CASE REPORT

An unusual presentation of herpes simplex encephalitis with negative PCR

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SUMMARY

A 74-year-old man presented with acute right-sided hemiparesis and epilepsy partialis continua in association with fever and confusion. Initial workup revealed possible cerebritis in the left medial frontal lobe without involvement of the temporal lobes. Cerebrospinal fluid (CSF) analysis revealed minimal lymphocytic pleocytosis but negative real-time herpes simplex virus (HSV) PCR. Acyclovir was discontinued on day 5 due to a negative infectious workup and clinical improvement. On day 9 his condition deteriorated and he was transferred to a higher level of acuity for advanced supportive care. Worsening encephalopathy and refractory status epilepticus ensued despite medical care. Repeat CSF analysis showed mild lymphocytic pleocytosis with negative real-time HSV PCR. Brain MRI revealed progression of cortical enhancement. Immunosuppressive therapy and plasma exchange were attempted without clinical response. On day 24, another lumbar puncture showed only mild lymphocytic pleocytosis. Brain MRI showed involvement of the right medial temporal lobe. Subsequently, acyclovir was resumed. The HSV-1 PCR result was positive on day 30. Unfortunately, the patient expired.

BACKGROUND

Herpes simplex is a serious cause of sporadic viral encephalitis in adults.¹ Herpes simplex encephalitis (HSE) is estimated to have an incidence between 1 in 250 000 and 1 in 500 000 persons per year.² Before the introduction of acyclovir in 1984, the mortality of HSE was about 70%, which has dropped to about 16% with the use of acyclovir.² HSE typically presents as an acute disease with a prodrome of fever, headache and nausea followed by symptoms more suggestive of encephalitis such as hemiparesis, focal deficits, seizures, altered level of consciousness and behavioural changes.^{1,3} Early recognition and treatment are important in reducing the morbidity and mortality of HSE.^{1,4} Untreated herpes simplex virus (HSV) is associated with a high mortality rate of 50–70%.⁴ We describe below a unique case of a patient with HSE who had a false-negative HSV PCR as well as an atypical isolated involvement of the medial frontal lobe until late stages of the disease. Without high clinical suspicion and early treatment of this disease, which has the potential to present in an unusual manner, a patient can have an unfavourable outcome.

CASE PRESENTATION

A 74-year-old man presented to the emergency department with twitching and weakness of the

right arm and leg of less than 48 h acute onset. The patient reported generalised malaise and fatigue during the preceding 2 weeks with worsening in the several days before presentation. He denied dysphagia, facial drooping, dysarthria, diplopia, headache or fever. His medical history included pulmonary fibrosis and amyloid lung nodules. He recently noted a non-specific rash on the right thorax 1 week prior to presentation. On initial examination, he was afebrile, lethargic and demonstrated weakness and spasticity of the right upper and lower extremities as well as rhythmic clonic jerking of the right upper extremity. Non-specific maculopapular lesions were noted on the patient's thorax. The initial thorough workup was abnormal for a subtle increased T2 signal within the left median frontal lobe seen in the contrast brain MRI (figure 1) as well as periodic lateralising epileptiform discharges over the left temporal region. On the basis of these results, the patient was diagnosed with epilepsy partialis continua with a differential diagnosis including viral encephalitis, paraneoplastic encephalitis or autoimmune encephalitis. Subsequently, the patient was started on an empiric therapy of acyclovir, ampicillin and ceftriaxone on day 1. He was also treated with intravenous benzodiazepines and fosphenytoin. Initial cerebrospinal fluid (CSF) analysis showed minimal lymphocytic pleocytosis (15 white cell counts (WCCs); 75% lymphocytic, glucose 60 mg/dL, protein 43 mg/dL) but otherwise negative real-time HSV PCR, among other infectious PCRs and cultures. On day 2, the patient's clinical status worsened with development of fever with T max 101.3° F, decline in mental status and respiratory decline requiring intubation. His repeat contrast brain MRI revealed left cingulate and medial frontal lobe cerebritis with adjacent oedema in the right frontal lobe. Dexamethasone therapy was added. With the addition of

Figure 1 There is a small focus of high T2 fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted signal intensity in the medial left frontoparietal cortex which could represent cerebritis. There is no signal abnormality within the medial temporal lobes on the T2 FLAIR sequence.

