



# Herpes Simplex Virus Type 1 Encephalitis: A Descriptive, Cross Sectional Study, 2011 - 2016, Iran

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## Abstract

**Background:** Encephalitis may arise from infectious or non-infectious etiologies. Infections, predominantly viruses, are the most common causes of encephalitis. Herpes simplex virus (HSV) is the most prevalent cause of viral encephalitis in the developed countries. HSV encephalitis occurs equally in both genders and most cases are caused by HSV type 1 (HSV-1).

**Methods:** The current descriptive, cross sectional study was conducted on patients admitted with HSV-1 encephalitis from 2011 to 2016 to Imam-Khomeini hospital complex in Tehran, Iran. The patients with clinical diagnosis of encephalitis whose cerebrospinal fluid (CSF) HSV-1 polymerase chain reaction (PCR) was positive were included. All clinical, laboratory, and imaging characteristics of patients along with their outcomes were evaluated and analyzed.

**Results:** In the current study, of 12 cases with encephalitis manifestations and positive CSF HSV-1 PCR results, 5 were male and 7 were female with mean age of 42 years. Fever and headache were the most common complaints. Headache was more common in the cases admitted earlier (P value = 0.001). The patients were studied by brain magnetic resonance imaging (MRI) and the findings confirmed encephalitis in all the cases. Five cases had unilateral temporal lobe lesions and 6 cases had bilateral lesions. There was a clear relationship between bilateral temporal lobe lesions and higher protein level in CSF (P value = 0.001); 25% of patients (3 cases) needed stay in the intensive care unit (ICU). Three patients died and 5 patients developed disabilities.

**Conclusions:** HSV encephalitis is a devastating disease. Clinical findings along CSF analysis and neuroimaging may result in the appropriate diagnosis. Despite appropriate treatment, undesired outcomes are common.

**Keywords:** Encephalitis, Herpes Simplex Virus, Human Viral Diseases, Iran

## 1. Background

Central nervous system (CNS) infections are medical emergencies and need prompt diagnosis and therapeutic interventions (1). Encephalitis is one of the most common infections of CNS defined as inflammation in the brain parenchyma causing clinical neurologic manifestations (1-4).

Encephalitis is a complicated syndrome that sometimes its cause remains unknown (5). Encephalitis may arise from infectious or non-infectious etiologies. Infections are the most probable (almost 50%) causes of encephalitis (6). Viruses are predominant causes of infectious encephalitis (3). Viral encephalitis is a medical emergency and its prognosis depends on the kind of causative pathogen and immune status of the patient (7). Herpes simplex virus (HSV) is the most prevalent cause of viral encephalitis in the developed countries with the annual inci-

dence rate of 1/250,000 - 500,000 people (2).

The prevalence of HSV encephalitis is almost 2 - 4 persons per 10 million people worldwide (2). HSV infections hurt human beings for years and are described by ancient Greeks (6). HSV is a large, double-stranded DNA virus, well-adapted with human kind and can live latently in the human body for many years after inoculation causing relapse of clinical disorders or viral shedding during asymptomatic phase (6, 8). Although almost all adults are inoculated by this virus, clinical manifestations are very different and various, which may be related to diversity in human genetics (8).

The first case of encephalitis due to HSV was reported in 1950 (6). HSV encephalitis occurs with 2 peaks in young adults and elderly and equally in both genders (2, 6). Most cases are caused by HSV-1 and less than 10% by HSV-2 (2, 6). HSV-2 encephalitis occurs mostly in neonates, immunocompromised patients, and old people (2, 9, 10). A study

recommended that patients with encephalitis whose cerebrospinal fluid (CSF) is negative for HSV-1 polymerase chain reaction (PCR), should be tested for CSF HSV-2 PCR, especially in the immunosuppressed cases (10).

HSV encephalitis occurs by reactivation of latent virus or when primary infection happens (6). The entry pathways of the virus to CNS are not discovered clearly and remained controversial (6). Two major probable ways include firstly retrograde transfer in olfactory bulb and trigeminal ganglion and secondly hematogenous distribution (6).

