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Clinical Manifestations and Laboratory Outcomes of Herpes Simplex Encephalitis: Experience from Imam Hospital, Tehran (2014–2019)

Soheila Khazaei[1]

[1] *Pediatrician-sub specialist of pediatric infectious diseases-MPH-Medical assistant professor-Iran Ministry of health and medical education-Mashhad medical university, Mashhad, Iran*

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ABSTRACT

Encephalitis is a relatively uncommon cause of hospitalization in pediatric wards, often associated with long-term, debilitating complications. The purpose of this study is to determine the prevalence and symptoms of herpes encephalitis at the Imam educational and therapeutic center.

This study employed a descriptive retrospective methodology, analyzing data from children discharged from the children's ward of Imam Hospital with a diagnosis of encephalitis between April 2014 and September 2019. Patient information was gathered by reviewing their medical files. The virology test utilized in this study was HSV PCR.

A total of 18 patients diagnosed with meningoencephalitis and herpes simplex encephalitis at Imam Hospital between 2014 and 2019 were included in the study. Of these, 11 were male (61%) and 7 were female (39%).

The most common clinical symptoms observed were fever (above 38°C), followed by a decreased level of consciousness and convulsions. Behavioral changes were the least prevalent symptom.

Given the high morbidity and mortality associated with this disease and the critical need for early treatment, a detailed patient history, a complete clinical examination, careful observation for symptoms of brain and meningeal involvement, and diagnostic tests such as CSF examination, CT scan, and MRI are essential. These steps can provide physicians with crucial insights for early diagnosis.

Furthermore, with the significant advancements in viral agent detection, laboratory methods like PCR and antibody sampling against HSV in blood and cerebrospinal fluid (CSF) can greatly aid in diagnosing the disease.

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Introduction

Herpes simplex encephalitis (HSE) is a life-threatening infection of the brain caused by the herpes simplex virus. Herpes simplex virus type 1 (HSV-1) is the primary cause of sporadic, progressive encephalitis, predominantly affecting the temporal lobe. It can manifest with a spectrum of clinical symptoms, ranging from aseptic meningitis and fever to severe, progressive forms that impair consciousness. Despite advances in antiviral treatment over the past two decades, HSE remains a serious condition with high rates of morbidity and mortality. (1- 3)

The incidence of herpes simplex encephalitis is estimated to be 2-4 cases per 100,000 people annually. Approximately one-third of affected individuals are children and infants, while two-thirds are adults. It is the most common cause of acute, sporadic encephalitis in children over six months of age and in adults. Seasonal variations or gender do not appear to influence the incidence of the disease. In the United States, the annual incidence is

***Corresponding author**: Dr. Soheila Khazaei, Pediatrician-sub specialist of pediatric infectious diseases-MPH-Medical assistant professor-Iran Ministry of health and medical education-Mashhad medical university, Mashhad, Iran*
Email: khazaeish@mums.ac.ir

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approximately 1 in 250,000 people. High mortality rates, a significant incidence of complications, and persistent neurological sequelae continue to be major concerns for affected patients.

Determining the exact annual global incidence of HSE is challenging, as only severe cases with obvious symptoms are typically hospitalized, leading to underdiagnosis of mild or self-limiting cases. Classic HSE presents with fever, headache, focal neurological deficits, seizures, and decreased level of consciousness. However, diagnosis based solely on clinical symptoms is often unreliable due to the possibility of other neurological syndromes mimicking these signs. Nevertheless, early diagnosis and prompt treatment are crucial given the disease's prognosis. (4- 5)

Cerebrospinal fluid (CSF) examination is essential for accurate diagnosis. MRI and CT scans of the brain can be helpful in diagnosing encephalitis, though their findings are not always specific for herpes simplex encephalitis. A CT scan may appear normal for up to 3-5 days after symptom onset, even in comatose patients. In severe cases, even contrast-enhanced MRI may yield normal results. Currently, the most sensitive and specific method for confirming HSE diagnosis is cerebrospinal fluid PCR for HSV. This test generally has a low rate of false positives and remains positive during the first week of treatment.

Therefore, the timely diagnosis of herpes encephalitis remains a significant challenge. The aim of this study is to identify the most common clinical symptoms and their correlation with findings from MRI, CT, and CSF analysis. This approach seeks to facilitate early diagnosis and, consequently, prompt treatment for patients with herpes encephalitis, particularly as the untreated mortality rate for this disease approaches 70%. (5- 7)

Materials & Methods

This study was a descriptive retrospective analysis of children diagnosed with encephalitis and discharged from the pediatric department of Imam Hospital between April 2014 and September 2019. Patient records were reviewed from the hospital archives to identify individuals diagnosed with meningitis, meningoencephalitis, or herpes simplex encephalitis who were admitted and treated during this five-year period. A total of 18 pediatric patients met the eligibility criteria. Data were collected through completed questionnaires based on file reviews and subsequently analyzed using SPSS software to determine frequencies.

Results

Out of the 18 patients diagnosed with meningoencephalitis and herpes simplex encephalitis at Imam Reza (AS) Hospital between 2014 and 2019, 11 were male (61%) and 7 were female (39%).

The clinical symptoms observed at the time of admission for these 18 patients are presented in the table below. The most common symptom was fever exceeding 38°C, followed by decreased level of consciousness and seizures. Behavioral changes were the least prevalent among the observed symptoms (table 1).

Table 1. Frequency of Clinical Symptoms in Patients with Herpes Simplex Encephalitis at Imam Hospital (2014-2019)

Clinical signs	Prevalence
Fever above C ° 38	88.9%
Loss of consciousness	2.72%
convulsions	2.27%
confusion	66.7%
Focal neurological symptoms	55.6%
Vomit	44.4%
Headache	22.7%
Behavioral changes	1/11%

CT Scan Findings

A CT scan performed on 11 patients. Among these, 39% exhibited decreased temporal lobe density, and 16.7% showed signs of cerebral edema. Additionally, 11.1% presented with cerebral hemorrhage on CT scans. No mass lesions observed in any of the patients.

