

Case Report

## Herpes simplex encephalitis

Hasan Karsen<sup>a</sup>, Cengiz Demir<sup>b</sup>, Mustafa Kasım Karahocagil<sup>c\*</sup>, Mahmut Sünnetcioğlu<sup>c</sup>, Hayrettin Akdeniz<sup>c</sup>

<sup>a</sup> Department of Infectious Diseases and Clinical Microbiology, Şanlıurfa State Hospital, Şanlıurfa/Turkey

<sup>b</sup> Department of Internal Medicine, Yuzuncu Yıl University, Faculty of Medicine, Van/Turkey

<sup>c</sup> Department of Infectious Diseases and Clinical Microbiology, Yüzüncü Yıl University, Faculty of Medicine, Van/Turkey

**Abstract.** We presented four cases diagnosed with *Herpes simplex virus* encephalitis of those treated in our clinic in 2006 one of whom died, one recovered without any sequels. Two cases were left with advanced motor mental sequel. In this paper, clinical and laboratory findings along with diagnosis and treatment of *Herpes simplex virus* encephalitis were discussed.

Key words: *Herpes Simplex virus*, encephalitis, diagnosis and treatment

### 1. Introduction

*Herpes Simplex virus* (HSV) is the most important causative agent of endemic focal encephalitis. Sensitivity and specificity of detection of HSV-DNA from cerebrospinal fluid (CSF) with polymerase chain reaction (PCR) method in diagnosis of HSV encephalitis is accepted as 98% and 94–100% respectively. PCR method is assessed as gold standard method in diagnosis of HSV encephalitis nowadays (1). In untreated or lately treated cases, mortality and sequel rates are very high, but early treatment can lead to good results. We presented 4 cases that were hospitalized, followed and treated in our clinic in 2006 as follows.

### 2. Case reports

Case 1: A 21 year-old male patient was admitted to Van State Hospital with complaints of fever, headache, nausea and vomiting, fatigue and loss of appetite which developed the previous day. The next day he had disorganized speech, uncontrolled movements, ravings and convulsions, and then he fainted and lost consciousness. The patient came to the Emergency Department of our hospital with these complaints. In his physical examination, the general status was bad, consciousness closed, arterial blood pressure 110/80 mmHg, pulse rate 110/min, temperature 40,7 °C, breath rate 30/min. He had neck stiffness, but Kernig and Brudzinski's signs were negative. On cardiac auscultation, there was a metallic valve sound. Examination of other systems was normal. 40 days earlier, a prosthetic aorta valve had been replaced and a pacemaker settled. He had been using coumadin tb 1x5 mg due to this operation. CT of the brain revealed no pathology. Lumbar puncture could not be performed due to his elevated protrombin time (PT): 61 sec (INR value 7.5). After 2 units of fresh frozen plasma and 1 ampoule vitamin K, PT reduced to 19 sec (INR 1.6) and lumbar puncture was done. In CSF examination, there was 50 leukocytes/mm<sup>3</sup> (80% mononuclear cells), CSF glucose 102 mg/dl (simultaneous blood glucose 138 mg/dl), CSF protein 283 mg/l (normal: 150–450 mg/l). The patient was hospitalized with a preliminary examinations, white blood cell count was 14.200/mm<sup>3</sup> (with differential of 78%

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\*Correspondence: Dr. Mustafa Kasım Karahocagil  
Department of Infectious Diseases and Clinical Microbiology  
Faculty of Medicine, Yüzüncü Yıl University  
65200 Van / Türkiye  
Telephone: + 90 432 2164705  
Fax: + 90 432 2167519  
Email: mkarahoca@hotmail.com  
mkarahocagil@yahoo.com.tr

polymorphonuclear leukocytes, 12% monocytes and 8% lymphocytes), hemoglobin (Hb) 12.8 g/dl, platelets 102.000/mm<sup>3</sup>, C-RP 243 mg/dl, Brucella Wright Test both in blood and CSF was negative. Gram and Ziehl-Neelsen staining of the CSF did not reveal any organism. In addition to antiedema and steroid treatment, the patient was given i.v. acyclovir 3x10 mg/kg/day with a preliminary diagnosis of herpes encephalitis based on clinical and laboratory findings. EEG of the patient could not be assessed because of the pacemaker interference. Brain MRI could not be performed due to prosthetic aorta valve. HSV-DNA was measured in CSF by PCR method (Herpes Simplex I-II PCR Test, Roche Light Cycler System) in the Central Microbiology Laboratory of Yüzüncü Yıl University Medical Faculty and was found positive (HSV type I DNA: 21.000 copy/ml). The consciousness of the patient recovered after 3 days of treatment and his temperature subsided at the fourth day of treatment. The patient was discharged with full recovery after two weeks treatment of acyclovir.