## 2. Methods

The current descriptive, cross sectional study was conducted on patients admitted to Imam-Khomeini hospital complex (a referral center for infectious diseases in Iran) from 2011 to 2016. The patients with clinical diagnosis of encephalitis whose CSF HSV-1 PCR was positive were included in the study. All clinical, laboratory, and imaging data were extracted from medical records by checklists, and subsequently described and analyzed. Clinical manifestations in the first visit were fever (body temperature  $> 37.9^{\circ}\text{C}$ ), headache, loss of consciousness, changes in the score of Glasgow coma scale (GCS), and bizarre behaviors. The laboratory data included CSF analysis (glucose, protein, and cell count and differentiation) and the first CBC (the complete blood count), ESR (erythrocyte sedimentation rate) and CRP (C-reactive protein). Reports of the first magnetic resonance imaging (MRI) of brain were studied and recorded. In addition, data on complications and nosocomial infections during the hospital stay were collected.

The outcomes of patients after at least 1 year from discharge were investigated by interviewing the patients or their families, asking about the quality of life, disabling neurologic sequels, and death. All patients or their legal guardians signed the consent form. All collected data were analyzed with SPSS version 19 (Chicago, USA).

To compare qualitative variables, Chi-square test and for quantitative variables the correlation coefficient were used.

## 3. Results

In the current study, of 12 cases with encephalitis manifestations and positive CSF HSV-1 PCR results, 5 were male and 7 female with the mean age of 42 years, which 3 of them (25%) were the drug abusers. Fever and headache were the most common complaints ( $n = 8$ ; 66.7%) and only 1 patient had seizures. Headache was more common in cases that referred earlier ( $P$  value = 0.001). Mean GCS score in the first day of admission was 12 (ranging 6 to 15).

All patients were studied by brain MRI that in most of the cases findings were compatible with those of encephalitis. Five cases had unilateral temporal lobe lesions and 6 patients had bilateral lesions in the same area. In 2 patients, also parietal lobe was involved and in 1 case the lesion was detected in frontal lobe. There was a clear relationship between bilateral temporal lobe lesions and higher protein level in CSF ( $P$  value = 0.001); 25% of the patients ( $n = 3$ ) needed stay in the intensive care unit (ICU). The main complication during admission was pneumonia, which occurred in 4 patients.

Important laboratory findings were as follows:

- No white blood cell (WBC) (0 - 3) was found in CSF analysis in 2 patients. Averagely, CSF WBC count was 44 cell/mm<sup>3</sup> (with an average of 74% lymphocytes and 26% neutrophils). All patients had lymphocytic pleocytosis in CSF.

- Mean Glucose concentration in CSF was 75 mg/dL (ranging 22 to 112).

- CSF protein level was greater than 40 mg/dL in 66.7% of the patients and the mean was 78 mg/dL.

- Three patients had no red blood cell (RBC) in CSF. The mean CSF RBC count was 162 cell/mm<sup>3</sup>, ranging 0 - 850. In older patients ( $> 50$  years), hemorrhagic component was less prevalent ( $P$  value = 0.023).

- Average inflammatory biomarkers were ESR = 21.4 mm/hour and CRP = 13 mg/dL.

The mean time of symptoms manifestation to hospital admission was 4 days. Drug abusers clearly referred later ( $P$  value = 0.001), but there was no relationship between later admission and mortality in the current study. Mean days from appearance of symptoms to starting acyclovir therapy was 5 days.

Three patients (25%) were transferred to ICU during the hospital stay and there was a correlation between ICU admission and lower GCS score ( $P$  value = 0.008). In terms of nosocomial infections, 4 patients (33.3%) had pneumonia and only 1 patient developed urinary tract infection (UTI).

Three patients died, 5 patients developed disabling neurological sequelae despite treatment with acyclovir, and only 4 patients returned to normal life. There was no clear correlation between mortality and other factors in the current study.

