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Clinical Spectrum of the Herpes Simplex Encephalitis in Children: Clinical Features, Neuroimaging, Treatment, and Outcomes

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Abstract

Objective: Herpes simplex encephalitis is one of the most common causes of sporadic encephalitis in children and it is associated with high mortality and morbidity. This study aims at describing the clinical spectrum of herpes simplex encephalitis in children by identifying their neurological imaging features and assessing potential treatment outcomes.

Methods: Clinical, laboratory, and imaging findings in 14 patients with herpes simplex encephalitis were retrospectively reviewed during the period between January 2005 and January 2010 at Selcuk University, Department of Pediatric Neurology.

Results: Our study consisted of 14 patients including a patient who had a relapsing course. The median age of the patients was 3,6 years. Seizure and fever were the most common findings at admission. Cerebrospinal fluid glucose concentration was normal in all patients. Protein and red blood cell levels were elevated in 28% patients. Polymerase chain reaction testing for HSV was positive in 92% and cranial magnetic resonance imaging was suggestive of herpes simplex encaphalitis in all the patients. Prominent thalamic involvement was observed in patients less than 2 years of age, however cerebrospinal fluid findings in these patients were normal. 9 patients were left with no neurological sequelae however persistent neurological sequelae was present in 5 patients.

Conclusion: The findings suggested how challenging it could get to diagnose herpes encephalitis in children, especially those under the age of 2. Due to its diagnostic possibility in children presenting with convulsion and other encephalitic processes, treatment with acyclovir must be initiated as soon as herpes encephalitis is suspected to avoid further neurological insults.

Key Words: Herpes Encephalitis; Children; Acyclovir; Neuroimaging.

Çocuklarda Herpes Simpleks Ensefalitinin Klinik Spektrumu: Klinik Bulgular, Nörogörüntüleme, Tedavi ve Sonuçlarının Değerlendirilmesi

Özet

Amaç: Herpes simpleks ensefaliti çocuklarda sporadik ensefalitlerin en sık görülen nedenlerinden biridir ve yüksek morbidite ve mortalite oranına sahiptir. Bu çalışmada çocuklarda klinik ve nörogörüntüleme bulgularıyla tedavi sonuçlarının değerlendirilerek herpes simpleks ensefalitinin klinik spektrumunun belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Selçuk Üniversitesi, Çocuk Nöroloji kliniğinde 2005-2010 yılları arasında herpes simpleks ensefaliti tanısı ile izlenen 14 hastanın klinik, laboratuvar ve görüntüleme bulguları geriye yönelik olarak değerlendirildi.

Bulgular: Serimiz rekürrens gösteren 1 olgu da dahil olmak üzere 14 hastadan oluşuyordu. Olgularımızın ortalama yaşı 3,6 yıl, en sık başvuru şikayetleri ise nöbet ve ateşti. Beyin omurilik sıvısı glukoz konsantrasyonu olguların tümünde normal bulunurken yüksek protein ve eritrosit değerleri olguların %28'inde tespit edildi. Herpes simpleks virüs polimeraz zincir reaksiyonu olguların %92'sinde pozitifti ve kraniyal manyetik rezonans görüntüleme bulguları olguların tümünde herpes simpleks ensefalitini düşündürmekteydi. 2 yaş altındaki çocuklarda beyin omurilik sıvısı bulguları normal olmasına rağmen talamik tutulum ön plandaydı. 9 olgu sekelsiz iyileşirken 5 olguda kalıcı nörolojik sekel gelişti.

Sonuç: Bu bulgular çocuklarda özellikle de 2 yaşın altındaki çocuklarda herpes simpleks ensefaliti tanısının zor olduğunu göstermektedir. Konvulziyon ya da diğer ensefalit bulgularıyla başvuran çocuklarda olası tanılar içerisinde herpes simpleks ensefaliti mutlaka düşünülmeli ve kalıcı nörolojik sekelleri önlemek için asiklovir en erken dönemde başlanmalıdır.

