



A SUCCESSFULLY TREATED CASE OF HERPES SIMPLEX ENCEPHALITIS

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Abstract : Herpes simplex encephalitis is a potentially lethal infection that should be recognised as soon as possible. The combination of clinical history and examination, brain computed tomography or magnetic resonance imaging and lumbar puncture has been used to establish a diagnosis. We present a case of 20 year old male presenting with fever, headache and later developed focal neurological deficit. His CSF examination showed no cells. His CT brain showed temporal lobe hypodensity and his MRI revealed temporal lobe hyperintense signals in T2 weighted images characteristic of herpes encephalitis. But his CSF PCR for HSV was negative though repeated twice. There was no elevation of oligoclonal antibodies specific to HSV in CSF after 1 week. The patient was successfully treated with acyclovir. Although we did not prove the presence of the agent microbiologically at the clinical onset of the disease, the CT and MRI findings and the dramatic response to acyclovir therapy are suggestive of a diagnosis of herpes simplex encephalitis. CSF PCR for herpes virus is highly

sensitive and specific and remains the standard for diagnosing herpes encephalitis. Clinicians should be aware of the pitfalls of CSF PCR testing, specifically false-negative results.

Keyword : Acyclovir, Encephalitis, Herpes virus, Polymerase chain reaction

INTRODUCTION:

The rapid diagnosis of central nervous system infection with herpes simplex virus is important because of the potential morbidity and mortality associated with the disease as well as the wide availability of acyclovir which has been proven to ameliorate the symptoms. Left untreated, more than 70% of cases of HSV encephalitis are fatal and only approximately 11% of patients recover normal premorbid function [1,8]. Treatment with acyclovir has been proven to reduce mortality to approximately 20% [9]. So far, the diagnosis of HSV encephalitis has relied on the combination of a compatible clinical scenario, a suggestive brain computed tomography scan or brain magnetic resonance imaging and the examination of the cerebrospinal fluid

by microscopy, biochemical analysis and polymerase chain reaction for the presence of HSV DNA.[2,5] HSV encephalitis has been left undiagnosed in the past, resulting in the patient's demise because of the lack of CSF pleocytosis, a normal CT and the absence of focal features on neurological examination [3,4]. We present a case that illustrates the importance of the clinical scenario in a patient with typical findings in imaging studies, but a negative CSF PCR and a normal CSF analysis. The high sensitivity and specificity of PCR for HSV leads physicians to rely on this test for making or excluding the diagnosis of HSV encephalitis, although false-negative results may occur. Cases with a high pre-test probability for HSV encephalitis and suggestive MRI and/or EEG examinations, although with false-negative PCR test, are seldom encountered or reported in the literature.[24,25]

CASE REPORT:

A 20 year-old man presented to our hospital with chief complaints of fever and headache. The patient was in good health until 1 week before admission to our hospital, when he suddenly developed worsening headache and fever. The headache was localized to the frontal region and was not accompanied by vomiting or seizures. He had no history of abdominal pain, dysuria, jaundice, cough or myalgia, joint pain. He had no significant past medical history. At the time of admission, he was conscious oriented to person, place, and time, was febrile. His physical examination was nil significant. Except for mild neck stiffness, his nervous system examination was otherwise normal. The patient was started on ceftriaxone, antimalarials and other supportive treatment. His fever investigations for malaria, dengue, leptospirosis, enteric fever were all negative. Urine analysis, culture of blood and urine were negative. His chest Xray was normal. Lumbar puncture

revealed clear fluid with glucose 69 mg/dl, protein 31 mg/dl, white blood cell count of 0, a red blood cell count of 0. CSF culture was also negative. On the third day after admission, he developed right sided hemiparesis with aphasia. His CT Brain taken then revealed a hypodense lesion of left temporal lobe - was reported as ?encephalitis ? infarct. His MRI showed increased T2 weighted signal intensity in the medial aspect of the temporal lobe, and was felt to be compatible with an acute phase of herpes encephalitis. Unfortunately, EEG couldn't be done for our patient. Acyclovir (10 mg/kg i.v., 3 times per day) was started for him. Repeat lumbar puncture was performed with glucose 79 mg/dl, protein 24 mg/dl, no cells. Serum HIV test was nonreactive. CSF HSV-PCR was sent for analysis which turned out to be negative. The patient's condition remarkably improved after 48 hours of antiviral treatment. His CSF PCR repeated on the third day after acyclovir was also negative. His CSF HSV antibody testing was negative. He completed 14 day course of acyclovir and was discharged in good health.





