Retrospective Study of Patients with Herpes Simplex Encephalitis and Positive CSF PCR

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Objective: *To determine the clinical presentations, laboratory and imaging findings of patients with HSE and positive CSF PCR then compare these with information from other viral encephalitis patients in order to find clinical clues that might help clinicians in early diagnosis and treatment of HSE while awaiting for the CSF PCR result.*
Material and Method: *A patient group with both HSE and positive CSF PCR and a control group of patients with other viral encephalitis were identified from Siriraj Hospital database within the period of 1997-2006. Medical notes of these patients were reviewed and relevant information, including clinical, laboratory and imaging study, were extracted. Then, descriptive statistics, unpaired t-test and Fisher's exact test were performed with the purpose to determine any clinical or laboratory clues that are significantly different between these two groups, which might help clinicians in making an early diagnosis of HSE.*
Results: *Seven HSE cases and 22 cases in control group were included. Fever, headache, alteration of consciousness, behavioral change, neck stiffness are the most commonly found clinical presentations in HSE patients with CSF PCR positive. CSF examination show CSF leukocytosis with lymphocyte predominate, decreased CSF:blood glucose ratio and elevated CSF protein in all cases. However, no single clinical or laboratory finding helps in differentiating HSE with positive CSF PCR from other viral encephalitides, except radiological abnormalities of temporal lobe, which yields a positive predictive value of 0.5 and a negative predictive value of 0.93.*
Conclusion: *Our study showed that HSE shares common clinical and laboratory findings with other viral encephalitides, except for temporal lobe involvement. Early diagnosis is important and empirical acyclovir should be commenced early in patients with viral encephalitis, especially for those with radiological abnormalities on the temporal lobe.*

Keywords: *Cerebrospinal fluid, Encephalitis, Herpes simplex, Encephalitis viral, Polymerase chain reaction*

J Med Assoc Thai 2009; 92 (Suppl 2): S95-100
Full text. e-Journal: *http://www.mat.or.th/journal*

Herpes simplex encephalitis (HSE) is consequence of herpes simplex virus (HSV) infection of the central nervous system[1]. It is a medical emergency, since it needs a correct immediate diagnosis and specific therapy, which usually leads to a dramatic influence upon survival and reduces the extent of permanent brain injury in survivors[2,3].

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HSE has various clinical manifestations, including fever, headache, altered level of consciousness, and symptoms and signs of cerebral dysfunction. These may consist of abnormalities that can be categorized into four: cognitive dysfunction, behavioral changes, focal neurological abnormalities and seizures[2,4]. The clinical manifestation also resembles either other viral encephalitides or encephalopathy from any cause[2-5]. With the view of making a correct diagnosis of HSE, further investigations are often required.

At the present time, Polymerase Chain Reaction (PCR) of the CSF is the diagnostic method of

choice of HSE[1,6]. PCR has a sensitivity of 98%, specificity of 94%, a positive predictive value of 95% and a negative predictive value of 98%[1,6]. A false-negative CSF PCR test may occur when the testing is performed within the first 72 hours of symptom onset or in the presence in CSF of porphyrin compounds derived from the degradation of haeme in erythrocytes[1,6]. Antiviral therapy appears to lower the amount of HSV DNA in the CSF but does not affect the rate of HSV DNA detection, if the treatment duration is less than 1 week[1,6]. This test is time-consuming and is not readily available in all hospitals, so the diagnosis and treatment may be delayed if the decision is made based on this test alone. Empirical treatment with acyclovir for every patient with viral encephalitis is usually done while waiting for the PCR result, but this treatment may cause adverse drug reaction and is expensive.

We conducted this study to determine the clinical presentation and laboratory findings of patients with HSE and positive CSF PCR and then to compare these with the information from patients with other viral encephalitides, for the purpose of finding clinical clues that may aid clinicians in providing early diagnosis and treatment of HSE during the wait for CSF PCR result.

Material and Method

We performed a retrospective search from Siriraj hospital database for all patients older than 15 years old with a diagnosis of HSE or viral encephalitis with in the period of 1997-2006.

The patients in this study were divided into 2 groups; the patient group was composed of patients with HSE with positive CSF HSV PCR. The control group was composeed of randomly selected patients with a clinical diagnosis of viral encephalitis who had negative CSF HSV PCR or positive CSF serology/PCR for other viruses. A ratio of study group to control group was 1:3. Patients without laboratory of CSF viral PCR or serology were excluded.