Anahtar Kelimeler: Herpes Ensefaliti; Çocuk; Asiklovir; Nörogörüntüleme.

INTRODUCTION

Associated with significant morbidity and mortality, herpes simplex encephalitis (HSE) is the most common cause of acute sporadic encephalitis in the world (1). The incidence of HSV encephalitis is estimated to occur in 1/250,000 to 1/500,000 individuals per year, and approximately 30% of these patients are children (2). The clinical presentation typically includes the abrupt onset of fever, headache, focal neurologic signs, seizures, and altered level of consciousness (3). The diagnosis of HSE is generally clinical and radiological

with confirmatory tests including cerebrospinal fluid (CSF) polymerase chain reaction (PCR) testing. PCR is used to detect HSV DNA in the CSF of patients with HSE and is considered to be the gold standard for establishing the diagnosis of HSE (4). Magnetic resonance imaging of the brain also has a high degree of sensitivity and specificity with characteristic lesions seen in the medial temporal lobes and other limbic regions (5, 6). Without treatment, the mortality rate is

approximately 70% (7). With Acyclovir treatment in patients with HSE, the mortality has been significantly reduced to 20%, but surviving patients have been reported to have severe neurologic sequelae (8, 9).
The aim of this study is to review our experience with HSE, the clinical manifestations, laboratory findings, and outcomes of treatment in children, and, especially, to identify clinical and neuroradiological findings associated with HSE in children less than 2 years of age.

MATERIALS AND METHODS

We retrospectively reviewed the clinical records of patients diagnosed with HSE, who were followed up by a secondary care pediatric neurological center at Selcuk University, Meram Medical School between January 2005 and January 2010. The records of patients aged 18 or older and of those with incomplete data throughout the follow ups at the time of evaluation were excluded from the study.

Diagnosis was based on the clinical signs of encephalitis, polymerase chain reaction (PCR) testing to detect HSV DNA in the CSF of patients and/or elevated anti-HSV antibody (Ig M and Ig G) in serum with supplemental abnormal findings on MRI or CT. Age, sex, presenting symptoms, treatment, radiologic examination (CT or MRI), EEG, and CSF analysis findings were reviewed in all patients. Cranial MRI (T1, T2, FLAIR weighted axial and sagittal sections) was examined by using 1.5 Tesla Siemens Magnetom Symphony (Siemens, Erlangen, Germany) at Selçuk University, Faculty of Medicine, Department of Radiology. The study protocol was reviewed and approved by the Ethics Board of Selçuk University, School of Medicine. The patients' data (clinical, laboratory, and neuroimaging data) were analyzed with the SPSS Version 11.0 statistical package. For quantitative variables, data were expressed as mean ± SD; for qualitative variables, data were expressed as n (%).

RESULTS

The study group consisted of a total of 14 children. The median age of the patients was 3.6 years (5 months-16 years); there were 7 were boys and 7 girls. 11 (78%) of 14 patients were less than 2 years of age. The duration of symptoms in majority of the patients was a day. Seizure, including status epilepticus in 8 patients, was the predominant presenting symptom (13 patients; 92%), thus requiring intensive care unit. The initial seizure types of 8 (57%) patients were categorized as focal motor seizures while generalized tonic-clonic seizures which were seen in 6 (42%) patients. 11 (78%) of the 14 patients presented with fever and 5 (35%) presented with hemiparesis.

Acyclovir therapy was started in 9 of the 14 patients within the first 24 hours of neurological symptoms; for the other 5 patients the therapy was started 3 days after symptom onset. 10 (71%) patients were given a 2-week course of acyclovir, 3 (21%) a 3-week course of acyclovir, and one received two 21-day courses each due to clinical relapses. The CSF protein levels and white blood cell count were normal in 72% of the patients and 70% (n:7) of those were less than 2 years old. CSF protein levels and RBC levels were elevated only in 4 (28%) cases. PCR testing of CSF for HSV1 was performed in 10 (71%) of the 14 patients and 8 of them tested positive. Of the remaining 4 patients, anti-HSV Ig M in serum was to be elevated. In our study we found 6 of the 8 patients under age 2 to be PCR positive. The clinical and CSF analysis findings of the patients are summarized in Table 1.

