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Original Article

Outcome of herpes simplex encephalitis in children

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Background and Purpose: Herpes simplex encephalitis (HSE) can cause high mortality and morbidity in children. Since local data of HSE in children are rare, we performed a retrospective study to evaluate the prognostic factors and outcome of HSE in Taiwan.

Methods: Children were enrolled into this study if they were diagnosed as having encephalitis and also had positive polymerase chain reaction for herpes simplex virus (HSV) from cerebrospinal fluid, and/or positive immunoglobulin M or at least four-fold elevation of immunoglobulin G against HSV type 1 or type 2 from serum during the period from December 1, 1984 to January 31, 2003.

Results: Forty patients were enrolled in this study. Twenty six patients (65%) had good outcome and 14 (35%) had poor outcome. No mortality or recurrence was found. Three-fifths of the patients were between 1 year and 6 years of age. Fever (75%) was the most common finding at admission, followed by seizures (63%), lethargy (60%), and altered consciousness (48%). Seizure and lethargy at the time of admission were more common in the poor outcome group (71% vs 58% and 64% vs 58%). Abnormal computed tomography/magnetic resonance imaging findings were found in 63% of patients in whom the examinations were performed. Abnormal electroencephalogram (EEG) findings were noted in 79% of tested patients. Acyclovir was used to treat 29 patients (73%). Abnormal neuroimaging or EEG findings were more prevalent in patients with poor outcome (75% vs 55% and 92% vs 71%), as well as delayed (≥3 days) initiation of acyclovir therapy (92% vs 71%). There was no significant difference between the poor and good outcome groups in gender, age distribution, and clinical presentation.

Conclusion: As we cannot predict the outcome of patients with HSE in the early beginning of illness and delay of treatment may cause disaster, early diagnosis and prompt acyclovir initiation are important requirements for successful management.

Key words: Acyclovir; Encephalitis; Herpes simplex; Treatment outcome

Introduction

Herpes simplex encephalitis (HSE) is an uncommon but grave central nervous system infection in children, with high rates of morbidity and mortality [1]. Early diagnosis and use of acyclovir have been reported to improve outcome and decrease case fatality rate [2]. Polymerase chain reaction (PCR) to detect herpes simplex virus (HSV) DNA in cerebrospinal fluid (CSF) can rapidly and specifically diagnose HSE and has been regarded as the best method for its detection [3,4]. However, even with early administration of therapy after the onset of disease, many survivors will still have significant residual neurologic deficits [5]. Since local data of HSE in children are rare [6], we performed a retrospective study to evaluate the prognostic factors and outcome of HSE at our hospital.

Methods

The medical records of children with a diagnosis of HSE hospitalized during the period from December 1, 1984 to January 31, 2003 were reviewed. Children were enrolled into this study if they were diagnosed

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as having encephalitis with positive PCR for HSV from CSF, and/or positive immunoglobulin M (IgM) or at least four-fold elevation of immunoglobulin G (IgG) against HSV type 1 or type 2 from serum [4]. The clinical symptoms/signs, blood cell counts, CSF cell counts, levels of glucose and protein in CSF, the dose and duration of acyclovir therapy, duration from onset of symptoms/signs to acyclovir therapy, computed tomography (CT)/magnetic resonance imaging (MRI) of brain and electroencephalogram (EEG) were evaluated in enrolled subjects.

The outcome was defined according to the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group as follows: (1) normal; (2) mild sequelae (with minor neuropsychological deficits); (3) moderate sequelae (with limitations to motor, speech, memory, or seizure disorders); and (4) severe sequelae (requirement for supporting care, or death) [7]. We classified patients with normal and mild sequelae as the good outcome group, and those with moderate and severe sequelae as the poor outcome group. The demographic data, clinical presentation, laboratory findings, and acyclovir treatment of the two groups were compared.

Data were analyzed using chi-squared test for observed frequencies. A p value of ≤0.05 was considered as having statistical significance.

Results

Forty patients were enrolled in this study. Among them, 27 children had positive results from HSV PCR, 12 had positive HSV IgM, and 13 had four-fold elevation of HSV IgG. In total, HSV PCR was performed on 31 patients, and the positive detection rate was 87%.