Case 2: Complaints of fever and headache started in a 19 year-old male patient. The next day tonic clonic generalized convulsions developed and he fainted. His temperature was measured as 40 °C at Van State Hospital. He was given symptomatic treatment and recovered consciousness 2 hours later. Approximately 7 hours later, he experienced tonic clonic generalized convulsion again and was referred to the Emergency Department of our hospital. There was no pathology in his brain CT. In lumbar puncture, there was 40 leukocytes/mm<sup>3</sup> (60% mononuclear cells) in the CSF, glucose 67 mg/dl (simultaneous blood glucose) 106 mg/dl protein 370 mg/l (normal: 150–450 mg/l). He was hospitalized in the Intensive Care Unit with preliminary diagnosis of encephalitis. In his physical examination, general status was bad, consciousness closed. The patient was intubated because of irregular and inadequate breathing. Arterial blood pressure was 100/60 mmHg, pulse rate: 120/min, temperature 39 °C, breath rate: 18/min. In neurological examination, neck stiffness was positive, but Kernig and Brudzinski's signs negative. Examination of other systems was normal. In laboratory examinations: WBC was 15.600/mm<sup>3</sup> (with differential of 88% polymorphonuclear leukocytes, 5% lymphocytes, 5% monocytes), Hb: 15.4 gr/dl, platelets: 214.000/mm<sup>3</sup>, C-RP 146 mg/l, Brucella Wright test in the CSF and blood was negative. There was no organism in Gram and Ziehl-Neelsen stainings of the CSF.

He was considered as herpes encephalitis based on his clinical and laboratory findings and i.v. acyclovir 3x10 mg/kg/day was started in addition to antiedema and steroid treatment.

Phenitoin and oxcarbazepine were added for his convulsions. Brain MRI did not reveal any pathology. EEG of the patient could not be entirely evaluated because of intubation and lack of compliance. HSV type 1 DNA was measured as 16.800 copy/ml in the Central Microbiology Laboratory of Yüzüncü Yıl University Medical Faculty. Tracheostomy was applied one week later. Chest tube was settled at the twelfth day because of development of pneumothorax during his follow up at the Intensive Care Unit. Secondary bacterial infections which developed due to *Acinetobacter* and *Pseudomonas spp.* were treated with appropriate antibiotics. Acyclovir treatment was completed to 21 days and stopped. Pneumothorax and general status of the patient improved, but he did not come to. The patient was left with advanced motor and mental sequels. He was referred to a Rehabilitation Center after one month of his hospitalization.

Case 3: Complaints of fever and headache started in a 26 year-old male patient. The next day, he suddenly fainted and came to 10 minutes later. He was admitted to the Emergency Department of our hospital with complaint of convulsion and fainted again when he was there. Brain CT was evaluated as normal. In neurological and psychiatric consultations, he was evaluated as normal and sent to his home. The day after, he was referred to a Private Hospital and brain MRI taken there revealed marked lateral ventricle temporal horns especially being apparent in the right side. The EEG taken at the same day showed sharp wave discharges on the temporal region. With these results, he was diagnosed with cephalgia and given cefazolin, metamizole sodium, oxcarbazepine and chlorpheniramine maleate. He used these drugs, but he did not benefit. His headache and temperature increased, he began to speak nonsense and show harmful behaviour to himself. He was referred to the Psychiatry Clinic; he was trying to insert his hand into the doctor's pocket and take his belongings. The next day, he was referred to the Neurology Clinic and given one ampoule diazepam, so after 5 days of these complaints, he was admitted to the Emergency Department of our hospital with closed consciousness. Brain CT was taken, yet revealed no pathology. In lumbar puncture, there was 570 leukocytes (80% mononuclear cells), glucose 65 mg/dl (simultaneous blood glucose)

