

Re-evaluating the Diagnostic Methods in Herpes Simplex Encephalitis

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KEY WORDS

■ *HERPES SIMPLEX ENCEPHALITIS* ■ *DIAGNOSIS*
■ *ELECTROENCEPHALOGRAPHY* ■ *POLYMERASE CHAIN REACTION*
■ *PERIODIC LATERALIZED EPILEPTIFORM DISCHARGE*

SUMMARY

Several methods are used in clinical practice to investigate herpes simplex encephalitis (HSE), including electroencephalography (EEG) and polymerase chain reaction (PCR) of the viral genome in cerebrospinal fluid. PCR is the most sensitive and specific of the diagnostic methods currently employed. We retrospectively examined the diagnostic utility of EEG and cranial imaging within the first 24–48 h of symptom onset in patients with suspected HSE. Patients with herpes simplex-positive PCR results were compared with those with herpes simplex-negative PCR results. Periodic lateralized epileptiform discharges and/or focal temporal slowing were present in 90% of the PCR-positive patients at symptom onset compared with only 30% of the PCR-negative group. The sensitivity of EEG recordings decreased after 48 h. Although no patients had computed tomography findings suggestive of HSE, magnetic resonance imaging results were consistent with HSE in 86% of those with herpes simplex-positive PCR results obtained after 48 h from symptom onset.

Introduction

CLINICAL CHARACTERISTICS OF herpes simplex encephalitis (HSE) are poorly defined; consequently, various ancillary methods are used to confirm a putative diagnosis and currently lumbar puncture together with cerebrospinal fluid (CSF) polymerase chain reaction (PCR) is the most sensitive and specific diagnostic procedure.¹ However, lumbar puncture is an invasive technique and herpesvirus genomic detection by PCR is not widely available in some countries.

Herpes simplex encephalitis is associated with various electroencephalogram (EEG) abnormalities, including unilateral or bilateral sharp waves, amplitude attenuation, focal or generalized slowing, epileptiform discharges and electrical seizures.² Periodic complexes and temporal slowing are the classic waveforms described in patients with HSE,³ although abnormal computed tomography (CT) and magnetic resonance imaging (MRI) signals in the medial temporal lobe can help to confirm its diagnosis.

The usefulness of early EEG and cranial imaging in suspected HSE cases in the era of PCR testing has not been determined.⁴ Prompt diagnosis of HSE is extremely important; therefore, we undertook a retrospective analysis of the utility of EEG and cranial imaging as secondary diagnostic methods in early-onset HSE.

Patients and Methods

PATIENTS

The study population consisted of all patients with a presumed HSE diagnosis, who were admitted to the University Hospitals of Cleveland during an 8-year period from October 1996 to December 2004, identified from medical records using the hospital registry. Presumptive clinical HSE symptoms included altered mental state, headache and fever. Patients with a confirmed HSE diagnosis all had a herpes simplex virus (HSV)-positive CSF PCR, while patients in the control group, each of whom had also had presumptive diagnosis of HSE, had an HSV-negative CSF PCR. Patients were either discharged from hospital or died during hospitalization.

EEG AND IMAGING DATA

All patients with a presumed HSE diagnosis had been treated with intravenous aciclovir 30 mg/kg per day (American Pharmaceutical Partners, Schaumburg, IL) following admission. Documented clinical symptoms at onset included seizures, fever (temperature >38.5°C), altered mental status, headache, meningeal signs and focal neurological deficit. Serial EEG records and cranial imaging (CT/MRI), including those obtained within 48 h of symptom onset, were reviewed. In all patients studied, the EEG was used to rule out the presence of epileptiform activity and to identify focal temporal slowing and periodic lateralized epileptiform discharges (PLEDs), which are classically used to support a diagnosis of HSE. An independent epileptologist and radiologist interpreted the EEG and imaging data. Data relating to medical therapy and in-hospital mortality were also collected. MRI was considered positive if there was evidence of signal changes in the mesial temporal lobe and adjacent structures on T2-, flair- and diffusion-weighted images with and without enhancement on gadolinium diethylenetriaminepentaacetic acid (GDTPA) administration.

PCR ASSAYS

All PCR assays were performed at the University Hospitals of Cleveland using the 'hot start' method with a proprietary primer (Roche Diagnostics, Indianapolis, IN). In both groups, CSF PCR was performed within 48 h of symptom onset.