DISCUSSION:

The presence of a totally normal CSF analysis in HSV encephalitis is unusual, especially in non-immunocompromised patients. In a study presenting only atypical forms of HSV encephalitis [2], only one patient out of 24 had a normal CSF examination, performed during day 1 of the illness. PCR allows for the detection of minute quantities of viral DNA or RNA present in fluids and tissues by nucleic acid amplification over a short time period [11] and has nearly replaced brain biopsy for diagnosis of HSV encephalitis in regions where the test can be performed. Negative PCR tests are associated with low CSF protein and leukocyte counts [10], and in such cases, clinical suspicion should dictate the treatment course. The sensitivity and specificity of CSF PCR for HSV exceeds 95%, allowing exclusion of HSV encephalitis in patients with high pre-test probability should the result return negative [12]. In the study by Lakeman and Whitley [12], PCR sensitivity and specificity were reported as 98% and 94%, respectively, with positive and negative predictive values of 95% and 98%, respectively, when compared with brain biopsy. However, in patients with high clinical probability of HSV encephalitis, a negative PCR result, while decreasing the likelihood of HSV encephalitis, does not entirely exclude the possibility of infection. Negative PCR results generally allow for the discontinuations of acyclovir treatment. Few reports exist identifying HSV encephalitis in patients with

negative PCR [13, 14, 15]. Puchhammer-Stockl et al. [14] reported 3 patients with MRI and clinical evidence of HSV encephalitis with negative PCR tests. Denes et al.

[13] reported a series of 3 cases of HSV encephalitis confirmed by CSF antibody testing in the setting of negative PCR tests. Unfortunately, tests for intrathecal antibody synthesis are underused. In part, this is because a week or more has to elapse after the onset of neurological symptoms before the virus-specific humoral response is measurable [15]. In addition, non-specific results may arise through cross-reaction with varicella zoster antibodies [6]. Hence the sensitivity and specificity values of the assay are only about 80% [7].

Possible explanations for negative PCR results have been suggested and include: PCR sent very early in the disease development (days 1-4 with neurological symptoms) and viral load too low for detection, although this is unlikely as the PCR technique by virtue of the amplification process allows for the detection of minute amounts of viral copies, as low as 10 copies of viral inhibitors, and a small-volume CSF sample [11, 14, 16]. In addition, low CSF cell counts, variation in primers used during PCR processing, sample dilution, and location of infection in the central nervous system have all been suggested as the cause for false-negative results [1, 14, 17]. Denes et al [13] recommend repeating the PCR 4 days after development of symptoms and before deciding the patient does not have HSE and prematurely concluding acyclovir treatment. Patients with normal diagnostic tests and mild clinical symptoms are more

likely to have negative PCR tests [18]. In our case, the patient had a repeat PCR sent 3 days after the development of symptoms, and despite suggestive MRI the result was negative. Radiographically, the most common areas of involvement are the medial temporal lobes, which are best observed with MRI [20]. Sensitivity of MRI is reported to be best 48 h after onset of symptoms and approaches 85% [23], although it can be falsely negative in very early stages on infection. In our case MRI revealed florid changes suggestive of HSV infection. EEG may serve as an occasional adjunct in the diagnosis of HSE, demonstrating periodic lateralized epileptiform discharges as characteristic findings [20]. Specificity of EEG remains low in the diagnosis of HSE when used as a single diagnostic exam but can be helpful when PCR is negative in patients with high clinical probability [20]. An electroencephalogram would have been useful in the diagnosis and management of HSVE in our patient. Unfortunately, one was not performed. Acyclovir is the only treatment shown to significantly improve prognosis [21]. The morbidity and mortality increases dramatically as the time to treatment increases [22]. Treatment course is weight based in adults, roughly 10 mg/kg every 8 h intravenously for 10-21 days. Repeat MRI after successful treatment with acyclovir is generally unnecessary [23].

CONCLUSION:

Suspicion of HSV encephalitis should remain high in all cases of acute encephalitis, especially in the absence of alternative diagnoses, even in cases when PCR examination is negative. In such cases, repeating lumbar puncture should be entertained with repeat HSV-PCR testing and possible serologic testing of the CSF. In our case, the patient had clinical symptoms, MRI suggestive of HSV encephalitis, although with two negative PCR tests separated in time.

In patients with high clinical suspicion and negative HSV-PCR, repeat lumbar puncture should be considered and empirical acyclovir treatment should be considered. In all such cases, treatment with acyclovir should ensue until the diagnosis of HSV encephalitis can be confidently excluded.

ABBREVIATIONS:

CSF- Cerebrospinal fluid CT- Computed Tomography DNA- Deoxyribonucleic acid EEG- Electroencephalogram HSV- Herpes Simplex virus MRI- Magnetic Resonance Imaging PCR- Polymerase Chain Reaction RNA- Ribonucleic acid

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