Original Article

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Infectious Diseases Section

Herpes Simplex Encephalitis (HSE) and its outcome in the Patients who were Admitted to a Tertiary Care Hospital in Mashhad, Iran, over a 10-year Period

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ABSTRACT

Introduction: The effective cure rate of acyclovir emphasizes the importance of an early diagnosis and treatment in reducing the considerable mortality and the morbidity in patients with Herpes Simplex Encephalitis (HSE).

Methods: The demographic as well as clinical features, the lab data and the neuroimaging findings of the patients with HSE, which were confirmed by Cerebrospinal Fluid (CSF) PCR and/or brain MRI, were reviewed and analyzed statistically over a 10-year period.

Results: Over a 10-year period, the characteristics of 45 patients with HSE were reviewed. 34 (76%) out of the 45 patients showed positive CSF HSV-1 PCR results. 8 (18%) had a normal CSF analysis and a CSF/blood glucose ratio of less than 0.5 was observed in 13 (29%) patients, while 14% had PMN-dominant pleocytosis. 68% of the patients for whom brain MRI was performed, had temporal lobe involvement. While 37 (83%) patients recovered completely, 6 (13%) survived with sequelae, and 2 (4%) died.

Conclusion: Because of the increasing number of atypical forms of HSE and the great impact of an early diagnosis and treatment on a favourable outcome, the acyclovir therapy should be administrated for any type of febrile encephalopathy of unknown aetiology, until HSE can be excluded.

Key Words: Herpes Simplex Encephalitis (HSE), PCR, Acyclovir, Febrile encephalopathy

INTRODUCTION

Herpes simplex virus 1 (HSV 1) belongs to the family, Herpesviridae, subfamily Alphaherpesvirinae and the genus Simplexvirus, Species herpes simplex virus [1]. HSV is the most commonly identified cause of the acute, sporadic viral encephalitis in the United States, which accounts for 10% to 20% of all the cases. The estimated incidence is approximately 2.3 cases per million persons per year. Unlike the enteroviral infections, the cases are distributed throughout the year, and the age distribution appears to be biphasic, with peaks at ages of 5 to 30 years and at more than 50 years of age [1]. If untreated, the fatality in herpes simplex encephalitis (HSE) can approach 70 percent and most of the survivors will have serious neurologic deficits [2]. The favourable prognosis for those with HSE, depends on an early diagnosis and the appropriate treatment [3-5].

Several studies have shown that the only factor which affects the patient's outcome is the time between the disease presentation and the antiviral administration.

The PCR method provides an opportunity for an early and an accurate detection of this potentially fatal infection, so that an aggressive antiviral therapy which is given, can prevent the mortality and limit the severity of the postencephalitic sequelae. In consideration of the increasing frequency of the atypical presentations of HSE and the previously reported contradictory results, this retrospective study reviewed the varied characteristics of the patients who presented with suspected HSE over a 10-year period.

METHODS

The clinical, laboratory, and the neuroimaging findings of 45 patients who were admitted to the Department of Infectious Diseases at Imam Reza Hospital, Mashhad, Iran, with HSE during the period from 2003-2012, were examined. All the adult patients (≥ 15years) with a final diagnosis of HSE, which was based on the clinical, laboratory, molecular and the neuroimaging findings were included. Their medical records were reviewed to collect the information which was available and the data were analyzed on the basis of the age, sex, clinical presentation, CSF analysis, PCR results on CSF, neuroimaging studies, and the outcome.

RESULTS

During the study period, 45 patients with a final diagnosis of HSV encephalitis had been admitted. Of these, 26 (58%) were females and 19 (42%) were males (F/M=1.36). Their mean age was 34.9 ±15.7 years (15-70). The peak age of the patients was between 15 and 35 years (58%); only two patients were older than 65 years. Based on the collected data, the patients were classified as 34 confirmed cases (i.e., with a positive PCR for the HSV-DNA), 4 probable cases (positive MRI findings and symptoms) and 7 possible cases (clinical signs only) [Table/Fig-1].

Forty patients (89%) had received acyclovir within the first week of the initial symptoms and 5 (11%) had received it only later. The most common presenting symptoms were fever (96%), headache (70%), delusions and hallucinations (60%) (4.7% of the patients had auditory and olfactory hallucinations), and behavioural disorders (54%). The other less common clinical features were the prodromal symptoms of upper respiratory tract infection (30%), nausea and vomiting (49%), and seizure (44%). Only 2 (4%) patients were fully conscious at the time of their hospital admissions; the remaining were confused (49%), stuporous (28%), or comatose (19%).