112 mg/dl), protein 577 mg/l (normal 150–450 mg/l ). Thus the patient was hospitalized with preliminary diagnosis of encephalitis. In his physical examination, general status was bad, consciousness closed, arterial blood pressure 130/70 mmHg, pulse rate 120/min, temperature 39.5 °C, breath rate 22/min. Neck stiffness was positive, Kernig and Brudzinski's signs negative. Examination of other systems was normal. In laboratory examinations, WBC was 16.700/mm<sup>3</sup> (with differential of 85% polymorphonuclear leukocytes, 7% monocytes and 6% lymphocytes), Hb 15.7 g/dl, platelets 177.000/mm<sup>3</sup>, C-RP 31 mg/l, Brucella Wright Test in the CSF and blood was negative. Gram and Ziehl-Neelsen stainings of the CSF revealed no organisms. IV acyclovir 3x10 mg/kg/day was started to the patient considering Herpes Encephalitis based on his clinical and laboratory findings in addition to antiedema and steroid treatment. HSV type 1 DNA was measured as 113.000 copy/ml with PCR method in the Central Microbiology Laboratory of Yüzüncü Yıl University Medical Faculty. The fever subsided on the 5th day, but reincreased on the 9<sup>th</sup> day. His breathing deteriorated and he was taken to the Intensive Care Unit. Appropriate antibiotics were added because *Acinetobacter* and *Pseudomonas spp.* were grown from blood cultures while he was in the Intensive Care Unit. Brain CT taken there revealed infarcts in the left hemisphere and pons, pressure to the left ventricle and shift to right from the left. On the 18<sup>th</sup> day of hospitalization, his fever subsided and acyclovir was completed to 21 days and stopped. He was left with advanced mental and motor sequels and therefore sent to a Rehabilitation Center for treatment.

Case 4: A 27 year-old female patient had a headache lasting for a week. Then her headache increased and she had also fever. After 3 days of complaints, she had difficulty recognizing her relatives, began to speak nonsense and the day after generalized tonic clonic convulsions developed two times lasting 2-3 minutes with 5 hours apart. She was referred to a doctor with these complaints, but she did not benefit from the treatment. After 6 days of her complaints, she was admitted to our Emergency Department with confusion. Brain CT of the patient revealed moderate edema in both hemispheres. In lumbar puncture, CSF had 380 leukocytes/mm<sup>3</sup> (80% mononuclear cells), glucose was 56 mg/dl (simultaneous blood glucose) 97 mg/dl), protein 564 mg/l (normal 150–450 mg/l). The patient was hospitalized with a preliminary diagnosis of

encephalitis based on her clinical and laboratory findings.

In her physical examination, general status was bad, consciousness confused, arterial blood 160/110 mmHg, pulse rate 110/min, temperature 38 °C, breath rate 18/min. Neck stiffness was positive, Kernig and Brudzinski's signs were negative. Gram and Ziehl-Neelsen stainings of the CSF revealed no organisms. IV acyclovir 3x10 mg/kg/day was started to the patient on considering herpes encephalitis based on her clinical and laboratory findings in addition to antiedema and steroid treatment. HSV type 1 DNA measured with PCR method revealed 95.400 copy/ml in the Central Microbiology Laboratory of Yüzüncü Yıl University Medical Faculty. EEG taken on the 4<sup>th</sup> day revealed multifocal sharp wave discharges on fronto-temporal regions of both hemispheres. Additionally focal sharp waves were observed on posterior regions of the right hemisphere. Brain MRI taken on the fifth day of her hospitalization revealed widespread signal increases on both hemispheres especially more marked on the left temporal region. Existing meningeal contrastings after injection of i.v. contrast substance were evaluated as encephalitis. Brain MRI taken on the 15<sup>th</sup> day of hospitalization revealed increased signal intensities in cortical, subcortical white matter of the left temporal lobe. Additionally there were signal increases on the right frontal anterior lobe, and contrast involvement was observed after i.v. contrast substance injection. In comparison of two MRIs, partly regression was observed in lesions on the left temporal lobe and the result was evaluated as herpes encephalitis. In clinical follow-up of the patient, fever did not subside, the temperature was always 38–38.5 °C. On the 6<sup>th</sup> day of hospitalization, respiratory failure developed, thereupon she was intubated and referred to the Intensive Care Unit. On the 8th day of hospitalization, her blood glucose levels increased and insulin was started. On the 9<sup>th</sup> day, tracheostomy was opened. On the 11<sup>th</sup> day, sinus tachycardia started (pulse 160/min) and antiarrhythmic treatment was added. In ICU, *Pseudomonas spp.* and MRSA were grown out of the tracheostomy materials, and required antibiotics were added. On the 30<sup>th</sup> day, coldness developed on her right leg and pulsations of her right leg were not able to be felt. Thus antithrombotic treatment was started. On day 31, she died due to cardiopulmonary arrest. Clinical and laboratory findings of the cases are shown in tables 1-2.

