Atypical Presentation of Herpes Simplex Virus 1 Encephalitis in Pediatric Age

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Abstract

BACKGROUND: The annual incidence of herpes simplex encephalitis (HSE) is 1:250–500 thousand in developed countries, which makes it the most common viral cause of encephalitis. Encephalitis caused by HSV-1 probably accounts for most of the cases in the Herpesviridae family and typically affects older children.

CASE REPORT: An atypical presentation of pediatric herpetic encephalitis is reported. The child presented with recurrent seizures that were initially unresponsive to several anticonvulsant drugs. EEG and MRI of the brain were useful as a diagnostic tool. The gold standard diagnostic test for HSE is the HSV DNA polymerase chain reaction (PCR), which is highly sensitive and specific test.

CONCLUSION: Based on the clinical presentation of the child, viral encephalitis was deemed to be the most likely aetiological condition.

Introduction

Herpes simplex virus 1 (HSV-1) encephalitis is an acute necrotizing brain infection that generally affects the frontal or temporal cortex and the limbic system [1]. In children, it can be a serious condition, and its outcome is mainly dependent on early diagnosis and the prompt start of treatment. The annual incidence of herpes simplex encephalitis (HSE) is 1:250–500 thousand in developed countries, which makes it the most common viral cause of encephalitis [2]. Encephalitis caused by HSV-1 probably accounts for most of the cases in the Herpesviridae family and typically affects older children. Herpes simplex virus is an enveloped double-stranded DNA virus and is generally categorized as HSV-1 and HSV-2. Both of them can affect the central nervous system and can replicate in the neuronal cells in a phenomenon known as neurovirulence [2].

A relevant characteristic of the herpes virus is its latency. Reactivation of latent HSV can occur after various insults, such as fever, trauma, and infections [3]. Possible clinical manifestations are fever, headache, neck stiffness, nausea, vomiting, seizures, and an altered state of consciousness. A lesion involving a specific brain area can result in other symptoms, such as anosmia, aphasia, language dysfunctions, hallucinations, and focal convulsions. Cerebrospinal fluid (CSF) could be useful as a diagnostic tool. The gold standard diagnostic test for HSE is the HSV DNA polymerase chain reaction (PCR), which is highly sensitive and specific [2].

We present this case report of a 2-year-old girl with fever and seizures, diagnosed as HSE, who showed an early relapse with no organic sign of disease except for seizures. We also discuss the case along with the available literature.
Case Report

A 2-year-old girl came to the Paediatric Department of the University of Catania for consultation. She was referred by a nearby hospital due to high temperature and clonic tonic seizures that responded poorly to benzodiazepine and other anticonvulsant drugs. Despite a continuous intravenous (iv) infusion of midazolam and oral valproic acid, the patient continued to present clonic tonic seizures with drooling and perioral cyanosis at every attempt to stop benzodiazepine treatment.

Electroencephalogram (EEG) showed slow theta and theta-delta intercritical activity that was widespread without a clear focus. The brain MRI resulted non-specific. At admission, the patient had poor general condition with normal temperature, a heart rate of 105 bpm, oxygen saturation of 100%, and no signs of meningeal involvement. The rest of the physical evaluation was also unremarkable. Upon neurological examination, she presented slightly clouded sensory perception, followed by phases of agitation and poorly structured language.

Therapy with acyclovir was immediately started due to a suspicion of viral encephalitis when considering the recurring trend of critical episodes. A PCR test for HSV-1 of the CSF was performed, resulting positive, and diagnosis of HSE was made. Treatment with acyclovir (65 mg/kg/day iv every 8 h for 30 days) and ceftriaxone (100 mg/kg/day iv every 12 h for 10 day) was continued. During hospitalization, the patient underwent numerous EEGs, which did not show typical epileptiform anomalies. Anti-HSV-1 immunoglobulins IgM and IgG were absent. There was no hyponatremia. Anti-neuronal and anti-myelin oligodendrocyte glycoprotein antibodies were absent from the CSF.

