A REVIEW ARTICLE ON HERPES SIMPLEX ENCEPHALITIS

A. Karimi MD[1],
S. Rafiee Tabatabaei MD[2],
M. Hadipour Jahromy MD[3]

Abstract:
Herpes Simplex encephalitis (HSE) is a life threatening outcome of Herpes simplex virus (HSV) infection of the central nervous system (CNS). HSV accounts for 2-5 percent of all cases of encephalitis.
One third of cases occur in those younger than 20 years old and one half in those older than 50 years old.
Clinical diagnosis is recommended in the encephalopathic, febrile patients with focal neurological signs. However, the clinical findings are not pathogonomic because numerous other diseases of CNS can mimic HSE. Diagnosis should be confirmed based on medical history, analysis of cerebrospinal fluid (CSF) for protein and glucose contents, the cellular analysis and identifying the pathogens by serology and Polymerase Chain Reaction (PCR) amplification .
The diagnostic gold standard is the detection of HSV DNA in the cerebrospinal fluid by PCR. But negative results need to be interpreted regarding the patients clinical signs and symptoms and the time of CSF sampling. Spike and slow wave patterns is observed in Electroencephalogram (EEG). Neuroimaging, especially Magnetic Resonance Imaging (MRI) is essential for evaluating the patients, which shows temporal lobe edema or hemorrhage. All patients with HSE should be treated by intravenous Acyclovir (10mg/kg q8hr for 14-21 days). After completing therapy, PCR of the CSF can confirm the elimination of replicating virus, assisting further management of the patient.
Keywords: Herpes Simplex Virus (HSV), Encephalitis, Children

1. Professor of Pediatric Infectious Diseases, Pediatric Infectious Research Center, Shaheed Beheshti University of Medical Sciences
2. Assistant Professor of Pediatrics, Pediatric Infectious Research Center, Shaheed Beheshti University of Medical Sciences
3. General Practitioner, Pediatric Infectious Research Center, Shaheed Beheshti University of Medical Sciences
Corresponding Author:
S. Rafiee Tabatabaei MD
Tel: +98 21 22226941
Fax: +98 21 22226941
Email:info@pedirc.org

Introduction

Viral encephalitis is a medical emergency. Involvement of the CNS is an unusual manifestation of human viral infection. The severity of brain involvement and the prognosis depends mainly on the specific pathogen and the immunological state of the host (1). Intranuclear inclusion bodies consistent with HSV infection were first demonstrated in the brain of a neonate with encephalitis by Smith and others in 1941(2).

Herpes Simplex Virus type 1 (HSV_1) is the major cause of devastating encephalitis, with a predilection for the temporal lobes and a range of clinical presentations. Despite of advances in antiviral therapy over the past two decades, Herpes Simplex Virus Encephalitis (HSVE) has yet remained as a serious illness with significant risks of morbidity and death(3).

This paper reviews the epidemiology, clinical presentation, physical examinations, diagnosis, prognosis and treatment of HSV-related diseases of the brain: encephalitis and meningoencephalitis.

Methods

We reviewed the epidemiology, the clinical manifestations at the time of admission, diagnostic evaluations, pathogenesis and treatment of HSVE. We searched the articles published from 1980 to 2006 in Medline and EMBASE. The search included information related to the research on human beings and in English. The keywords were: Herpes Simplex Encephalitis, Viral encephalitis, HSV meningoencephalitis, alone and with epidemiology, definition, diagnostic tools, therapy and treatment.

The reference list of the articles and other resources, such as textbooks, were also reviewed.

The final choice of literature and the references were based on our judgment of their relevancy to our subject. Recommendations were based on our own knowledge and clinical experiences.

Epidemiology

HSV-1 is the most common cause of sporadic encephalitis and has been identified in 10-20% of cases of encephalitis in some studies (4). The lower percentages of HSV-1 cases reported in some studies (3%) reflects the difficulty of physician's practices to confirm the diagnosis (5,6). There is a bimodal distribution of HSVE, with one third of cases occurring in those younger than 20 years old and one half in those older than 50 years old. The bimodal age distribution may reflect the primary HSV infection in the younger age group and

the reactivation of latent HSV in older patients(7). There is a predominance of males with a male to female ratio of 2:1(8).