The demographic data and clinical presentation of children with HSE at admission are shown in Table 1. Males were predominant, the male-to-female ratio being 1.9. Three-fifths of the patients were between 1 year and 6 years of age. Four patients had underlying diseases: one had autism and mental retardation; one had focal epilepsy; one had Hashimoto's disease, and one was a premature delivery at gestational age 30 weeks.

Fever was the most common complaint at the time of admission. Seizures or lethargy was found in nearly two-thirds of the patients and altered consciousness in nearly one-half of the patients.

Table 1. Comparison of demographic data, clinical presentation, abnormal neuroimagings and electroencephalographic findings, and acyclovir therapy in children with herpes simplex encephalitis with poor and good outcome

	Poor outcome (n = 14) No. (%)	Good outcome (n = 26) No. (%)	p
Gender			
Male	7 (50)	16 (62)	
Female	7 (50)	10 (39)	
Age			
<1 year	3 (22)	5 (19)	
1-6 years	9 (64)	15 (58)	
6-12 years	2 (14)	4 (15)	
12-18 years	0 (0)	2 (8)	
Symptoms/signs			
Fever	10 (71)	19 (73)	0.689
Seizures	10 (71)	15 (58)	0.307
Lethargy	9 (64)	15 (58)	0.476
Altered consciousness	7 (50)	12 (46)	0.714
Vomiting	4 (29)	9 (35)	0.491
Behavior change	2 (14)	3 (12)	0.778
Headache	2 (14)	1 (4)	0.276
Abnormal CT/MRI	9 (75, 9/12)	11 (55, 11/20)	0.227
Abnormal EEG	11 (92, 11/12)	15 (71, 15/21)	0.180
Acyclovir therapy			
<3 days	1 (8, 1/12)	5 (29, 5/17)	0.182
≥3 days	11 (92, 11/12)	12 (71, 12/17)	0.182
No acyclovir therapy	2 (14)	9 (35)	0.159

Abbreviations: CT = computed tomography; MRI = magnetic resonance imaging; EEG = electroencephalogram

Table 2. Abnormal neuroimaging and electroencephalographic findings in children with herpes simplex encephalitis

Examination	Abnormal/total No. (%)
Computed tomography	13/29 (45)
Magnetic resonance imaging	8/14 (57)
Computed tomography or magnetic resonance imaging	20/32 (63)
Electroencephalogram	26/33 (79)

MRI produced a higher rate of abnormal findings than CT in our patients (57% vs 45%; Table 2). Combined use of the two neuroimaging studies found abnormalities in 63% of patients. The abnormal findings of CT included: brain edema in 4 patients, increased enhancement in 4, infarction in 3, and subdural fluid collection in 2. The major abnormal finding of MRI was high signal intensity in T2-weighted image, 3 of which were suspected to be infarction.

Nearly four-fifths of patients had abnormal EEG findings. These included: slow waves in 15 patients, focal epileptogenicity in 6, slow waves with low voltage background rhythms in 3, and slow waves with focal epileptogenicity in 2.

The leukocyte counts and erythrocyte counts in CSF ranged from 0 to 630/μL and 0 to numerous; after excluding the extreme one, the mean counts were 29.4/μL and 155.9/μL, respectively (Table 3).

Twenty nine patients (73%) received acyclovir but only 6 (15%) started acyclovir therapy within three days of disease onset.

Twenty six patients (65%, including 25 patients without sequelae and 1 with mild sequelae) had good outcome and 14 (35%, including 12 patients with moderate sequelae and 2 with severe sequelae) had poor outcome. No mortality or recurrence was found in our patients.

There was no significant difference between the poor and good outcome groups in gender and age distribution, as well as clinical presentation, although seizures and lethargy were more common in the poor outcome group (71% vs 58% and 64% vs 58%; Table 1). Abnormal neuroimaging, EEG findings, and delayed (≥3 days) initiation of acyclovir therapy were more prevalent in the poor outcome group than in the good outcome group (75% vs 55%, 92% vs 71%, and 92% vs 71%, respectively; Table 1). The laboratory data for CSF also showed no significant difference between the poor and good outcome groups (Table 3).