The metabolic test, serum amino acid, serum ammonia, and blood lactic acid were also normal. Lymphocyte subpopulations were normal. The patient also underwent an electrocardiogram, cardiac ultrasound, and eye examinations, which were normal. The child continued to present seizures, so add-on iv levetiracetam was started, which resulted in a progressive resolution of the critical episodes and a gradual weaning of midazolam infusion. The result of a brain MRI at 3 weeks after the onset of symptoms was unremarkable. Furthermore, a few days later, a new lumbar puncture showed the absence of HSV-1 DNA. Clinical symptoms improved progressively until the complete disappearance of seizures under anticonvulsant treatment. The patient was discharged in good general condition with the following therapy: valproic acid at 11 mg/kg every 8 hours, levetiracetam at 20 mg/kg every 12 h, and micro B6 drops.

About 2 weeks after discharge, the child presented a new episode of fever and generalized clonic-tonic seizures, so she was hospitalized again. Anticonvulsant therapy and midazolam in continuous infusion were performed until the seizures resolved. The results of EEG were unremarkable again. The patient was discharged and is undergoing monthly clinical follow-up. Anticonvulsant treatment is still continuing. At the 6-month follow-up, no new episodes of seizures or fever were recorded.

Discussion

HSE typically presents as a febrile syndrome accompanied by seizures, alterations of the conscious level, focal neurologic signs and progressive deterioration. However, especially in children younger than 2 years of age, the clinical picture may be more non-specific [4].

In our case, a 2-year-old girl presented at the emergency room with a typical encephalitic syndrome, HSE was immediately suspected, and the treatment was promptly started. EEG and MRI showed non-specific signs; however, PCR test resulted positive for HSV-1.

Viral encephalitis is a medical emergency and the most common cause of sporadic fatal encephalitis in patients older than 6 months of age in the Western world [5]. It is a complex neurological syndrome caused by inflammation of the brain parenchyma. It is often rapidly progressive, and a wide number of etiological agents are involved [6]. The causes of encephalitis can be broadly categorized as infections, immune-mediated (or inflammatory), or unknown. Globally, the three most common causes of infectious encephalitis in children are HSV, varicella-zoster virus (VZV), and enterovirus [7], [8].

HSE is a life-threatening consequence of HSV infection of the central nervous system and is regarded as the most common cause of sporadic fatal encephalitis in patients >6 months of age in the Western world. Untreated HSE has a mortality rate of 70% in adults, with <3% of patients returning to normal function [5]. Survival rates are improved if treatment is started within 4 days after the onset of the illness [9]. HSV is a ubiquitous human pathogen that causes a wide spectrum of illnesses ranging from minor clinical signs to severe complications such as encephalitis [10]. Most childhood cases of HSV-1 infection are caused by oral transmission [4], [11], [12], [13], [14], [15]. The involvement of neural tissue results in either latency or unknown. Globally, the three most common causes of infectious encephalitis in children are HSV, varicella-zoster virus (VZV), and enterovirus [7], [8].

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An important characteristic of herpes viruses is their latency. Following primary infection of the epithelial cells with HSV, the virus enters the sensory neurons and is transported to the sensory ganglia, where it becomes latent and lies quiescent through mechanisms that are poorly understood [3]. Reactivation of latent HSV can occur after several insults such as fever, infection, trauma, and immunodeficiency. Thus, an individual infected with HSV is always a potential reservoir of infectious virus [3].

The most common symptoms in the clinical presentation of HSE in children are altered mental status, dysphasia, fever, headache, irritability, seizure, and visual field defects [17]. Hyponatremia (< 135 mEq/l) is a peculiar laboratory parameter, so the presence of hyponatremia among patients with viral encephalitis could be helpful for the early diagnosis of HSE before CSF PCR results become available [18]. The prognosis for patients with this condition depends on correct and immediate diagnosis and the introduction of appropriate treatment to decrease the extent of permanent brain damage [19]. Medical history, physical examination, characteristics of clinical symptoms, and an analysis of the CSF are very important for the diagnosis.