No seasonal or gender factors have been defined yet relating to the incidence of HSE cases (9). Both types 1 and 2 may cause neonatal HSV meningoencephalitis(10).

More than two third of encephalitis cases due to HSV-1 seems to result from reactivation of endogenous latent HSV-1 in individuals previously exposed to the virus; the other cases without any evidence of prior exposure to HSV seems to be affected due to a primary infection of HSV(9, 11). Cases of HSV-2 encephalitis usually imply the primary infection rather than reactivation (12). Some cases of HSV-2 meningoencephalitis have been reported in adult patients with AIDS (13,14). In recurrent herpes labialis, whereby the reactivation of virus from the trigeminal ganglia occurs, HSE is a very uncommon event (15).

Clinical presentation

Currently, HSE is estimated to occur in about 1 in 250,000 to 1 in 500,000 individuals per year(15).

The various clinical presentations are often unreliable, as numerous neurological syndromes could mimic HSVE. The classic presentation of HSVE is the sudden onset of fever, headache, focal neurological signs, seizure, and/or deterioration of consciousness (3).

Meningial signs are uncommon (16).

Table 1. Clinical findings in HSVE.

Findings	Initial clinical findings (%)
Alteration of consciousness	97
Memory loss	92
Personality changes	85
Fever	81
Dysphasia	76
Persistent seizure	71
Headache	67
Autonomic dysfunction	60
Personality changes	46
Ataxia	40
Seizures Focal Generalized	**38** 28 10
Vomiting	33
Cranial nerve defects	32
Hemiparesis	24
Visual field loss	14
Papilledema	14

In some studies the incidence of some of the clinical manifestations might vary compared with the information in table 1 (16).

The clinical findings at the time of admission in 18 children with the diagnosis of HSE are listed in table 2 based on the study of Karimi A et al (Under Publication). The frequency of headache and CSF pleocytosis are higher in patients with confirmed HSE than in patients with diseases that mimic HSE. Irrespective of age, the typical patients with HSE present with fever and changes in personality. Seizures, whether focal or generalized, occur in only about two third of the patients with confirmed disease(17).

Patients with meningitis typically have headache, nuchal rigidity and fever, but there isn't any altered sensorial or focal neurological findings (18).

It is recommended the diagnosis of HSVE must be suspected in all cases of febrile diseases accompanied with headache, altered level of consciousness, and signs and symptoms of cerebral dysfunction.

Physical examination

The Physical exam consists of a combination of general and neurological examinations.

HSV-1 encephalitis might be accompanied with Gastrointestinal and upper respiratory manifestations (1). The presence of oral or genital lesions is of no help in the diagnosis or exclusion of HSV encephalitis. No correlation exists between isolating HSV from sites extrinsic to CNS and the diagnosis of HSVE (16). In neurological examination, the existence of behavioral, cognitive and focal neurological signs and seizures indicate the brain malfunction.

The severity of clinical signs depends on the condition of the patient immune system and his/her age. The very young and the very old patients manifest the most serious signs of encephalitis (1). Despite this, the diagnosis of HSV infection should carefully be considered even in patients with mild or atypical presentations of encephalitis (19).

Table 2. Clinical findings at the time of admission in Karimi et al study (Under Publication)

Clinical Findings	Frequency (%)
Fever	88.9
Alteration of consciousness	72.2
Seizures (Focal, generalized)	72.2
Confusion	66.7
Focal neurological signs	55.6
Vomiting	44.4
Headache	22.7
Behavioral changes	11.1

Diagnostic investigations

The diagnosis is based on any two of the followings:
(1) A compatible clinical pattern
(2) Isolation of the virus
(3) Development of specific antibodies
(4) Demonstration of characteristic cells, histological changes, viral antigen, or HSV DNA in scraping CSF, or biopsy material (10).

CSF

CSF analysis is indicated in patients with altered mental states, provided it is not contraindicated because of increased intracranial pressure. Because of the similarity of CSF analysis results in confirmed disease and those mimicking HSE, CSF findings are nondiagnostic in patients with HSE (17). CSF analysis displays elevated levels of mononuclear cells and proteins. As the disease progresses, both protein and WBC count raise.