Discussion

HSE is an important cause of acute necrotizing encephalitis, with an incidence of 1 in 250,000 to 1 in 500,000 [8]. Whereas in the past, brain biopsy was the gold standard for diagnosis of HSE, PCR is now the preferred diagnostic test despite the possibility of false-positive and false-negative results [9,10]. False-negative CSF PCR may be encountered if the CSF is collected too early (first 24 to 48 h) or too late (after 10 to 14 days) [11]. Initial negative PCR results have also been observed in CSF samples drawn before day 3 of the disease and are significantly associated with a low level of protein and <10 leukocytes/μL in the CSF [12]. HSV PCR produced a positive result in most of our patients. Among the four PCR-negative patients, three did not have elevated leukocytes in the CSF, and in the remaining one the PCR test was performed at the beginning of the disease.

Positive HSV IgM in the serum indicates primary HSV infection; however, as shown in our patients, it is not sensitive in the early stage of disease. Four-fold increase of HSV IgG can also diagnose HSV infection, but it takes one to two weeks to get the second serological result, and this sign is not helpful for early diagnosis and management. Serum HSV antibody measurements are not useful in the diagnosis of HSV encephalitis in adults. In children and young adults, HSV serology may help define whether HSE is part of a primary or a reactivated HSV infection, although the clinical features,

Table 3. Comparison of cerebrospinal fluid laboratory data in children with herpes simplex encephalitis with poor and good outcome

	Range (median)		Mean level
	Good outcome (n = 26)	Poor outcome (n = 14)	
Leukocyte count (cells/μL)	0-250 (3)	0-630 (4)	29.4
Erythrocyte count (cells/μL)	Nil to numerous (1)[a]	0-511 (11)	155.9
Glucose (mg/dL)	46-168 (68)	1-95 (65)	67.5
Total protein (mg/dL)	13-137 (34)	6-400 (30)	51.6

[a]One patient had numerous erythrocyte count and was omitted.

therapy, and prognosis of these two forms of HSV encephalitis are similar [4].

Most of our patients were young children, and their presenting symptoms/signs were different from those of adults [13]. Although patient age has been reported to be a major determinant of prognosis [14], that report included adults and children. Only children were included in this study, and we did not find a difference in prognosis among different age groups. Fever is the most common sign. Seizures, lethargy, altered consciousness, vomiting, and behavior change, when accompanied by fever, can suggest the possibility of encephalitis. Headache is a common complaint in adults but it was rather rare in children. We did not find a significant difference in clinical presentation between poor outcome and good outcome groups, although abnormal neurologic conditions — i.e., seizures and lethargy — were more common in the poor outcome group.

Neuroimaging studies are indicated in patients with suspected HSE. The sensitivity and specificity of MRI is better than CT scanning, especially during the early stages of the illness [15]. Nonetheless, normal MRI result cannot rule out HSE [16]. Diffusion-weighted MRI may help to find the tiny abnormalities and provide useful information for the diagnosis of HSE [17]. Because our patients received only CT, only MRI, neither or both at different times in the disease course, we were unable to compare the abnornal detection rates. However, the rate of abnormal findings of MRI or CT in the poor outcome group was higher than that in the good outcome group (75% vs 55%).

The EEG is usually abnormal in HSE [18]. The typical patterns of findings are unilateral or bilateral periodic focal spikes against a background of slow activity, but this constellation of findings is not specific for the diagnosis [19]. In our poor outcome group, the abnormal rate of EEG was higher than that of the good outcome group (92% vs 71%). EEG may thus be considered as a predictor for outcome.

It is well documented that treatment with acyclovir improves the outcome of HSE. The mortality rate for acyclovir recipients is around 10% in children compared with nearly 20% in adults [14,20,21]. In this study, no patient died of HSE. In previous reports, the rates of moderate sequelae ranged from 25% to 36% and of severe morbidity from 0 to 100% [20-22]. Thirty percent of our patients had moderate sequelae and 5% had severe sequelae.

Some patients can recover without sequelae even with no antiviral drug administration [23]. In our study, eleven patients did not receive acyclovir; two of them had moderate neurological sequelae and 9 patients recovered without sequelae. Those patients who recovered well without acyclovir therapy may be only mildly infected. When we analyzed the acyclovir treatment patients, we found a higher ratio of treatment delay (initiation of acyclovir therapy ≥3 days) in the poor outcome group (0 to 19 days; median, 6 days). Delayed initiation of acyclovir therapy has been regarded as a poor prognostic factor [13]. Unfortunately, we cannot predict the outcome of the patients with HSE in the early beginning of illness and delay of treatment may cause disaster. Thus, early diagnosis and prompt acyclovir initiation are the most acceptable approach to management.

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