Table 1. Clinical findings of the cases

Case	1	2	3	4
Age - Gender	21- Male	19 - Male	26 - Male	27 - Female
Symptoms	Fever, headache, nausea, vomiting, faintness, coma	Fever, headache, Tonic-clonic generalized convulsion, coma	Fever, headache, nonsense speech, faintness, convulsion, coma	Fever, headache, nonsense speech, proposagnosia, * convulsion, coma
Temperature	40.7 °C	40 °C	39.5 °C	38 °C
consciousness	Closed	Closed	Closed	Closed
At Admission				
Signs of Meningeal Irritation	Neck stiffness + Kernig sign – Brudzinski –	Neck stiffness + Kernig sign – Brudzinski –	Neck stiffness + Kernig sign – Brudzinski –	Neck stiffness + Kernig sign – Brudzinski –
EEG	Not performed due to metal heart valve	Normal	Sharp wave discharges	Bilateral multifocal sharp wave discharges
CT	Normal	Normal	Normal	Slight edema
MR	Not performed due to prosthetic valve	Normal	Marked ventricle horns	Signal increase in both hemispheres, contrast involvement in meninges
Lasted duration when treatment was started	3 days	3 days	5 days	6 days
Outcome	Recovery	Refereed to a rehabilitation center due to sequels	Refereed to a rehabilitation center due to sequels	Exitus

\*Proposagnosia: Difficulty recognising faces

Table 2. Laboratory findings of the cases

Cases	1	2	3	4
CSF Leukocyte Count/mm <sup>3</sup>	50 (80% MNL)	40 (60% MNL)	570 (80% MNL)	380 (80% MNL)
CSF Protein	283 mg/L	370 mg/L	577 mg/L	564 mg/L
CSF Glucose/ Blood Glucose	102/138	67/106	65/112	56/97
CSF HSV-DNA	21.000 copies/ml	16.800 copies/ml	113.000 copies/ml	95.400 copies/ml
WBC count	14.200 (78% PNL)	15.600 (88% PNL)	16.700 (75% PNL)	9.500 (3% PNL)

MNL: Mononuclear leukocytes. PNL: Polymorphonuclear leukocytes

### 3. Discussion

*Herpes simplex virus* has a worldwide distribution. Humans appear to be the only natural reservoir. Primary infections occur in the first years of life parallel to the disappearance of the antibodies acquired from the mother. Although specific antibodies develop after recovery, virus does not leave the human body

and a lifelong carriage begins. 70–90% of adults possess antibodies to HSV-1 (2).

Herpes encephalitis is the most frequent type of all encephalitides and the one with the highest mortality rate. Its annual estimated incidence is about 2–3 cases in one million persons. 95% of cases of herpes encephalitis is caused by HSV subtype 1. It enters into the body through the oropharyngeal mucosa, conjunctiva and damages

skin. It remains latently in the neurons and causes recurrent infections. Antibodies developed against the virus exist in 90% of humans, but how the virus is activated to cause In the clinical picture of encephalitis, there is a prodromal period consisting of fever and headache which lasts 2-3 day. Then psychotic behaviour abnormalities, epileptic seizures, hemiplegia, speech disorders, amnesia, stupor and coma may develop (2-4). All of our cases had fever and headache and then faintness and epileptic seizures developed and eventually the clinical picture deteriorated with the development of coma. Thus, HSV encephalitis should be taken into consideration in variety of diagnosis of all patients with fever, headache and altered consciousness. HSV is a neuronophagic virus which characteristically causes focal hemorrhagic necrosis in temporal lobe. This property is accepted as a distinctive finding in the differential diagnosis from other encephalitides (5). But this finding was not present in all our cases, therefore temporal lobe pathology should not be always sought in HSV encephalitis. A case beginning with talamic involvement has been reported in the literature (6). While pathological signs can be established only at the fifth day in the brain CT, these signs can be established at the second day in the MRI. In our cases, only in case 4, there was a slight edema in brain CT because it was taken after 5 days of the disease onset. MRI could not be performed in case 1 because of the existing pacemaker. In case 2, MRI was taken after 3 days, but no pathology was observed. In cases 3 and 4, MRI taken at the second and sixth days of the disease respectively revealed miscellaneous pathologies above mentioned. Consequently when pathology does not exist in brain MRI taken at the second day or after, HSV encephalitis should not be ruled out. In the last ten years, the diagnosis of HSV encephalitis had been tried to be made by temporal lobe biopsy or cultural methods or histochemical analyses which are difficult methods to apply and quite invasive. Nowadays, detection of HSV-DNA in the CSF with PCR method has been the gold standard for the diagnosis of HSV encephalitis. HSV-DNA in the CSF can be found positive from 24 hours on after the initiation of disease symptoms to one week later after the beginning of the treatment. The sensitivity and specificity of the detection of HSV-DNA has been found to be 98% and 94–100% respectively in the studies performed (7). It has been shown that the diagnostic value of