Table 1. Summary of the clinical data of the patients

Patient No	Sex	Age (months)	Duration of symptoms	Presenting symptoms	Status Epilepticus	Initial seizure type	CSF findings	CSF HSV PCR
1	M	14m	1 day	Seizure, fever	+	FM	N	+
2	M	74m	2 days	Seizure, hemiparesis	+	FM	N	+
3	F	17m	1 day	Fever		GTC	N	+
4	M	126	2 days	Seizure, hemiparesis	+	FM	Protein ↑ RBC↑	
5	M	234m	3 days	Seizure, fever	+	GTC		+
6	F	12m	1 day	Seizure, fever	+	GTC	N	+
7	F	11m	1 day	Seizure, fever	+	GTC	N	+
8	M	56m	3 days	Seizure, fever		FM		
9	F	144m	2 days	Seizure, fever, hemiparesis	+	FM	Protein ↑ RBC↑	+
10	F	78m	2 days	Seizure, fever	+	GTC	N	
11	F	16m	1 day	Seizure, fever		FM	N	+
12	F	98m	1 day	Seizure, hemiparesis		FM	Protein ↑ RBC↑	+
13	M	13m	1 day	Seizure, fever		GTC	N	+
14	M	134m	1 day	Seizure, fever, hemiparesis		FM	Protein ↑ RBC↑	

CSF: Cerebrospinal fluid; CSF HSV PCR: Cerebrospinal fluid herpes simplex virus polymerase chain reaction; FM: Focal Motor; RBC: Red blood cell; GTS: Generalized Tonic- Clonic.

A CT scan was performed in 2 patients while we perfomed MRI was for 12 patients. Brain imaging revealed bilateral involvement in 8 (57%) of the 14 patients and frontotemporal involvement was seen in 5 (35%) of 14 patients. We observed temporoparietal involvement in 2 (14%) patients and parietooccipital involvement only in one patient. In 6 (%42) of the 14 patients, abnormal radiologic findings demonstrated only in the thalamus (n:3) or temporal areas (n:3). All the patients with thalamic involvement and 80% of the patients with bilateral involvement were under 2 years of age. Intracranial hemorrhage was found in 5 (35%) of our patients. Radiological findings of the patients are summarized in Table 2.

Table 2. Distribution of brain lesions of HSE patients on MRI and CT scans

Anatomical distribution	No (%) of patients
Bilateral involvement	8 (57%)
Frontotemporal	5 (35%)
Temporoparietal	2 (14%)
Parietooccipital	1 (7%)
Thalamus	3 (21%)
Temporal lobe	3 (21%)

Electroencephalogram (EEG) studies were carried out for all patients and the most common abnormality was found to be generalized background slowing, which was observed in 8 (57%) of patients, followed by focal slowing in 6 (42%) patients, and periodic lateral epileptiform discharges (PLEDS) in 5 (35%) patients. All of the patients survived with no losses during the follow-ups while 9 patients were left with no neurological sequelae though neurological sequelae was detected in 5 patients.

DISCUSSION

HSE is the major cause of sporadic acute focal necrotizing encephalitis, having high mortality and morbidity rates. Because effective antiviral therapy improves outcome in younger patients, early diagnosis of HSE has become important, particularly for children.

