

Herpes Simplex Virus Meningoencephalitis in Children

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

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List of Abbreviations

Abb.	Full term
<i>ADEM</i>	<i>Acute disseminated encephalomyelitis</i>
<i>CMV</i>	<i>Cytomegalovirus</i>
<i>CSF</i>	<i>Cerebrospinal fluid</i>
<i>CT</i>	<i>Computed tomography</i>
<i>DNA</i>	<i>Deoxyribonucleic acid.</i>
<i>EBV</i>	<i>Ebstein-Barr virus</i>
<i>EEG</i>	<i>Electroencephalography</i>
<i>ESR</i>	<i>Erythrocyte sedimentation rate</i>
<i>FDA</i>	<i>The Food and Drug Administration</i>
<i>GS</i>	<i>Glucocorticosteroids</i>
<i>HHV6</i>	<i>Human herpes virus 6</i>
<i>HSE</i>	<i>Herpes simplex encephalitis</i>
<i>LAT</i>	<i>Latency Associated Transcript</i>
<i>MRI</i>	<i>Magnetic resonance imaging</i>
<i>PCR</i>	<i>Polymerase chain reaction</i>
<i>TK</i>	<i>Thymidine kinase</i>
<i>VZV</i>	<i>varicella-zoster virus</i>
<i>HSV</i>	<i>Herpes simplex virus</i>

Abstract

Background: Acute encephalitis is relatively uncommon but potentially detrimental CNS inflammation usually caused by infection. Herpes simplex virus have been reported in encephalitis cases. However, clinical and epidemiological characteristics of HSV in encephalitis are not fully established. This study aimed at investigating the presence of HSV DNA in the CSF of meningoencephalitic patients using PCR together with the clinical spectrum of the disease.

Methods:

50 children with encephalitis were prospectively investigated over a period of 6 months. All patients were subjected to CSF examination and HSV DNA detection using PCR technique. Demographic and clinical data were collected from the patients.

Results:

The age range of the patient was 6 months – 54 months (43.5months $\pm$ 12.4) mean $\pm$ SD. Most infections occurred during the warm months of the year.

HSV DNA was detected in 3 samples (6%). of affected patients. The most frequent neurological manifestations were altered mental state in (100%) and convulsion, vomiting and diarrhea in (66.7%). MRI abnormal findings were reported in (48%) of cases. 40% of the patients showed abnormal CT brain finding. All patients were managed in intensive cares.

Conclusions: to our knowledges this study is the first study to estimate the prevalence of HSV in patients presented by encephalitis. The study revealed that 6% of patients presented by picture suggestive of encephalitis diagnosed by PCR technique as HSV encephelitis so other causes of encephalitis have to be investigated.

Keywords: HSV, Encephalitis, Pediatrics, PCR

Introduction

Viral encephalitis is an inflammation of the brain parenchyma, presents as diffuse and or focal neuropsychological dysfunction. Although it primarily involves the brain, the meninges are frequently involved (meningoencephalitis). Acute encephalitis is most commonly a viral infection with parenchymal damage varying from mild to profound. The term “acute viral encephalitis” is used to describe restricted CNS involvement (i.e., involvement of the brain, sparing the meninges); however, most CNS viral infections involve the meninges to a greater or lesser extent, leading to aseptic meningitis or causing mild meningoencephalitis rather than pure encephalitis (*Gendelman and Persidsky, 2005*).

Encephalitis refers to an inflammatory disorder of the brain resulting in altered mental status, seizures, or focal neurologic deficits, usually accompanied by signs of inflammation in the cerebrospinal fluid and magnetic resonance imaging (MRI) findings ranging from normal to extensive abnormalities. The causes of encephalitis are numerous, and most patients undergo extensive testing for infectious etiologies without discovery of a causative agent (*Gable et al., 2009*).

The recent discovery that several forms of encephalitis result from antibodies against neuronal proteins has led to a definitive diagnosis in many of these cases. The antibodies target receptors and cell surface proteins involved in synaptic

transmission, plasticity, or neuronal excitability, and associate with syndromes that despite being severe frequently respond to immunotherapy (*Lancaster et al., 2011*).

In developing countries, the annual incidence of viral encephalitis is most likely underestimated, because of problems with pathogen detection, but it most probably affects at least 50,000 individuals per year (*Sejvar and Marfin, 2006*).

Children and young adults are typically the groups that are most often affected. However, severity is usually more pronounced in infants and elderly patients (*Kullnat and Morse, 2008*).

Herpes simplex virus (HSV)-1, HSV-2, varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus-6 collectively cause approximately 4% of cases of viral meningitis, with HSV-2 being the most common offender. The viruses may attack at any time of the year. HSV-1 remains the most common cause of sporadic encephalitis, while HSV-2 infections of CNS mostly are restricted to aseptic meningitis. CMV infections occur mostly in immune-compromised hosts (*Whitley and Gnann, 2002*).