The protein level averages approximately to 100mg/dl. Elevated protein is reported in 80% of patients which rises to the striking levels as the disease progresses (9, 19, 20).

Early in infection, the neutrophils might be dominant, a lymphocytic pleocytosis of about 10-500 cells/mm3 occurs in 85% of HSE patients, while less than 8% of patients with biopsy or PCR-proven disease are reported to have a normal CSF cell count. RBCs are frequently detected in the CSF (10, 16). The presence of red blood cells is not diagnostic for HSE. Also there might be a mild hypoglycorrhachia (11).

In Karimi et al study (Under Publication), CSF analysis in 18 children with HSE resulted the CSF pleocytosis in 33.3% of cases, RBC detection in 61% of them and elevated levels of CSF protein in 50% of cases.

Nearly 5-10% of patients have a normal CSF results on the first admission. The later observations should be carry out especially in children in whom the presentations include fever, encephalopathy, altered mental state, and initially normal CSF examinations. However, repeating the CSF analysis even within 24 hours will usually reveal abnormalities (15).

EEG

In 80% of the patients there is typical findings in EEG .There is a temporal focus showing periodic lateralized epileptiform discharge as well as the background slowing (21). These findings are suggestive but not pathogonomic (16). In the early stages of disease, the abnormal electrical activities usually involve one temporal lobe and then spread to the contralateral temporal lobe as the disease evolves (22).

These changes in EEG are observed within the first 5-7 days of illness (23, 24).

CT

CT findings may be characteristic late in illness and consist of low-density, contrast -enhanced lesions in the temporal lobe, mass effect, edema, and hemorrhage; early in the illness, when diagnosis is critical , CT findings are more often unremarkable (16).

30-40% of patients might have normal CT scan (8). Follow up imagings 1-2 weeks after the disease onset demonstrate more widespread abnormalities with involving contralateral lobe, insula and cingulate gyrus.

In Panagariya A study, CT scan showed asymmetric fronto-temporal lesions with or without hemorrhage in 64% of cases (8).

According to Karimi A et al study (Under Publication), 81% of patients which undergone brain CT scan had shown abnormal changes (4 patients: hyperdensity in temporal lobe, 3 patients: brain edema, 2 patients: brain hemorrhage).

MRI

MRI is more sensitive and specific than CT for evaluating viral encephalitis (25).

Findings include hyperintensity of the temporal lobe on T2-weighted images with gadolinium enhancement. MRI findings may be abnormal at the initial evaluation of HSVE because of its high sensitivity to the changes in brain water content (16).

Of 8 children who did brain MRI in Karimi A et al

study (Under Publication), 22% had temporal lobe hyperintensity on T2-weighted images. Typical early findings include gyral edema on T1 weighted imaging (T1W1) and high signal intensity in the temporal lobe or cingulate gyrus on T2W1, FLAIR and DW1 and later hemorrhage. Hypointensity on T1, hyperintensity on T2W1, FLAIR, high signal on DW1 are other findings (26).

PCR

PCR technology provides the most convenient test. Prior to the advent of PCR, brain biopsy with virus isolation -which has a specificity of 100%-was the accepted standard method of diagnosis (27). PCR has a sensitivity of 98-99% and a specificity of 94-100%.(8, 27).

HSV DNA PCR from CSF was done in 9 patients with HSE in Karimi A et al study (Under Publication) and 8 patients had positive DNA PCR in CSF. PCR analysis can confirm the positive results one day after the onset of symptoms. However, the negative result does not essentially exclude the diagnosis (16).

In the patients with a high likelihood of HSE (e.g. typical EEG, MRI or CSF pleocytosis) a negative test only reduces the disease likelihood to about 5%. In patients with the low likelihood of HSE, a negative CSF HSV PCR result reduces disease likelihood to less than 1 % (28 , 29).

PCR analysis allows the antiviral therapy to be performed efficiently and helps to detect the existence of a resistant strain of the virus (1).