STATISTICAL ANALYSIS

Statistical analysis was carried out using χ^2 and Fischer exact tests to compare proportions. Mantel–Haenszel stratified analysis was used to adjust for confounding variables. We calculated the sensitivity and specificity of EEG using HSV PCR as the gold standard.¹

Results

Over the 8-year study period, 35 patients were admitted to the neurology department with presumed diagnoses of HSE. Of these, 10 patients had CSF PCR confirmation of HSE and 25 were HSV PCR-negative. Among HSV PCR-negative patients, discharge diagnoses included: epilepsy (five patients) and antiepileptic drug withdrawal (six patients); systemic infection associated with alteration in mental state (nine patients); and ischaemic stroke (five patients). Table 1 shows baseline characteristics and initial clinical presentation of patients with positive HSV PCR results compared with those with negative HSV PCR results. As the table shows, mean age and time of symptom onset were comparable between the two groups. The spectrum of clinical symptoms and neurological findings were also similar between the two groups except for fever, which occurred with statistically significantly greater frequency in the HSV PCR-positive group ($P < 0.01$).

Among the HSV PCR-positive group, 90% (nine of the 10 patients) had either PLEDs and/or focal temporal slowing on EEG during the first 48 h from symptom onset, whereas among those with a negative HSV PCR, PLEDs and/or focal temporal slowing was found in only 30% (six of 20 patients). EEG sensitivity (PLEDs and/or focal temporal slowing) was 90% (Figure 1) and specificity was 70%. Of the 35 patients studied, 12 had an EEG on day 4 and seven on day 8. EEG sensitivity decreased when measured serially during the disease course, to 60% on day 4 and 50% on day 8 following symptom onset.

Table 1: Clinical presentation based on the results of herpes simplex virus (HSV) polymerase chain reactions (PCR) in the cerebrospinal fluid (CSF) in patients with suspected herpes simplex encephalitis

Clinical features	HSV PCR-positive <i>n</i> =10	HSV PCR-negative <i>n</i> =25
Age, years	61.1 (±15.6)	56.6 (±19.0)
Onset of symptoms, days	2.10 (±1.7)	2.16 (±1.8)
Seizure, <i>n</i> (%)	6 (60)	7 (28)
Fever, <i>n</i> (%)*	9 (90)	10 (40)
Altered mental state, <i>n</i> (%)	10 (100)	22 (88)
Headache, <i>n</i> (%)	5 (50)	9 (36)
Nausea and vomiting, <i>n</i> (%)	4 (40)	2 (8)
Coma, <i>n</i> (%)	1 (10)	0
Meningeal signs, <i>n</i> (%)	3 (30)	2 (8)
Hyperreflexia, <i>n</i> (%)	0	0
Hemiparesis, <i>n</i> (%)	4 (40)	3 (12)
Babiniski sign, <i>n</i> (%)	3 (30)	2 (8)
Cranial neuropathy, <i>n</i> (%)	0	0
CSF total protein, mg/dl	74.8 (±42)	61.7 (±13.7)
CSF glucose, mg/dl	65.8 (±25)	70.2 (±18.9)
CSF white blood cells (range), mean lymphocytes (%)	(11–422), 83	(1–6), 78

* $P < 0.01$; Age and symptom onset data are expressed as the mean ± standard deviation

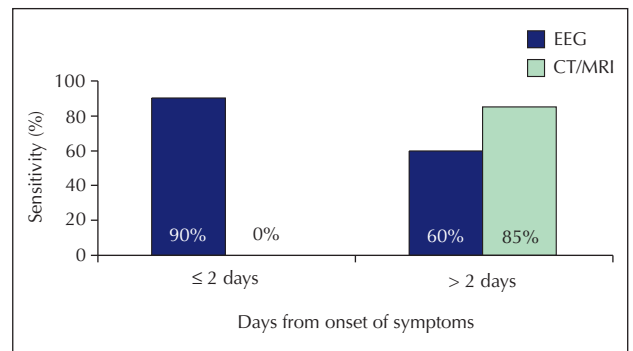


Figure 1: Sensitivity of electroencephalogram (EEG) and cranial imaging (CT/MRI) in herpes simplex encephalitis with respect to disease onset. CT, computed tomography; MRI, magnetic resonance imaging

All patients underwent cranial imaging, with either head CT and/or MRI scans, within 48 h of symptom onset. Eight of 10 HSV PCR-positive patients had cranial CT scans and only two patients had MRI scans, whereas head CT was performed in 76% (19/25) and MRI in 36% (nine of 25) HSV PCR-negative patients. None of the patients in either group had acute abnormalities on cranial imaging (CT or MRI) within the first 48 h following symptom onset. After 48 h of symptom onset, six of seven (86%) patients with a positive HSV PCR had temporal lobe abnormalities on MRI, whereas only six of 15 (40%) patients with a negative HSV PCR had an abnormal MRI scan. Calculated sensitivity for MRI was 85% (Figure 1) and specificity 60% after 48 h following symptom onset. No significant association was observed between normal head imaging (eight head CT scans and two MRI scans) within 48 h of symptom onset in HSV PCR-confirmed patients with abnormal EEGs. The lack of a standardized approach to imaging in both groups may have influenced the sensitivity and specificity analysis.