The classical clinical presenting symptoms of HSE are non-specific, including fever, seizures, altered level of consciousness, behavioral disturbance, and focal neurologic symptoms. As noted in previous series and case reports (1-4,10), most children with HSE, as it was the case in our study, suffer from seizures and fever as the most common presenting clinical symptom. The cerebrospinal fluid findings of patients with HSE are abnormal in majority of cases, typically with a predominance of lymphocytes as well as increased protein concentration and high red blood cell count indicating a hemorrhagic process (3, 11-12). This typical abnormal CSF findings are highly suggestive of HSV, but lumbar puncture early in the illness may be normal and the normal feature of CSF does not rule out a diagnosis of HSE. In our study, the majority of patients (72%) had normal CSF findings, and only 4 (28%) showed elevated protein and RBC levels. Findings from this study, however, do not correspond to previous reports that report CSF pleocytosis, elevated protein levels, and elevated RBC counts. This suggests that in younger patients (especially those younger than 2 years) CSF features of HSE may be more varied than it is thought to be. HSV PCR is considered to be the gold standard for establishing the diagnosis of HSE. In literature, studies report to have observed a HSV PCR sensitivity of only 70– 75% of children with HSE (3, 10, 13). In the present study, HSV PCR was performed in 10 cases, and results were positive in 8 (80%). Of the two PCR negative patients, one was without pleocytosis or elevated protein levels while PCR testing was performed at a later stage of the disease in the other. It has been previously reported that false negative results could also be related to the presence of a low protein level and leucocyte count in the CSF, and CSF sampling in the very early or late stages of the disease (3, 14). In our patients, the HSV PCR positive results were similar to those results reported in the studies that have been referred to above.

MRI is considered to be more sensitive than CT especially during the early stages of the illness (10, 15). Neuroimaging studies of HSE typically reveals necrotic-haemorrhagic lesions localized in the medial temporal lobes, the insula, and the orbital region of the frontal lobes (16, 17). The majority of the cases in our study showed bilateral involvement including frontotemporal and temporoparietal lobes, whereas 43% showed unilateral disease, thus 3 patients with thalamic involvement and 3 patients showing temporal involvement, respectively. Extratemporal involvement in HSE is not rare. Evaluating 38 patients with HSE, De Tie`ge et al. have found that there were extratemporal lesions in 40% of the cases (3). In the study conducted by Panisset et al., unilateral thalamic involvement was observed in 50% of the cases (18). Our results confirmed that the range of neuroradiological features varies in children as it has been described in previous studies and the proportion of extratemporal lesions is higher than it is in adults (3, 12, 19).

The EEG is usually abnormal in HSE. Although the most common EEG findings of HSE are unilateral or bilateral periodic focal spikes, focal or diffuse slowing, all of these features are not pathognomonic patterns of HSE (20,21). In our study, abnormal EEG findings were present in all the patients and consisted mainly of generalized background slowing and focal slowing. Previous studies have shown that PLEDs have a high sensitivity and specificity for adult HSE (11). In our study, 5 (35%) of the 14 patients displayed PLEDs on EEG tracing. These findings are lower than they are in adults, and further suggest that EEG signs in children may be different from those of adults. Throughout our study, relapse was observed in only one patient. In a series conducted by Schleede et al. 8 of 32 children experienced relapse while this was in 7 of 27 children in Ito et al.'s study (22, 23). Although the pathogenesis of these relapses are not clearly understood, it has been suggested that incomplete inactivation of viral replication, inadequate duration, or dosage acyclovir treatment along with postinfectious encephalopathy have a role to play in

these relapses (22). As far as morbidity or mortality rates are concerned, we did not experience death in any of our patients though significant neurologic sequelae including refractory epilepsy and developmental delays were present in 5 of our patients. All the patients with poor outcome were found to have had treatment initiated 3 days after the onset of the symptoms. As emphasized in previous studies, it is of utmost importance to reduce the morbidity of HSE as early as possible by starting iv acyclovir therapy. Previous studies suggest that neurologic sequelae and risk of relapses are related to delayed initiation and/or inadequate duration of acyclovir treatment (3, 10, 22, 23). Our results also confirm these studies. The retrospective methodologies used in our study can be considered as a limitations. Besides, because of the relatively small number of subjects we have studied, we were unable to draw strong correlations.

CONCLUSIONS

In conclusion, our data confirm the difficulty of diagnosing HSE particularly because of its nonspecific symptoms especially in younger children. However, keeping in mind the diagnostic possibility of HSE in children presenting with convulsion or encephalitic process, acyclovir treatment should be initiated as soon as HSE is suspected. Larger studies are still needed to establish clinical and neuroradiological features of HSE in young children.

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