasrollah for his laboratory assistances.

Conflict of interest: None declared.

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