The detection of HSV 1 in the CSF through PCR is the gold standard diagnostic test for HSE. PCR has 94% sensitivity and 98% specificity compared with HSV culture from brain biopsy [20]. However, PCR has supplanted viral culture and brain biopsy for the identification of HSV infections of the central nervous system in children [21]. Other important diagnostic tests are brain MRI and EEG [22], although they were not useful in this case.

The spectrum of imaging abnormalities in HSE includes edema, hemorrhage, and necrosis. The involvement of the inferior frontal and infero-medial temporal lobes and insular cortex leads to a hypothesis that the infection’s way into the brain follows the small branches of the trigeminal nerve [23]. Abnormalities occur in the temporal lobe in 80% of patients, and 10% have extra-temporal abnormalities [7], [8]. Computed tomography (CT) of the head may also be useful, but it is less sensitive than MRI. The results of EEG are abnormal in 80% of patients with HSE and usually show periodic lateralizing epileptiform discharges in the temporal lobe [24].

Early detection and diagnosis of HSV1 encephalitis is crucial as the prompt administration of acyclovir within 4 days after the onset of the illness can dramatically reduce both morbidity and mortality [19]. Acyclovir is the most extensively studied inhibitor of HSV replication [3]. Intravenous acyclovir is the mainstay of treatment. The current recommended dose is 45 mg/kg per day in 3 divided doses for children and 60 mg/kg per day in 3 divided doses for neonates [2]. However, it is ineffective against latent infection and does not eradicate the virus from the ganglia. The standard of care in the past decade has seen an increase in the duration of treatment from 14 days to 21 days [24]. This approach has shown a lower incidence of adverse neurological outcomes.

Early relapse of HSE has been firstly described in 1984. Since then, several cases were published in literature. However, the exact prevalence is still unknown [15]. In our case, the young patient showed again signs and symptoms of HSE after 14 days from first being discharged, despite the acyclovir treatment. The majority of relapses syndromes appear during the first month from the onset of symptoms, following a successful treatment with acyclovir.

Maia et al. [15] published in 2010 the case of a 7-month-old boy with an HSE relapse which was related to a deficiency of UNC93B and TLR3. Therefore, relapses might be related to an immunological dysfunction.

In our case, there were no reasons to suspect an immune system impairment of the child. Therefore, we did not perform detailed studies of the immune response. Specific IgM and IgG tested negative, but it has been demonstrated that seroconversion might happen after 10–15 days from the onset of symptoms; since the serum sample was taken around the time of the onset of symptoms, negativity of this test is not suggestive.

Conclusions

Based on the clinical presentation of the child, viral encephalitis was deemed to be the most likely aetiological condition. Early diagnosis and treatment are very important for this serious disease. The outcome was characterized by early-onset epileptic encephalopathy with relapses and a poor response to antiepileptic treatment. The fever probably triggered the reactivation of an asymptomatic HSV-1 infection and manifested with recurrent seizures. Another feature is the absence of specific HSE abnormalities in the results of EEG and MRI, as well as a normal evaluation in the neurological examination.

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We confirm that we have read the journal’s guidelines on issues involving ethical publication and affirm that this report is coherent with these guidelines.

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Gulizia et al. Herpes Encephalitis in Children

Hyponatremia is predictive of HSV-1 encephalitis. Viral meningoencephalitis: 


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PMid:7844669


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PMid:1313097


PMid:29961528


PMid:21813725


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PMid:30890685


PMid:63. http://doi.org/10.1093/infdis/171.4.857


PMid:7706811


PMid:20023175


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Availability of Data and Material

Data about the clinical case are available at the corresponding author.

Consent for Publication

The parents of the child signed an informed consent for the publication of this case.

References


PMid:24953748


PMid:30805531


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