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Herpes simplex virus encephalitis: Clinical manifestations, diagnosis and outcome in 106 adult patients

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ABSTRACT

Background: Herpes simplex virus (HSV) is one the most common causes of sporadic encephalitis worldwide.
Objective: We aimed to determine clinical characteristics and prognosis of HSV encephalitis (HSVE) cases reviewed retrospectively from several collaborating centers.
Study design: We searched hospital archives of the last 10 years for patients with HSVE diagnosis, i.e. clinical presentation compatible with encephalitis and brain involvement on magnetic resonance imaging (MRI) or detection of HSV DNA in the cerebrospinal fluid by polymerase chain reaction (PCR). Clinical characteristics were noted and patients were phone-interviewed. HSVE cases were grouped and analyzed as proven and probable, based on virological confirmation by PCR. Univariate and multivariate analyses were used to determine factors associated with prognosis.
Results: A total of 106 patients (63 males; mean age, 44 years; range, 18–83 years) were included. Most common symptoms were changes in mental status, fever, headache, and seizure. HSV PCR was positive in 69% of patients tested, while brain involvement was detected on MRI in 95%. Acyclovir was started mostly within five days of main symptom and continued for ≥14 days. Case fatality rate was 8%, while 69% of patients recovered with sequelae. Favorable prognosis was observed in 73% of patients. Multivariate analysis identified the duration of disease before hospital admission (odds ratio (OR) = 1.24) and the extent of brain involvement on MRI at the time of admission (OR = 37.22) as two independent risk factors associated with poor prognosis.
Conclusions: Although HSVE fatality regressed considerably with acyclovir treatment, many patients survive with sequelae. Our results emphasize the importance of early diagnosis and prompt treatment of HSVE.

Abbreviations: CI, confidence interval; CSF, cerebrospinal fluid; HSV, herpes simplex virus; HSVE, herpes simplex virus encephalitis; MRI, magnetic resonance imaging; OR, odds ratio; PCR, polymerase chain reaction.

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1. Background

Herpes simplex virus encephalitis (HSVE) is one of the most common causes of sporadic necrotizing encephalitis globally [1,2]. HSVE is characterized by fever, headache, mental status changes, seizures, and focal neurological deficits that develop acutely [3]. HSVE is caused by invasion of the brain parenchyma by HSV through primary infection or reactivation of the latent virus. Encephalitis typically involves the temporal lobe and is best visualized by magnetic resonance imaging (MRI) of the brain [4]. The detection of HSV DNA in cerebrospinal fluid (CSF) using polymerase chain reaction (PCR) confirms the diagnosis of HSVE [5].

HSVE-related fatality rate and morbidity were around 70% and 50%, respectively, before the development of effective antiviral therapy [3,6,7]. With the introduction of acyclovir in mid-1980s [8,9], HSVE became a much more treatable disease, and consequently HSVE-related one-year fatality rate declined to 5–15% [2,10]. Despite this, neuropsychiatric sequelae are still common [10]. Poor prognosis was shown to be associated with delays in the diagnosis and treatment of HSVE [11–14].

2. Objective

We aimed to determine the diagnosis, treatment, and prognosis-related clinical features of HSVE cases reviewed retrospectively from several collaborating centers in Turkey.

3. Study design

Archives of infectious disease and neurology departments of 17 hospitals were searched retrospectively for adult HSVE cases. To be included in the study, a patient should have presented with the clinical characteristics of encephalitis (changes in mental status, abnormal behavior, speech disturbances, epilepsy) alongside typical involvement of brain on MRI and/or PCR detection of HSV DNA in CSF. Due to the retrospective nature of the study spanning several years, PCR methodology used to detect HSV DNA varied between the centers. A total of 106 patients diagnosed in a time frame of 10 years, from 2001 to 2012, constituted our HSVE group. All cases were above 18 years of age. Demographic data, duration and characteristics of complaints related to encephalitis, physical examination findings, laboratory values at the time of admission, PCR detection of HSV DNA in the CSF, electroencephalography, brain computed tomography (CT), and MRI were retrieved. For each case, medical notes were extensively reviewed and symptoms deemed to be related to encephalitis were recorded. Symptoms were classified as "main symptom", when it caused emergency department admission and "first symptom", when it was present from the beginning of the illness. Treatment related characteristics such as acyclovir duration, start of treatment in relation to main and first symptoms, and development of nephrotoxicity (defined as absolute increase in serum creatinine of ≥0.3 mg/dL within 48 h of treatment) were noted. Patients with somnolence, stupor, or coma at admission were regarded as having severely depressed level of consciousness for the purpose of analysis. MRI brain involvement was categorized as unilateral, bilateral, or extensive.

