

## Frequency of Herpes Simplex Encephalitis in Children of a Tertiary Care Hospital: a cross-sectional study

Nimra Zahid, Atika Sher, Mehtab Hussain

Department of Pediatrics, Liaquat National Hospital, Stadium Road, Karachi, Pakistan

### Abstract

#### Introduction

Herpes Simplex encephalitis is a life-threatening condition. The burden of Herpes Simplex Encephalitis in children is not known in Pakistan. So, this study was conducted to determine the frequency of Herpes Simplex Encephalitis in children presenting with clinical encephalitis to a tertiary care hospital.

#### Methods

This cross-sectional study was conducted in the Department of Paediatrics, Liaquat National Hospital, Karachi from 7<sup>th</sup> April 2018 to 6<sup>th</sup> October 2018. A total of 149 consecutive patients of age between 1 month to 12 years, either gender presenting with signs or symptoms of encephalitis (clinical assessment) were included in this study. Patients with encephalopathy secondary to sepsis, metabolic causes, or space-occupying lesions were excluded from this study. After taking informed consent, a lumbar puncture was done by a trained senior resident and cerebrospinal fluid was sent for detailed report, culture, and herpes simplex polymerase chain reaction. Data were recorded on preapproved proforma and analyzed using SPSS.

#### Results

Mean age was  $4.30 \pm 3.11$  years. Overall, 59.7% of the patients were male and 40.3% were female. In the cerebrospinal fluid detailed report, the mean white blood cells, red blood cells, glucose, and proteins were  $86.63 \pm 344.69$  /cm<sup>3</sup>,  $2283.62 \pm 17342.38$  /cmm,  $90.61 \pm 33.3$  mg/dL, and  $66.49 \pm 112.02$  g/dl respectively. In this study, 30.9% of children were malnourished. The frequency of Herpes Simplex Encephalitis was 29 (19.5%). Stratified analysis by gender, age, and malnutrition was not found to be effect modifiers.

#### Conclusion

Results showed 19.5% HSV-PCR positive cases among encephalitis children. Gender, age, and malnutrition were not found to be effect modifiers.

#### Keywords

Frequency, herpes simplex, encephalitis, polymerase chain

reaction

#### Introduction

Encephalitis in children is a life-threatening diffuse inflammation of the brain with unacceptably high mortality rates. Viruses, such as Herpes Virus is one the common cause of encephalitis. However, other pathogens, fungus, parasites also cause encephalitis.<sup>1</sup>

The annual incidence of Herpes simplex encephalitis (HSE) is 1/1000000.<sup>1</sup> The prevalence of HSV encephalitis ranges from 2.5% to 5%.<sup>1</sup> In 90% of the cases, HSE is caused by herpes simplex virus I (HSV-1), and the rest is caused by the herpes simplex virus 2 (HSV-2). The severity and treatment response of HSE varies with the immunological status of the patient. HSV-2 causes disseminated infections among patients with the compromised immune system or newborn babies.<sup>5-6</sup>

Herpes simplex encephalitis (HSE) is one of the treatable causes of encephalitis if diagnosed and treated early. Early recognition of encephalitis in children is vital for improving the outcome, but it is often difficult to diagnose due to a wide range of non-specific symptoms.<sup>7</sup> Mostly clear cerebrospinal fluid (CSF) is not diagnostic of encephalitis and is difficult to distinguish viral meningitis from encephalitis. Even with the recent development of new tests, the etiology of encephalitis in 50% of cases remains unknown. Red blood cells (RBC) in the CSF may indicate HSE. However, it's again difficult to distinguish that presence of RBC in the CSF is due to HSE or traumatic lumbar puncture (LP).<sup>2-4</sup>

Identification of HSV double-stranded DNA polymerase chain reaction (PCR) of CSF is currently considered standard for the diagnosis of HSE. PCR is not only diagnostic of HSV but it helps clinicians with clinical decision making and management.<sup>8-11</sup> The reported sensitivity and specificity of CSF PCR to yield HSV was 90% and 92% respectively.<sup>8</sup> In Pakistan, the literature on the burden of HSE is scarce. Therefore, this study aimed to find out the burden of HSE among patients presenting with signs and symptoms of encephalitis in our setting for early recognition and treatment of HSE to prevent complications of encephalitis.

#### Methods

This descriptive cross-sectional study was conducted in the

*Corresponding author: Atika Sher,  
Assistant Professor, Department of Pediatrics,  
Liaquat National Hospital, Stadium Road,  
Karachi, Pakistan.  
Email: dratikas@yahoo.com*

Department of Paediatrics, Liaquat National Hospital, and Medical College Karachi from 7<sup>th</sup> April 2018 to 6<sup>th</sup> October 2018.

In this study, participants were selected through non-probability consecutive sampling. Patients of age between 1 month to 12 years, either gender presenting with signs or symptoms of encephalitis (clinical assessment) were included in this study. Encephalitis was defined as a patient hospitalized with encephalopathy (defined as altered level of consciousness evident on a clinical basis lasting 24 hours or more, lethargy (mother complaining feeling of dullness), or behavior change) with at least 2 of the following characteristics: fever (100°F or more), seizure (on clinical basis up rolling of eye and stiffening of the body), focal neurologic deficit (on a clinical basis like hemiparesis), CSF pleocytosis (white blood cell [WBC] count 5 cells/mm<sup>3</sup>), and CSF HSV-PCR either positive or negative on CSF analysis consistent with encephalitis.

Patients with encephalopathy secondary to sepsis, toxins (clinically assessed), metabolic causes (assessed on Urea, Creatinine & Electrolytes - UCE), or space-occupying lesion on magnetic resonance imaging (MRI) were excluded from this study.