## 4. Discussion

Initial clinical manifestations of HSV encephalitis are nonspecific (11). The key to the early diagnosis and treatment is being aware of important clinical findings including loss of consciousness lasting more than 24 hours (disorientation, cognitive and behavioral changes, and confusion), fever, headache, recent convulsion, and focal neuro-

logic signs (6, 12). Granerod et al., conducted a study from 2005 to 2008 on 203 patients with encephalitis and found that the most common feature was fever (72%) followed by headache (60%) (13). In a prospective study by Glaser et al., in California on 1570 cases suspicious to encephalitis, the most prevalent sign was fever (75%) followed by seizure (59%) (5). In the current study, fever and headache were the most common features in 8 cases (66.7%). Fever was less common in the elderly ( $P$  value = 0.042) and patients with fever had higher GCS score on the first day of admission ( $P$  value = 0.040).

Imaging has an important role in diagnosis of viral encephalitis and can also assist to make a better judgment about pathogenic agent and outcome of the disease (11). In the study by Granerod et al., sensitivity and specificity of brain MRI to diagnose HSV encephalitis were very high (11). In the same study, sensitivity of computed tomography (CT) scan to diagnose initial stages of HSV encephalitis was close to zero, while sensitivity of MRI in the same stage was 100%. This major difference gives MRI much higher priority to CT for diagnosis and is recommended before lumbar puncture (7, 11). CT scan is recommended only when MRI is unavailable (7). Most cases of HSV encephalitis in the current study had lesions in temporal and frontal lobes (11). Some researchers suggested that T2 and fluid-attenuated inversion recovery (flair) views are preferred to diffusion weighted imaging (DWI) to detect HSV encephalitis (3, 11). Although “UK national guideline for the management of suspected viral encephalitis 2012” recommends DWI as the procedure of choice for imaging, being performed during the first 24 hours of admission (maximum up to 48 hours) (2).

In a multicentric study from 1991 to 1998 by Frank Raschilla et al., on 85 definite cases of HSV encephalitis, 89% had lesions in temporal lobe and in 36% frontal lobe was involved (14). In another study on 9 patients with HSV encephalitis and positive CSF HSV PCR, 8 cases had lesions in inferomedial side in 1 or both temporal lobes. In the current study, there was no clear correlation between severity of manifestations and the extent of brain lesions in MRI (15).

In the current study, all cases had lesions in MRI, which were compatible with encephalitis. Half of the patients had bilateral temporal lobe lesions and the other half had unilateral temporal lobe lesions. There were some additional lesions in frontal (25%) and parietal (16.6%) lobes, but generally there was no clear correlation between complications, outcomes, and mortality with the extent of brain involvement in MRI.

In electroencephalography (EEG) of more than 80% of patients with HSV encephalitis, temporal lobe dysfunction was detected by periodic lateralizing epileptiform dis-

charges (3). The stereotypical sharp and slow wave complexes are observed routinely during the days 2 to 14 of the disease onset (3). Most patients of the current study were not assessed by EEG.

Pressure of CSF in patients with HSV encephalitis is normal or mildly elevated (6). CSF analysis in such patients typically shows mild mononuclear pleocytosis (10 - 200 cell/mm<sup>3</sup>), which can be polymorphonuclear dominant in the first days. Protein level in CSF is mildly to moderately high (50 - 100 mg/dL). Patients may have a few RBC in CSF indicating hemorrhagic encephalitis. Low glucose in CSF is not common and 10% of patients have normal CSF (3, 6). In the current study, average leukocyte count in CSF was 44 cell/mm<sup>3</sup> (ranging 0 - 180). Only 3 patients (25%) had no RBC in CSF. All patients had lymphocytic pleocytosis. Quantity and type of WBCs in CSF help in diagnosis of viral encephalitis. Blood lymphocytosis is in favor of viral encephalitis as well (7). WBC differentiation in CBC was not assessed in the current study patients, but the first WBC count in blood was averagely 10,400 cell/mm<sup>3</sup> (ranging 6700 - 19,400).

ESR is an inflammatory marker that is usually normal in viral encephalitis and elevated ESR suggests carcinomatosis or tuberculosis in CNS (7). In the current study, the mean quantity of inflammatory index was in normal range.