MRI Findings

An MRI was conducted on 8 patients. Of these, 22.2% displayed hyper intensity in the temporal lobe on T2-weighted views.

Seasonal Distribution

The referral of patients showed a seasonal pattern: 27.8% of patients were admitted during spring, summer, and winter, with a slightly lower proportion (16.7%) admitted in autumn.

Cerebrospinal Fluid (CSF) Analysis

CSF analysis performed on all 18 patients, and all cases revealed abnormal changes (table 2).

Table 2. Frequency of CSF Changes in Patients with Herpes Simplex Encephalitis at Imam Hospital (2014-2019)

CSF	Percent abnormal	Average	Middle	standard deviation
WBC	33.3%	6/42	2	7/118
RBC	%61	4/402	5/7	7/118
Pr	50%	6/42	2	7/118
CSLU	55.5%	6/42	2	7/118

The average age of patients was 229.8 months with a standard deviation of 31.8 months. The youngest patient was 36 hours old and the oldest patient was 10 years old.

Discussion

This study aimed to identify the most common clinical and laboratory symptoms of herpes simplex encephalitis (HSE) in children. Herpes simplex virus (HSV), a DNA virus belonging to the Herpesvirus family, can cause HSE. While HSE is generally more common in the elderly and in infants, this study focused on pediatric cases.(13-14)

Previous research has presented varied findings regarding demographic, age, sex, and seasonal indicators of HSE. Whitery et al. did not specify these demographic details in their study. Panagariya's research indicated a common age range above 40 years and below 20 years, with a male-to-female ratio of 2:1, and a higher prevalence during summer and rainy seasons.

In contrast, our study, conducted at Imam Hospital, observed an age range from 36 hours to 10 years (mean age 229.8 months, SD 31.8 months). We found no significant seasonal variation in disease prevalence. However, the male-to-female ratio in our cohort was approximately 1.5:1. Ponizak et al. reported an age range of 2 weeks to 15 years in their study (15-17).

Regarding clinical symptoms, fever was the most frequent presentation of HSE in our patients. Neurological symptoms, in order of prevalence, included seizures, decreased level of consciousness, local symptoms, impaired consciousness, headache, and behavioral changes. Panagariya's study also identified fever and constitutional symptoms as the most common, while Mekan et al. reported fever, convulsions, and mental symptoms as common clinical indicators.

Cerebrospinal fluid (CSF) analysis is crucial for diagnosing encephalitis, although it may not always definitively confirm the presence of the virus. Typical CSF findings can include mononucleosis (50-200/mm^3), elevated protein levels, and, in cases with cerebral hemorrhage, the presence of red blood cells. Importantly, a normal CSF profile does not rule out HSE, especially in the early stages of the disease. In our study, all 18 patients underwent CSF analysis, and all exhibited abnormal changes. Specifically, CSF white blood cell count was elevated in 33% of patients, CSF red blood cells were present in 61%, cerebrospinal fluid protein was abnormal in 50%, and CSF sugar was decreased in 55% of patients. Panagariya's study reported similar CSF changes in 90% of their patients.

Mekan and colleagues reported that a significant number of HSE patients exhibited extra-temporal lesions on CT and MRI scans, with approximately 82% showing CSF abnormalities (18-19). Similarly, Shian noted that all children hospitalized with an HSE diagnosis over a seven-year period had abnormal CT scans, most demonstrating decreased density in the temporal and frontal lobes. In a majority of children who underwent MRI in Shian's study, demyelinating changes were observed in the temporal lobes, and frontal involvement was also noted. Normal CT findings were reported in only 30-40% of patients in these studies.

In our study, out of 11 patients who underwent CT, 9 (81%) showed abnormal brain changes, with 40% exhibiting decreased density in the temporal lobe and 11% showing hemorrhage. For the 8 patients who underwent MRI, 22.2% demonstrated hyperdensity in the temporal lobe. This contrasts with Jha et al.'s 2004 study, where only 4 out of 10 patients who underwent CT showed abnormal brain changes.

Given the high morbidity and mortality associated with HSE, prompt diagnosis and treatment are critical. A detailed patient history, comprehensive clinical examination, observation of symptoms related to brain and meningeal involvement, and diagnostic tests such as CSF analysis, CT scans, and MRI are essential for early diagnosis. Furthermore, advancements in laboratory methods like PCR and antibody sampling from blood and CSF for HSV can significantly aid in diagnosis.

Polizak's research suggested that abnormal MRI findings could confirm the diagnosis with high accuracy. Panamagaria considered frontotemporal MRI changes to be characteristic for diagnosing the disease. However, more precise diagnostic criteria are still needed. Herpes encephalitis is a severe disease with a high mortality rate and diagnostic challenges.

Conclusion

Herpes simplex encephalitis (HSE) is a life-threatening infection of the brain caused by the herpes simplex virus (HSV-1), which is the most common cause of sporadic progressive encephalitis. It primarily affects the temporal lobe and can manifest in a range of clinical symptoms, from aseptic meningitis and fever to severe, progressive forms affecting consciousness. Despite significant advances in antiviral treatment over the past two decades, HSE remains a serious disease associated with high rates of morbidity and mortality.

The primary challenge in managing HSE lies in its early diagnosis. This study aimed to identify the most common clinical symptoms and their correlation with MRI, CT, and CSF analysis findings to facilitate earlier diagnosis and, consequently, prompt treatment. Without treatment, the mortality rate for HSE can reach approximately 70%.

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