Outcome assessment was conducted on 97 (92%) patients, as there was no follow-up information on nine patients. To determine the level of morbidity, we conducted a standardized telephone interview with the patients and/or their relatives, at least six months after discharge. Twenty-nine cases (30%) could not be reached for a telephone interview. For these cases, the last observation on their medical files was extrapolated as the outcome. To verify this approach, we extrapolated the outcome of interviewed patients using the last observation in their medical files and calculated the performance of this method. The sensitivity and specificity of predicting poor outcome using the last observation method was 86% and 94%, respectively. Thus, we included these 29 patients in our analyses.

We scored the level of morbidity according to the publication by Whitley et al. with modifications [9]:

- No sequelae: patient states that his/her health is exactly like the pre-encephalitic period.
- Mild sequelae: patient has subjective minor disability compared to pre-encephalitic stage such as memory impairment or decrease in attention span; not on anti-epileptic treatment; able to work and function autonomously.
- Moderate sequelae: patient has subjective major disability compared to pre-encephalitic stage or is on anti-epileptic treatment; mostly self-sufficient in daily routine; states that his/her life has significant differences compared to the pre-encephalitic stage; cannot sustain a regular job.
- Severe sequelae: major neuropsychiatric disability or chronic care patient; Kluver-Bucy syndrome; need constant help for daily routine.

PCR positive and PCR negative/not done cases were grouped as "proven" and "probable", respectively, and compared for any statistically significant differences. To identify the factors that determine the outcome, patients with fatality or severe sequelae were classified as "poor prognosis", while patients with no or mild-to-moderate sequelae were classified as "favorable prognosis."

Univariate analyses were carried out for comparing poor and favorable prognosis within proven, probable and total groups. Mann–Whitney *U* test was used for comparing continuous variables since the data did not follow normal distribution. Chi-square or Fisher's exact tests were used for comparing categorical variables. Multivariate analysis was carried out with covariates that showed a p value of <0.1 at univariate analysis of the total group. Backward stepwise logistic regression was used to assess the effects of independent variables by controlling the confounders. Multicollinearity was checked through evaluating variance inflation factor. The strength of associations was described by odds ratios (ORs) and 95% confidence intervals (CIs).$p < 0.05$ was accepted as statistically significant.

4. Results

Our screen yielded 106 cases of HSVE (63 males and 43 females; mean age, 44 years; range, 18–83 years). All cases exhibited the clinical characteristics of encephalitis with compatible MRI findings ($n = 101$) and/or PCR detection of HSV DNA in CSF ($n = 55$).

All patients were admitted through the emergency department. The most common symptoms were mental status changes such as confusion/disorientation (81%) and abnormal behavior (66%), fever (76%), headache (70%), speech disturbances (57%), and seizure (55%). At the time of admission, 90% of patients had abnormal level of consciousness, 32% exhibited meningeal irritation signs, and 26% had focal neurological deficit (Table 1).

To understand the evolution of symptoms, we sought to determine a main symptom that brought the patient to the emergency room and a first symptom that was present from the beginning of the encephalitic process. Main symptoms were predominantly neurological such as seizure (32%), abnormal behavior (23%), loss of consciousness (13%), and confusion/disorientation (13%). Duration from the onset of main symptom to hospital admission was 2.3 ± 2.6 days (range, 1–20 days, Table 1). Among first symptoms, headache (50%) and fever (22%) were the most frequent. Duration

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