The epidemiological data, clinical presentation and course, physical examination results, laboratory examinations (CSF examination, computerized tomography (CT) or magnetic resonance imaging (MRI) of the brain, electroencephalography (EEG)) were extracted for each patient.

We used descriptive statistic, unpaired t-test and Fisher's exact test for analysis of data.

Results

A total of seven cases in patient group with a final diagnosis of HSE and positive CSF HSV PCR were identified, three males and four females. The mean age of these patients at time of clinical presentation was 47 years (range 20-67 years). A total of 22 cases were included as a control group, 14 males and 8 females. All cases in control group were negative for CSF HSV PCR. Four of these 22 cases had positive PCR for other viruses, including cytomegalovirus (CMV) 1case, JC virus 1case, enterovirus 1 case, Japanese encephalitis virus (JE virus) 1case. Mean age of control cases at time of clinical presentation was 36 years (range 15-77 years)

Among all 29 cases, the clinical presentations varied. Fever, headache and alteration of consciousness and sign of meningeal irritation were among the most common findings of both groups. Cognitive dysfunction, behavioral change and seizure are more common in the patient group than in the control group. However, seizure was found in less than half of the patient group. Abnormal reflex and cortical signs were found only in the patient group, whereas other clinical signs such as rash, cranial nerve abnormalities and motor signs were only found in the control groups. Clinical data of both groups is summarized in Table 1.

Cerebrospinal fluid examination was performed in all 29 cases. Cerebrospinal fluid leukocytosis with predominant lymphocyte and CSF erythrocytosis were found in both groups. Increased CSF protein was found to be more common in the control group than in the study group. CSF glucose depression was found in 5 of 7 cases of the patient group, whereas it was found only 11 in 21 cases of the control group (Table 2).

Brain imaging was performed in 5 of 7 of the patient group and in 17 in 22 of the control group. Of 5 cases in patient group, 4 patients had abnormal radiological findings, which most common areas of involvement were the temporal lobe, followed by the frontal lobe and the insular lobe in equal frequency. Whereas, in the control group, the area of abnormalities were scatter involve all region brain without obvious predilection (Table 3).

Among the patient group, EEG was performed in 3 cases; 2 cases revealed evidence that suggested focal cortical dysfunction related to abnormality on imaging. In the control group, 12 cases underwent EEG and abnormalities were found in 10 cases. Most of the EEG abnormalities in the control groups were of diffused slow activity. Only four cases suggested focal epileptogenic foci or activity from one hemisphere. None of these were related to abnormality in imaging findings except one (Table 3).

Table 1. Clinical data compared between study group and control group

Clinical data	% of occurrence		Value		p-value
	Patient	Control	Patient	Control	
Clinical presentation					
Median and range age (year)			48 (20-67)	36 (15-77)	0.169[a]
Median and range of day of fever before admission (day)			5 (1-10)	5.15 (1-14)	0.519[a]
Median and range of day of fever until change of mentation (day)			3 (1-9)	3.25 (0-9)	0.607[a]
Clinical symptoms					
Fever	100	90.9			1.00[b]
Headache	100	77.3			0.296[b]
Rash	0	4.5			1.00[b]
Altered level of consciousness	85.7	86.4			1.00[b]
cognitive dysfunction	71.4	31.8			0.092[b]
behavioral changes	71.4	54.5			0.665[b]
Focal neurological abnormalities	0	4.5			1.00[b]
Seizure	42.9	27.3			0.642[b]
Clinical signs					
Rash	0	4.5			1.00[b]
Cranial nerve abnormalities	0	4.5			1.00[b]
Motor abnormalities	0	9.1			1.00[b]
Abnormal reflexes	28.6	0			0.052[b]
Cortical signs	28.6	0			0.052[b]
Neck stiffness	85.7	63.6			0.382[b]