After taken approval from the ethical review committee of the hospital and College of Physicians and Surgeons Pakistan (CPSP), patients who fulfilled the inclusion criteria were included in this study. After explaining the study purpose informed consent was taken from the patient's parents/ guardians. The patient's history and physical examination were conducted by the principal investigator. After all aseptic measures, the LP of the patient was done by a trained pediatrician and sent to the laboratory of Liaquat National Hospital for CSF DR, gram stain (GS), culture & sensitivity (CS), and HSV-PCR. Reports were collected by the duty doctor. History, physical findings, and laboratory results were recorded on a predesigned Performa.

The sample size was calculated by using the World Health Organization (WHO) sample size calculator.<sup>12</sup> A total of 149 patients were needed to be enrolled with confidence level  $z(1-\alpha)$  of 95%, desired precision (d) 3.5%, and HSV-PCR positive 5%.<sup>1</sup> Data were entered and analyzed in SPSS version 22. Frequency and percentage were calculated for qualitative variables i.e. gender (male/female), malnutrition, and CSF HSV-PCR (positive, negative). Mean $\pm$ SD was calculated for quantitative variables i.e. age and laboratory measures. Effect modifiers like age, gender, malnutrition were controlled through stratification by using the chi-square test, and a p-value of <0.05 was considered significant.

## Results

Out of 149 children, the mean age of patients was 4.30 $\pm$ 3.11 years, 59.7% were male and 40.3% female. The overall mean white blood cells, red blood cells, glucose, and proteins were

86.63 $\pm$ 344.69 /cm<sup>3</sup>, 2283.62 $\pm$ 17342.38 /cmm, 90.61 $\pm$ 33.3 mg/dL, and 66.49 $\pm$ 112.02 kDa respectively. Among total study subjects, 30.9% were found as malnourished. (Table 1) In this study, the frequency of HSE in children was 29 (19.5%).

The results showed that mean age, white blood cells, red blood cells, glucose, and proteins, were 4.72 $\pm$ 3.74 years, 15.68 $\pm$ 21.02 /cm<sup>3</sup>, 199.55 $\pm$ 207.8 /cmm, 71.55 $\pm$ 29.72 mg/dL, and 41.13 $\pm$ 35.17 gm/dl respectively. The results showed that there were no significant effect modifiers identified after stratified analysis. (Table 2)

**Table 1: Distribution of continuous variables**

	Mean	SD
Age (Years)	4.3	3.11
CSF WBC count (cells per cmm)	86.63	344.69
CSF RBC count (cells per cmm)	2283.62	17342.4
CSF glucose (mg/dl)	90.61	33.3
CSF protein (kDa)	66.49	112.02

**Table 2: Comparison of patients' characteristics by HSV status**

	Positive	Negative	P-value
Age (Years)			
<= 5years	20 (18.7%)	87 (81.3%)	0.704
>5 years	9 (21.4%)	33 (78.6%)	
Gender			
Male	14 (15.7%)	75 (84.3%)	0.161
Female	15 (25.0%)	45 (75%)	
Malnutrition	7 (15.2%)	39 (84.8%)	0.382

## Discussion

In this study, the frequency of HSE in children was 19.5% and age, gender, and malnutrition are not effect modifiers. A study reported a lower prevalence of HSE in the pediatric population compared to adult cases of acute encephalitis, for which incidence rates between 10% and 20% have been reported.<sup>13</sup> In a study, the frequency of encephalitis was 5%<sup>11</sup> which is lower compared to the frequency in this study.

The classic clinical presentation of HSE consisting of fever, altered level of consciousness, focal motor seizures, dysphasia, and hemiparesis, which was present in 75% of cases in the childhood population. In this study, we found fever, seizures, altered sensorium, and unconsciousness are common clinical

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presentations. Other clinical features such as ataxia, decreased visual acuity, tremor, dysphasia, or hemiparesis were not found in this study.

CSF analysis, EEG testing, and diagnostic imaging are all used to aid in the diagnosis of HSE. Although typical laboratory results are highly suggestive of HSV (CSF pleocytosis, elevated protein levels, and elevated RBC counts), the absence of these features does not rule out a diagnosis of HSE. In a study, 16% did not demonstrate CSF pleocytosis, 50% had normal CSF protein levels, and only 19% showed elevated RBC counts.<sup>13</sup>

Other authors postulated that the presence of HSV DNA in the CNS might be attributable to reactivation of latent HSV or transport of HSV to the CNS after reactivation of latent infection in peripheral sensory or autonomic ganglia. Although PCR is useful for detecting the presence of viral DNA, it cannot distinguish between infectious virions, damaged virions, and cell-associated DNA. This may illustrate that, although the addition of PCR to our diagnostic repertoire has resulted in the diagnosis of HSE in many more cases, perhaps it has also identified cases in which, although HSV DNA is present, it may not be involved in the pathogenesis of the presenting disease.<sup>14-15</sup>

There are a few limitations of this study. The main limitations of the present study include a single-center experience and a nonrandomized study design. It was conducted in an urban environment; therefore, the results might not be generalizable to larger populations. Finally, a second lumbar puncture was not performed on those with initial negative HSV PCR as recommended in the literature.

## Conclusion

In conclusion, the study results showed 19.5% HSV-PCR positive cases among encephalitis children. However, patients with female gender, age more than 5 years, and malnutrition were more likely to have a positive HSV-PCR, although this was statistically insignificant. There is a need for large hospital-based surveillance to understand the seasonality, clinical

presentation, determinants/predictors, and response to treatment.

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