The HSV-PCR results from the CSF were positive in 34 patients (76%). In the 7 suspected cases (16%), no result was available, as the test had either not been performed or it had not been recorded, while the 4 probable cases (9%) had characteristic MRI findings but negative PCR results. HSV-1 was detected in all the specimens; HSV-2 was not found. Of the 26 patients with available results of the brain CT scanning, only 13 (50%) had abnormal findings. During the first few years of the study period, brain MRI was not a routine diagnostic examination. As a result, no MR images were available for 5 of the 34 confirmed cases and 6 of the 7 possible cases.

For the remaining 34 patients, brain MRI suggested encephalitis in 31 (92%), of whom 68% had unilateral right- or left-sided lesions and 32% had a bilateral involvement. In the patients with abnormal MRI findings, 68% had temporal involvement, either isolated or as a part of a more diffuse process. Analysis of the CSF samples at the time of admission revealed pleocytosis in 82%; 8 (18%) had no WBCs in the CSF. Among those with pleocytosis, 54% had less than 50 cells/ µl. In 14% samples, the polymorphonuclears were predominant. The CSF protein content was more than 50 mg/dl in 42% samples and a CSF/blood glucose ratio of less than 0.5 was observed in 13 (29%) samples.

Eight patients (18%) showed a normal CSF analysis, of which 5 were positive for the HSV-DNA by PCR. The diagnosis of HSE in the other 3 cases, was based on the clinical and the MRI findings. Two (6%) of the confirmed cases with HSV-PCR positive results showed normal brain MRI results, while 5 (15%) showed a normal CSF analysis [Table/Fig-1].

Thirty-seven patients (83%) recovered;completely 6(13%) survived with sequelae, and 2(4%) died. No statistically significant correlation was found between any of the clinical symptoms and the outcome. The only predictor of a favourable outcome was the early administration of acyclovir (p-value=0.001). Both the patients who died had received an antiviral drug only a week after the onset of their illnesses. Those who were fully conscious on admission, survived without any neurologic sequelae, while the outcome for the patients who were in a comatose state was less positive (62% recovered fully, 25% survived with sequelae and 12% died). Despite these results, the correlation between the level of consciousness at the time of the hospital admission and the outcome was not statistically significant (p-value=0.573) [Table/Fig-2].

DISCUSSION

Investigation	Probable Cases**		Confirmed Cases*		Possible Cases***	
Clinical findings	**%**	**Number**	**%**	**Number**	**Clinical findings**	**%**
Fever	7	100	4	95	32	100
Headache	5	50	2	70	24	72
Seizure	3	25	1	47	16	43
Delusions / hallucinations	3	20	2	68	22	43
Bizarre behavior	4	50	2	56	19	57
Loss of consciousness	6	100	4	97	33	86
CSF analysis	**Number**	**%**	**Number**	**%**	**Number**	**%**
No WBC	2	25	1	15	5	29
Lymph dominant	4	50	2	76	26	57
PMN dominant	1	25	1	9	3	14
Brain MRI findings	**Number**	**%**	**Number**	**%**	**Number**	**%**
Not performed	6	-	-	-	5	86
Normal MRI	1	-	-	6	2	14
Unilateral lesion	-	75	3	62	18	-
Bilateral Lesion	-	25	1	32	9	-
Outcome	**Number**	**%**	**Number**	**%**	**Number**	**%**
Full recovery	4	50	2	91	31	57
Neurologic sequelae	3	25	1	6	2	43
Death	0	25	1	3	1	-
Total	**34**		**4**		**7**	

[Table/Fig-1]: Classification of the clinical signs, laboratory data and neuroimaging findings of 45 patients with HSE
* Positive PCR for HSV-DNA, ** Demonstrative MRI findings + symptoms, *** Compatible clinical scenario

Outcome	Level of consciousness							
	Fully conscious		Confused		Stuporous		Comatose	
	N	%	N	%	N	%	N	%
Full recovery	2	100	19	90	11	84	5	62
Survival with sequelae	0	0	2	9	1	8	3	25
Death	0	0	0	0	1	8	1	12

[Table/Fig-2]: The correlation between outcome and the level of consciousness at the time of hospital admission