(a) = Unpaired t-test, (b) = Fisher's Exact test

Table 2. Laboratory findings compared between study group and control group

Laboratory findings	% of occurrence		Value		p-value
	Patient	Control	Patient	Control	
CBC Findings					
Mean WBC count (cell/mm^3)			8,437 $\pm$ 2,727	11,490 $\pm$ 5,187	0.150[a]
PMN predominate	100	91			1.00[b]
Lymphocyte predominate	0	9			1.00[b]
Mean platelet count (cell/mm^3)			185,857 $\pm$ 42,428	227,476 $\pm$ 81,988	0.213[a]
CSF examination findings					
CSF leukocytosis	100	85.7			0.551[b]
Mean CSF WBC count (cell/mm^3)			390 $\pm$ 303	110 $\pm$ 160	0.052[a]
PMN predominate	0	5			1.00[b]
Lymphocyte predominate	100	95			1.00[b]
CSF erythrocytosis	42.9	81			0.142[b]
Mean CSF RBC count (cell/mm^3)			9,461 $\pm$ 23,744	388 $\pm$ 925	0.351[a]
CSF protein elevation	66.7	90.5			0.204[b]
Mean CSF protein (g/L)			171.17 $\pm$ 198.21	89.86 $\pm$ 75.61	0.367[a]
Mean CSF glucose (mg/dL)			67.57 $\pm$ 23.64	69.27 $\pm$ 28.11	0.842[a]
Mean CSF:blood glucose ratio			0.45 $\pm$ 0.079	0.59 $\pm$ 0.16	0.073[a]
Decreased CSF:blood glucose ratio	100	47.6			0.053[b]

(a) = Unpaired t-test, (b) = Fisher's Exact test

Table 3. Brain imaging and EEG findings compared between study group and control group

Investigation	% of occurrence		p-value (Fisher's exact test)
	Patient	Control	
Brain imaging findings			
Area of involvement			
Frontal lobe	40	11.8	0.21
Temporal lobe	80	23.5	0.039
Parietal lobe	0	11.8	1.00
Insular lobe	40	11.8	0.21
Occipital lobe	0	5.9	1.00
Basal ganglia	0	5.9	1.00
Brain stem	0	5.9	1.00
Meningeal enhancement	40	41.2	1.00
Bleeding	20	0	0.227
EEG findings			
Epileptiform discharge	33.3	25	1.00
PLED	33.3	0	0.20
Other characteristic suggest of cerebral involvement	33.3	16.7	0.516
Status epilepticus	33.3	0	0.20
Diffuse slow activity	66.7	66.7	1.00

When data were compared between the study group and the control group (Table 1-3), no clinical significance in clinical findings, CSF examination findings, or EEG findings among two groups were seen. For radiological finding, temporal lobe involvement was significantly higher in the study group with a positive predictive value of 0.5 and a negative predictive value of 0.93.

Every case in the patient group received acyclovir treatment, which resulted in clinical improvement. No deaths occurred in this population.

Discussion

HSE patients with CSF PCR positive have variable clinical presentation. The common features are fever, headache, alteration of consciousness, behavioral change, and neck stiffness**.** CSF examination revealed CSF leukocytosis with lymphocyte predominate, decreased CSF:blood sugar ratio in all patients and elevated CSF protein, in decreasing frequency. Brain imaging has temporal lobe involvement in most cases. Our data are compatible with the literature[1-5] and past studies[7,8].

When compared with other viral encephalitis patients, no statistical differences were observed in clinical presentation and laboratory findings, except for temporal lobe involvement on brain imaging. The frequent involvement of the temporal lobe probably represents the invasion of HSV along olfactory tract to the limbic system, as suggested by animal model[4].

The results from our study suggested that the clinical and laboratory characteristics of patients with herpes simplex encephalitis with positive CSF HSV PCR did not differ significantly from those with negative CSF HSV PCR, except for the occurrence of temporal lobe involvement on the brain imaging. Based on our data, an involvement of the temporal lobe yields a positive predictive value of 0.5 and a negative predictive value of 0.93. In other words, patients with abnormal temporal lobe on imaging have 50% chance of having positive CSF PCR for HSV and patients with no temporal lobe involvement very rarely have positive CSF PCR for HSV. This finding shows that imaging is an important part in clinical decision-making for patients with encephalitis.

Our study is limited by the small number of patients with positive CSF PCR, which might affect the statistics. In addition, the control group might have been contaminated by HSE patient with negative CSF PCR, which again might alter the results. Further prospective studies are required to study these findings in detail.