The management of patients with encephalitis is more difficult and challenging than cases of meningitis and needs more accuracy and speed in diagnostic procedures (1). For all patients with clinical manifestations of encephalitis, intravenous (IV) acyclovir (10 mg/kg per dose 3 times a day) should preferably be started immediately and then, diagnostic procedures should be followed (6). Duration of treatment is usually 14 - 21 days (3). Gnann et al., in a trial on 87 patients, after completion of standard treatment with IV acyclovir, evaluated patients in 2 groups, 1 with extended treatment by oral valacyclovir (2 g 3 times a day) for 3 months and the other receiving placebo. The study concluded no clear differences between the groups in terms of mortality and neurologic disabilities (16). Adjunctive therapy with corticosteroids may be helpful to improve the outcomes of disease, but it is not recommended (3, 12). In the current study, all patients were treated by IV acyclovir and the mean duration of treatment was 18 days (ranging 15 to 28 and shorter courses were used in the expired patients) and for all patients acyclovir therapy was started in the first 24 hours of admission and none were under treatment with corticosteroids or extended oral acyclovir therapy.

Post-operative HSV encephalitis is a rare complication of neurologic surgeries, which may cause serious adverse effects (17). In the current study, none of the patients had

the history of neurologic surgeries.

HSV encephalitis is accompanied by significant mortality, especially in patients not receiving appropriate treatment. In such patients, mortality is about 70% and the 97% of the remaining have devastating neurologic dysfunctions (6). In a retrospective study from 1984 to 2003 on 40 children with HSV encephalitis in Taiwan, lethargy on the day of admission was associated with unpleasant outcomes, but age, gender, and other manifestations had no association with specific outcomes. In the mentioned study, delay in starting acyclovir therapy was accompanied by unpleasant outcomes (18). In another study with 13% mortality and 15% severe disability in the first 6 months, the most important correctable factor in patients with unpleasant outcomes was delay in starting acyclovir therapy (14). In the study by Mailles et al., in France on 253 patients with encephalitis, the most prevalent cause was HSV-1 (46%) and the most common risk factors for mortality included age, cancer, recent immunosuppressive therapy, falling into coma, and sepsis after 5 days of hospitalization. The most prevalent cause of mortality was bacterial infection (19). In another study on HSV encephalitis, the indices associated with unpleasant outcomes were age above 30 years, GCS < 6, and lasting more than 4 days from beginning of manifestations to the start of acyclovir therapy (3). In the current study, mortality was 25%, one-third of the patients returned to normal life and about 40% were involved with unwanted neurologic outcomes. One mortality case was in a patient whose first CSF analysis appeared normal and brain MRI pattern had involvement of gyrus rectus in frontal lobe, which is not a characteristic of HSV encephalitis. According to these findings, acyclovir therapy was stopped and the patient died 5 days later, before CSF HSV PCR revealed the infection. The second mortality was a patient with HIV and fever, hallucination, and loss of consciousness. Initially, CNS opportunistic infections in the context of AIDS were considered; therefore, the patient received toxoplasmosis treatment instead of HSV encephalitis therapy. Acyclovir therapy was started promptly after brain MRI strongly suggesting HSV encephalitis, but the patient died after 5 days. The third mortality was a patient with diabetes and several drug-resistant nosocomial infections in ICU who were finally expired due to sepsis. Moreover, there was no association between mortality and other factors that may be due to small sample size. The most important limitations of the current study were defects in the data accurate recording and referral to patients' files.

#### 4.1. Conclusion

HSV encephalitis is a devastating disease that any delay in its diagnosis and treatment may lead to ominous out-

comes. This entity presents with nonspecific symptoms, mostly fever and headache. CSF analysis and neuroimaging usually helps in early and correct diagnosis. Although most patients have lymphocytic pleocytosis in their CSF, lack of WBC and RBC in CSF analysis does not rule out possibility of HSV encephalitis. MRI is a useful tool for diagnosis, since it shows abnormalities pertinent to encephalitis early in the course of disease in almost all patients. With regard to the mortality cases, it is important to remember a few points. First, in patients clinically suspected to encephalitis, if the initial CSF analysis and brain MRI were not in favor of HSV encephalitis, acyclovir therapy should not be discontinued until CSF PCR negative rules out the diagnosis. The second point is that even in patients with AIDS or other immunocompromised conditions, HSV could be the most important cause of encephalitis and should always be considered in the differential diagnosis, and finally various cautions should be considered seriously to prevent nosocomial infections, particularly in the patients stayed in ICU.

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#### Footnotes

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