Among patients with fever and an abnormal EEG, 87% (seven of eight patients) had PCR-confirmed HSE compared with 12% (one of eight) patients in the PCR-negative group ($P = 0.005$). Age was not associated with abnormal EEGs or in-hospital mortality. There was no clear association between other clinical signs and abnormalities on EEG or cranial imaging. In our cohort of 35 patients, five (14%) died, three had abnormal PLEDs on EEG, and two were febrile and belonged in the HSV PCR-positive group.

Discussion

In its early stages, the clinical characteristics of HSE can be easily confused with other infectious diseases, especially in elderly patients presenting with an altered mental state. Our study reinforces this notion: fever was significantly more common among patients in the HSV PCR-positive group, suggesting a higher likelihood of an infectious process. Thus, in the correct clinical setting, clinical features of fever, altered mental state and seizure in association with an abnormal EEG can help to predict a clinical diagnosis of positive HSV PCR. Even though two of the three patients who died from HSE were febrile, we could not establish if fever or age played a role in predicting.

Although the pathological and clinical significance of an abnormal EEG in patients with HSE has not been determined, periodic complexes and temporal slowing have frequently been reported as characteristic findings.^{2,5} Correlation between these EEG findings in

HSE and the diagnostic gold standard (CSF PCR) has not, however, been established. Diagnosis of HSE can be achieved with a high degree of certainty when using CSF PCR detection for viral DNA, which has a sensitivity of 98%.¹ However, immediate access to PCR is not available in some countries, which can limit its clinical utility. The presence of red blood cells with xanthochromia in the CSF suggests a haemorrhagic lesion, and indeed this was observed in one patient with a positive HSV PCR.

Our results support the use of EEG early in the onset of HSE, especially when used in conjunction with clinical presentation; sensitivity is 90% in HSV PCR-positive cases. Because of its relatively low specificity, the clinical utility of EEG remains limited, especially when it is used as the sole method for diagnosis of HSE. The low specificity of EEG in HSE diagnosis is explained by the fact that PLEDs and focal temporal slowing can also be seen in patients with other structural lesions of the brain (including stroke, neoplasm, and degenerative disorders).⁶ Additionally, PLEDs have been reported with other viral encephalitides.⁷ Nonetheless, we believe it is unlikely that HSE will be misdiagnosed, especially when diagnostic testing is performed within 48 h of disease onset. Used in combination with fever, progressive obtundation and seizures, EEG is useful for evaluating subclinical epileptiform discharges, which one could consider to be rare occurrences in HSE.⁸ It is unclear why EEG sensitivity in our patient population decreased with disease progression, although this may be related to the monophasic presentation of a viral syndrome, which certainly impacts on the value of an EEG for periods beyond 48 h post-onset.

Cranial MRI is useful in HSE; it may show focal oedema in the medial portion of the temporal lobe and the orbital surface of the frontal lobe, insular cortex, and angular gyrus, and GDTPA administration can enhance abnormal gyri or meninges.⁴ Our data reinforce the usefulness of cranial MRI when obtained after 48 h following symptom onset: sensitivity reaches 85%. Schroth *et al.*⁹ evaluated MRI findings in four patients with early diagnosis of HSE, in whom changes occurred 2–10 days after disease onset, although none of these patients was studied within the first 48 h of disease onset. At 60%, MRI specificity remained low in our cohort. This can be explained by the fact that abnormal signals in the medial temporal lobe can be seen in other structural lesions such as acute cerebral ischaemia, infiltrative lesions, and other types of viral encephalitis.¹⁰ Although cranial imaging obtained within the first 48 h of symptom

onset showed no clear benefit in either patient group, our data remain inconclusive because of the limited number (two of 10) of MRI scans obtained in the HSV PCR-positive patients within that window of time. Earlier reports of abnormal diffusion signals in HSE were not found in any patients in the HSV PCR-positive group.¹¹ In agreement with Baringer,¹² our data did not support the use of cranial CT as a method of choice to evaluate HSE. Head imaging, however, remains an indispensable method for evaluating acute neurological syndromes.

Conclusion

Although EEG abnormalities such as PLEDs and focal temporal slowing are classically associated with HSE, they appear more sensitive than cranial imaging if obtained during the first 48 h of symptom onset. EEG sensitivity decreases with disease progression. Evidence suggests that cranial imaging is normal at disease onset, thus the presence of fever and an abnormal EEG may aid the diagnosis and perhaps help to predict outcome in HSE. On the other hand, brain MRI is superior to EEG ≥ 48 h from onset. All patients with suspected HSE should be treated with antiviral agents regardless of the EEG.⁴ The association between high in-hospital mortality and abnormal EEG or MRI in patients with HSE is unclear at this point. We postulate that a subgroup of patients may have had more extensive brain injury and co-morbidities than those who survived. Future MRI studies in HSE are necessary to validate its sensitivity and specificity.

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Conflicts of Interest

No conflicts of interest were declared in relation to this article.

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