Conclusion

HSE patients with CSF PCR positive have various clinical presentations that are not different

from other forms of viral encephalitis except for temporal lobe involvement. Early diagnosis is important; the treatment with acyclovir should be commenced on suspicion of HSE even before a specific etiological diagnosis is possible, especially in cases with abnormal temporal lobe on imaging.

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การศึกษาย้อนหลังผู้ป่วยโรคสมองติดเชื้อ herpes simplex ที่มีผลตรวจน้ำไขสันหลังเป็นบวกด้วยวิธี PCR

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วัตถุประสงค์: *เพื่อเปรียบเทียบลักษณะทางคลินิก, ผลการตรวจทางห้องปฏิบัติการ และภาพรังสีระหว่างผู้ป่วยโรคสมองติดเชื้อ herpes simplex ที่มีผลการตรวจน้ำไขสันหลังเป็นบวกด้วยวิธี PCR กับผู้ป่วยโรคสมองติดเชื้อไวรัสอื่น ๆ ทั้งนี้เพื่อหาปัจจัยที่จะช่วยในการวินิจฉัยโรคสมองติดเชื้อ herpes simplex และเริ่มให้การรักษาได้ในระยะแรกเริ่มขณะที่รอผลการตรวจน้ำไขสันหลังด้วยวิธี PCR*

วัสดุและวิธีการ: *กลุ่มผู้ป่วยที่ป่วยด้วยโรคสมองติดเชื้อ herpes simplex ที่มีผลการตรวจน้ำไขสันหลังเป็นบวกด้วยวิธี PCR ส่วนกลุ่มที่สองเป็นกลุ่มควบคุมซึ่งประกอบด้วยผู้ป่วยโรคสมองติดเชื้อไวรัสชนิดอื่น ๆ โดยที่ทั้งสองกลุ่มนี้ได้มาจากการค้นฐานข้อมูลผู้ป่วยโรงพยาบาลศิริราชตั้งแต่พ.ศ.2540-2549 ข้อมูลทางคลินิกถูกศึกษาจากรายงานผู้ป่วย ใช้วิธีทดสอบ Unpaired t-test และ Fisher's exact test ในการเปรียบเทียบข้อมูลกลุ่มผู้ป่วยทั้งสองกลุ่ม เพื่อดูว่าปัจจัยใดมีความแตกต่างอย่างมีนัยสำคัญ*

ผลการศึกษา: *พบผู้ป่วยโรคสมองติดเชื้อ herpes simplex จำนวน 7 ราย และผู้ป่วยโรคสมองติดเชื้ออื่น ๆ จำนวน 22 ราย อาการไข้, ปวดศีรษะ, อาการสับสน, พฤติกรรมเปลี่ยนแปลง และคอแข็งเป็นอาการที่พบได้บ่อยในผู้ป่วยสมองติดเชื้อ herpex simplex การตรวจน้ำไขสันหลังพบว่ามีเม็ดเลือดขาวสูงในผู้ป่วยโรคสมองติดเชื้อ herpes simplex ทุกราย อย่างไรก็ตามไม่มีอาการหรืออาการแสดงทางคลินิกหรือผลการตรวจทางห้องปฏิบัติการใดที่แตกต่างจากกลุ่มผู้ป่วยสมองติดเชื้อไวรัสอื่นอย่างมีนัยสำคัญ ยกเว้นความผิดปกติที่บริเวณ temporal lobe ในภาพถ่ายรังสีซึ่งให้ positive predictive value 0.5 และ negative predictive value 0.93*

สรุป: *การศึกษานี้พบว่าผู้ป่วยสมองติดเชื้อ herpes simplex มีลักษณะทางคลินิก และผลตรวจทางห้องปฏิบัติการหลาย ๆ อย่าง ไม่ต่างจากผู้ป่วยสมองติดเชื้อไวรัสอื่น ๆ ยกเว้นการตรวจภาพรังสีซึ่งพบว่ามีความผิดปกติบริเวณ temporal lobe ได้บ่อยกว่า ดังนั้นจึงควรรีบให้การรักษาผู้ป่วยสมองติดเชื้อไวรัสด้วยยา acyclovir โดยเฉพาะผู้ป่วยที่การตรวจภาพรังสีพบว่ามีความผิดปกติที่ temporal lobe*