Although PCR analysis of CSF for HSV DNA is the gold standard for diagnosis of HSE, supportive techniques such as neuroimaging, EEG and examination of CSF may also be favorable in establishing the diagnosis of disease (29). Quantitative HSV PCR is known to be valuable in determining the prognosis of HSV encephalitis (30). In one study, the morbidity and mortality rates were higher in patients with a high copy number (more than 100 HSV DNA copies/mm3 of CSF) than in those with lower copy numbers. In general, higher levels of HSV DNA were reported in the CSF analysis of patients with a longer duration of symptoms; patients with a high copy number had a mean of 6.5± 3 days of symptoms compared with 3.8±3 days of symptoms for those with the less DNA in their CSF (30).

In another study, it has been shown there wasn't any obvious correlation among HSV-1 load in the CSF and the severity of clinical signs or the findings in cranial imaging and the overall outcome (29, 31). However, the amount of HSV-1 DNA in the CSF decreases following the Acyclovir therapy.

Serology

CSF (intrathecal) antibody measurements are not recommended for acute diagnostic purposes. Intrathecal HSV antibody response might be helpful to confirm the diagnosis in the cases in which the PCR is negative because of the late sampling of CSF from the onset of disease.

In children and young adults, HSV serology might be helpful to define whether the HSE is a result of a primary or reactivated HSV infection, although the clinical features, therapy, and prognosis of both types of HSVE are similar (29).

Brain biopsy

Brain biopsy has to be considered in the patients who have negative PCR results despite of having typical signs and symptoms of HSVE. Decision of analysis suggests that obtaining a biopsy is especially critical in a patient with low CSF glucose levels (16).

Brain biopsy is worthwhile in confusing clinical presentations and acute or chronic complications which occur in about 3% of patients (15).

Differential diagnosis

Sometimes it is very difficult to distinguish the HSVE and other diseases. Especially in the children, the likelihood of distinguishing HSVE from other similar diseases is poor (16).

Table 3. HSV encephalitis differential diagnosis (16)

Autoimmune / vascular diseases	
Neoplastic diseases	
Infectious diseases:	Fungal (e.g. Cryptococcus)
	Bacterial (e.g. Abscess, Cerebritis, …)
	Protozoal (e.g. Toxoplasmosis , Amebic)
	Rickettsial
	Viral (e.g. Mumps virus, coxsackie virus, echovirus, arbovirus,…)
Metabolic diseases	
Toxins	
Adrenal Leukodystrophy	
Alcoholic encephalopathy	

Treatment

The first antiviral drug reported to be efficient in treating HSE was Idoxuridine; however, in a controlled clinical trial the drug has been proved to be not only ineffective but also toxic (15).

Subsequent therapeutic trials presented Vidarabine as an efficient medication for managing biopsy-proven HSE; after a while this drug was also replaced by Acyclovir following further investigations.

The current standard of therapy for HSVE in children is intravenous Acyclovir (10 mg/kg/dose given over 1-hour q8hr for 14-21 days) (32, 33, 34, 35).

Acyclovir decreases the mortality rate to 19%, Six months after the beginning of therapy. Importantly, 38% of patients, irrespective of age, recover and return to the normal function. However, conversely, most patients are left with significant neurologic impairment (15). Returning to the normal activity is more likely in young patients (less than 30 yrs old) with the better consciousness state than older patients who are semicomatose or comatose. Notably, 90% of individuals younger than 30 years old were children and adults.

New therapeutic protocols, such as anti-inflammatory agents and antiapoptotic agents should be explored (29).

Prognosis

The mortality rate in untreated HSVE patients is about 70 percent, and the survivors generally suffer severe and permanent neurological disabilities.

In patients with HSVE the prognosis for survival or for recovery without serious permanent residua is guarded. Early diagnosis and therapy improve the outcome (10, 16).

The outcome of Acyclovir therapy in children depends on factors such as:

-Age

-the level of consciousness at the time of admission

-Duration of encephalitis

-Viral load

Early onset of therapy in the first four days increases the 18-month survival from 72% to 92 % (29, 33). So it is strongly recommended to commence the Acyclovir therapy as soon as the diagnosis is suspected, while the investigations are in progress.

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