Herpes simplex encephalitis (HSE) is an acute or subacute 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 cerebrospinal fluid (CSF) findings are suggestive of HSE, no pathognomonic

clinical findings reliably distinguish HSE from other neurologic disorders with similar presentations (*Whitley and Gnann, 2002*).

Untreated HSE is progressive and often fatal in 7-14 days (*Whitley and Gnann, 2002*). Mortality in patients treated with acyclovir was 19% in the trials that established its superiority to vidarabine (*Whitley, 2006*). Subsequent trials reported lower mortalities (6-11%), perhaps because they included patients who were diagnosed by polymerase chain reaction (PCR) rather than brain biopsy and who thus may have been identified earlier with milder disease (*Tyler, 2004*).

PCR analysis of CSF for the detection of HSV. DNA has virtually replaced brain biopsy as the criterion standard for diagnosis (*Steiner et al., 2010*). Schloss and colleagues report that whereas quantitative PCR is more rational than a nested PCR, the former has little prognostic use PCR is highly sensitive (94-98%) and specific (98-100%). Results become positive within 24 hours of the onset of symptoms and remain positive for at least 5-7 days after the start of antiviral therapy (*Schloss et al., 2009*). Clinical severity and outcome appear to correlate with viral load as assessed by quantitative PCR techniques, but not all investigators have confirmed this correlation. False-negative findings may occur early in the course of the disease when viral DNA levels are low (within 72 hours of the onset of symptoms) or when blood is present in the CSF, because hemoglobin may interfere with PCR (*Weil et al., 2002*).

Aim of work

The present study is carried out to identify HSV as a causative agent in the aetiology of viral meningoencephalitis in patients attending Ain-Shams University Children hospital.

Chapter One

Viral Meningoencephalitis

Encephalitis refers to an (acute, usually diffuse, inflammatory process affecting the brain). While meningitis is primarily an infection of the meninges, a combined meningoencephalitis may also occur. An infection by a virus is the most common and important cause of encephalitis, although other organisms may sometimes cause encephalitis. Encephalitic illness caused by alteration of normal immune function in the context of a previous viral infection or, following vaccination is also well recognized (acute disseminated encephalomyelitis, ADEM). Infectious encephalitis may also be difficult to distinguish from an encephalopathy that may be associated with numerous metabolic causes (*Paterson et al., 2014*).

Encephalitis means inflammation of the brain parenchyma and strictly speaking, this is a pathological diagnosis. However, because of the obvious practical limitations of this, surrogate clinical markers of inflammation are used (*Solomon et al., 2012*).

Meningitis and meningoencephalitis pose major risks of morbidity and mortality. In the general population the risk of meningitis has been estimated at 2.5 per 100,000 patient-years (*Ross et al., 2012*) and the risk of meningoencephalitis at 3.5-7.4 per 100,000 patient-years (*Granerod and Crowcroft, 2007*). Mortality rates are estimated at 3–20% for meningitis and up to 20–30% for encephalitis.

Morbidity and mortality rates vary markedly and depend on the age of the patient, cause of the disease, site of infection, and time from detection to treatment (*Ross et al., 2012*).

Causes of encephalitis:

Encephalitis can be due to a non infective condition such as in acute disseminated encephalomyelitis (ADEM) or to an infective process, which is diffuse and usually viral. Herpes simplex virus type 1 (HSV-1), varicella-zoster virus (VZV), Epstein– Barr virus (EBV), mumps, measles and enteroviruses are responsible for most cases of viral encephalitis in immuno-competent individuals (*Koskiniemi et al., 2001*). Other non-viral infective causes of encephalitis may include such diseases as tuberculosis, rickettsial disease and trypanosomiasis (*Werner, 2011*).

Viral encephalitis:

Causes of viral encephalitis:

- Herpes simplex virus (HSV-1, HSV-2)
- Other herpes viruses: varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpes virus 6 (HHV6).
- Other viruses adenoviruses, influenza A, enteroviruses, poliovirus, measles, mumps and rubella viruses.

(*Steiner et al., 2012*)

Epidemiology

Viral encephalitis has public health concern widely due to its high morbidity and mortality and impact on child health (*Falchek, 2012*).

Viruses are recorded as causative of such lesion are many, there is considerable geographical and seasonal variation describe the prominence of every virus. However, this does not mean closing the door in front of new emerging viruses. Climate changes and increase travel movement increase the viral outbreaks (*Sleman, 2015*).

In developing countries, there are no fixed trustable data regarding encephalitis registry due to obstacles in diagnosis, documentation and pathogen detection.

Children and young adults are the typical targets of viral encephalitis; the course of disease in children is totally different from that seen in adults. The disease is more pronounced in infants than young children. Majority of patients presented with meningitis, mainly occur in children with slight male predominance (*Gondim, 2015*).

Herpes simplex virus (HSV) encephalitis is the most commonly diagnosed viral encephalitis in industrialized nations, with an annual incidence of 1 in 250,000 to 500,000 (*Wilhelmus, 2015*).