Herpes simplex encephalitis (HSE) is the most common type of fatal sporadic encephalitis worldwide. HSE has a bimodal distribution by age, with the first peak occurring in those who are younger than 30 years and a second occurring in those who are older than 50 years [1]. In this study, which was conducted on 45 adult patients with HSE, the age range had a peak in 15- to 35-year-olds (58%). However, roughly 15% of the patients were older than 50 years,; two patients were older than 65 years. With regards to the CSF patterns of the cases, 7 (16%) had an entirely normal analysis. After being adjusted for the classification, 4 confirmed cases (out of 34 ≈ 11%) were found to have a completely normal CSF. Although the CSF abnormality has been suggested as a criteria to differentiate encephalopathy from encephalitis, HSV encephalitis with a normal CSF analysis has been reported [6-9]. It is worth pointing out that 14% of our patients with an abnormal CSF analysis had pleocytosis, with a predominance of the polymorphonuclears (PMN). For the confirmed cases, a PMN-dominant pleocytosis was observed in 3 of 29 (10%) cases. The bacterial smears and the cultures were negative in all. Hypoglycorrhachia or a CSF/blood glucose ratio of less than 0.5 was presented in 29% of the patients. In contrast to this, a retrospective study on the adults with HSE, which was done by Riera-Mestre et al., demonstrated that hypoglycorrhachia required the consideration of diagnoses other than HSE [10]. Being consistent with the results of this study, previous studies of Momméja-Marin et al., and Davis et al., have demonstrated that a low CSF glucose concentration does not rule out a viral CNS

infection [11,12]. As was previously emphasized by Cunha: "If the CSF glucose levels are decreased and fungal and tubercular meningitis are excluded as the possibilities, the differential diagnosis is often between HSV-1 encephalitis and a bacterial CNS infection [13].

We classified our cases into three groups, based on their accuracies and the values of their diagnostic approaches. The PCR sensitivity and specificity were reported as 98 and 94%, respectively, as compared to those of the brain biopsies [14]. Thus, all the 34 PCR positive patients who had high pre-test probabilities were classified as the confirmed cases. However, in the patients with high clinical probabilities of HSE, a negative PCR result does not exclude the possibility of an infection [14]. There were 4 probable cases with negative PCR results, in whom the brain MRI findings were suggestive of HSE. Seven possible cases also had high pre-test probabilities, but their PCR results were either negative or not available and a brain MRI had not been performed for most of them (6 out of 7 cases). Of the confirmed cases, 27 out of 29 (93%) had abnormal brain MRI findings, which were suggestive of encephalitis, but 2 PCR-positive patients showed normal MRI results . These results are comparable with those of the study of Domingues et al, in which all the MRI examinations except one were abnormal among the PCR-positive patients [15]. Therefore, a normal brain MRI examination does not rule out HSE and approximately 10% of the patients with PCR documented HSV encephalitis will have normal MRI results [16].

This study also highlighted the fact that the only factor which was associated with a favourable outcome in the patients with HSE was an early administration of acyclovir (p-value=0.001). Both the patients who died had only received an antiviral drug after a delay. In another retrospective study, the factors which were associated with a delay in the acyclovir administration were evaluated in the patients with a positive CSF for HSV by PCR [17]. These authors found that the independent risk factors for a late administration of acyclovir were a severe underlying disease, alcohol abuse, and a delay of >1 day from the admission to the first imaging of the brain. There was also an association between a finding of <10 leukocytes/µl in the CSF on admission and the late initiation of an antiviral drug. They concluded that the patients with HSE often presented with severe underlying diseases, chronic alcohol abuse, or atypical CSF findings, but that such factors should not be allowed to delay the diagnosis and the administration of acyclovir. The dosage of acyclovir in the patients with normal renal functions is 10 mg/kg intravenously, every 8 hrs for 14–21 days. However, a relapse of herpes simplex encephalitis has been reported after the completion of the acyclovir therapy 18. 2 out of 32 confirmed cases in our study (6.2%) relapsed 6-8 days after the treatment with acyclovir for 14 days. A negative CSF PCR result at the end of the therapy has been associated with a better outcome, thus suggesting that another CSF specimen should be subjected to PCR for HSV at the end of the therapy; if the result is positive, the antiviral therapy should be continued [18]. Three of our patients had a positive CSF PCR at the end of 21 days. So, they received acyclovir for a longer duration until the PCR results became negative for two of them. The other patient, a 73-years old female, remained PCR positive despite taking the acyclovir therapy for one month. Interestingly, the result of her CSF PCR became negative after one week of treatment with ganciclovir (5 mg/kg IV at a constant rate over 1 hour, every 12 hours). A resistance to acyclovir has rarely been reported in an immunocompetent, previously therapy-naive adult [19].

CONCLUSION

Because of the great diversity in its clinical, laboratory and neuroimaging features, the growing number of its atypical forms and the fact that an early diagnosis and treatment is essential for a favourable outcome, HSE should be considered in the differential diagnosis of febrile encephalopathy with an unknown cause, and the acyclovir therapy should be started promptly, until such a diagnosis is clearly excluded.

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