the detection of HSV-DNA is the same as the temporal lobe biopsy. In the same study, it has been shown that antiviral therapy has very little effect on the sensitivity and specificity of the detection of HSV-DNA in the CSF with PCR. Although HSV-DNA is found positive in all samples taken before treatment and in 98% of the samples taken one week after treatment, it has been found positive in 49% and only in 21% of the samples taken in the second week and 15 days and over after treatment respectively (7). HSV-DNA was positive in all our cases from the first day of the disease. It is not known whether the high titers of HSV-DNA are associated with the prognosis or not (5). There was no such relation in our cases too. Because HSV-DNA could not be measured in all laboratories and the duration between the transfer of the CSF to an advanced center and the obtaining of the result can affect negatively on morbidity, treatment should be started immediately in patients whose symptoms are consistent with HSV encephalitis. Although leukopenia and predominance of mononuclear leukocytes are generally expected in viral infections; on the contrary there was leukocytosis and predominance of polymorphonuclear leukocytes in all our cases. Therefore, when the patient was evaluated, this should be taken into account. Cell count in the CSF was between 40–470/mm<sup>3</sup>. CSF glucose was in normal limits in all our cases. CSF protein was normal in the first two cases, and slightly elevated in the last two cases. In herpes encephalitis, it has been stressed on the evidence of erythrocytes in the CSF (500/mm<sup>3</sup>) in the lumbar puncture (8). But there was no red blood cell in the CSF of neither of our cases. Akvan Oğuz et al. (9) have reported two cases with entirely normal CSF findings which were diagnosed with HSV encephalitis by means of HSV-DNA detection. Thus when evaluating the CSF findings, one should not make a mistaken diagnosis and delay the treatment taking into account this finding. While the mortality rate is 70% in untreated cases, success rate may increase to 92% when treatment is started early (2). Of our cases, the patient in whom treatment was started on day 6 died and two patients in whom treatment was started on days 3 and 5 were left with advanced irreversible mental-motor sequels, and they were sent to an advanced center for rehabilitation. In the patient who recovered, treatment had been started on day 3. That is, our overall success rate was 25%. This was attributed to the delay in diagnosis because they were referred to us at least 3 days after the disease onset. Acyclovir is accepted to be the most efficient therapeutic agent and it is reported that

addition of steroid to treatment is useful (10,11). In the studies performed, while the mortality rate is reported as 50-55% in patients treated with vidarabine, it has been found 20-30% in patients treated with acyclovir (12). Intravenous use of acyclovir at a dose of 3x10 mg/kg/day for 21 days is accepted to be the most appropriate choice in treatment of herpes encephalitis (13, 14). The same treatment modality was used in all our patients. Although brain CT of case 3 taken on day 5 of the disease was normal, the CT taken on day 10 of the disease (day 5 of hospitalization) revealed infarcts on the left hemisphere and pons, pressure to the left ventricle, and shift to the right side from the left. Also while our case 4 was conscious on admission and although treatment was started immediately, her consciousness gradually closed in a couple of days and eventually died. Treatment was started 3 days after the beginning of the disease symptoms in our case 2, but the clinical picture did not improve and on the contrary advanced mental-motor sequels developed. In all these three patients, although treatment was started early within hours of hospitalization on considering herpes encephalitis, the fact that one of whom died and two of whom developed advanced mental-motor sequels made us consider that whether acyclovir alone is always adequate in the treatment of herpes encephalitis or not. In some studies, in severe cases of herpes encephalitis and in cases not responded to acyclovir alone, the combination of acyclovir and other antiviral agents (vidarabine and beta-interferon) has been used together and it has been obtained good results (6, 15, 16). We also wanted to use combination of acyclovir and vidarabine in our patients. However, since we could get no positive result from the researches and attempts we made both in the country and abroad, we were forced to suffice with acyclovir. In conclusion, for early diagnosis, detection of HSV-DNA in the CSF with PCR has been accepted as the gold standard method.

Therefore the most important analysis in patients whose symptoms are consistent with herpes encephalitis is the detection of HSV-DNA in the CSF with PCR.

The primary drug to be preferred in the treatment is acyclovir, however, especially in irresponsive and severe cases it could be benefited from other antiviral agents.

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