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dexamethasone and continuation of the medication regimen, the patient showed marked clinical improvement and was extubated on day 5. On the basis of infectious disease recommendations, acyclovir was discontinued on day 5 due to the presence of a slightly abnormal CSF, negative infectious PCRs and remarkable clinical improvement. However, the patient remained on dexamethasone therapy. On day 9, the patient deteriorated with increasing right-sided weakness, decrease in mental status and recurrence of epilepsy partialis continua. Consequently, the patient was transferred to a higher level of acuity where he continued to decline and was reintubated secondary to respiratory failure and refractory status epilepticus. On day 9, a second CSF analysis was obtained with negative real-time HSV PCR and mild lymphocytic pleocytosis (35 WCC, 95% lymphocytes). Later on, the patient continued to decline despite advanced supportive therapy, steroids included. On day 12, a contrast brain MRI revealed progression of enhancement along the frontal cortex. Treatment with plasmapheresis was attempted for possible autoimmune versus paraneoplastic encephalitis without clinical response. A second comprehensive workup was carried out which yielded negative results for autoimmune and paraneoplastic antibodies (ie, anti-NMDAR (*N*-methyl-D-aspartate receptor), anti-Hu, anti-VGKC (voltage-gated potassium channel), anti-Ma2 antibodies, among others). A third CSF analysis obtained on day 24 revealed 17 WCC, 95% lymphocytes, 48 mg/dL protein and 86 mg/dL glucose. The repeat contrast brain MRI on day 24 revealed involvement of the right temporal lobe (figure 2). Owing to these new findings, intravenous acyclovir was resumed on day 24. The HSV-1 real-time PCR result was positive on day 30. Unfortunately, the patient developed hospital-acquired pneumonia requiring intubation and passed away on day 30 from complications of septic shock.

INVESTIGATIONS

Haematological and blood chemistry studies were normal. Initial diagnostic imaging studies consisted of a normal non-contrast CT head, a non-contrast head MR angiography negative for vasculitis or venous thrombosis, and a contrast brain MRI which revealed a subtle increased T2 signal in the left medial frontal lobe. The CSF analysis on day 1 revealed 15 WCCs with a 75% lymphocytic predominance, glucose 60 mg/dL, protein 43 mg/dL in addition to a non-reactive rapid plasma reagin (RPR), negative varicella-zoster virus PCR, negative real-time HSV PCR, negative HSV culture and negative West Nile IgM. Routine EEG revealed periodic lateralising epileptiform discharges over the left temporal region and moderate diffuse slowness consistent with encephalopathy. On day 2, the repeat

Figure 2 There is a diffuse cortical high T2 fluid-attenuated inversion recovery signal intensity with predominant involvement of the right medial temporal lobe.

contrast brain MRI revealed cerebritis in the left cingulate gyrus and left medial frontal gyrus which extended into the right medial frontal lobe (figure 1).

On day 9, the repeat CSF analysis revealed 35 WCC, 95% lymphocytes and negative real-time HSV PCR. The comprehensive workup yielded negative results for paraneoplastic antibody screening, autoimmune panel, HIV, West Nile virus, varicella zoster, treponema and *Borrelia burgdorferi*.

On day 12, contrast brain MRI revealed the previously seen findings but with new subtle enhancement along the cortex. The CSF obtained on day 24 revealed 17 WCC, 32% lymphocytes, 48 mg/dL protein and 86 mg/dL glucose. On day 24, the contrast brain MRI revealed an extension of increased T2 signal within the bilateral striatum nuclei and diffusely increased along the right temporal lobe (figure 2). On day 30, the real-time HSV-1 PCR came back positive.

DIFFERENTIAL DIAGNOSIS

In this case, the differential diagnosis for rapidly progressive encephalitis associated with epilepsy partialis continua and MRI findings of cerebritis included autoimmune encephalitis such as paraneoplastic limbic encephalitis versus autoimmune central nervous system vasculitis versus infectious encephalitis. Owing to the patient's medical history of pulmonary amyloidosis, the diagnosis of cerebral amyloid angiopathy-related inflammation was also considered.

TREATMENT

The treatment of epilepsy partialis continua consisted of intravenous benzodiazepines, lacosamide and fosphenytoin and advanced to anaesthetics along with other sedatives. Empiric antibiotic therapy and acyclovir for possible viral encephalitis were discontinued after negative CSF analysis results on day 5. However, intravenous steroid therapy with dexamethasone was administered almost throughout the hospital course. Adjunctive therapy with plasma exchange was attempted without success. Acyclovir was resumed on day 24 and continued until the patient expired.

OUTCOME AND FOLLOW-UP

Unfortunately, the patient in this case passed away with rapidly progressive septic shock.

DISCUSSION

There have been few cases published regarding patients who presented with a slightly abnormal CSF analysis with HSV encephalitis. Currently, real-time PCR is the gold standard for the diagnosis of HSE. Real-time PCR is the ability to monitor the progress of the PCR as it occurs (ie, in real time). Data are therefore collected throughout the PCR process, rather than at the end of the PCR. The higher the starting copy number of the nucleic acid target, the sooner a significant increase in fluorescence is observed. Real-Time PCR has 95% sensitivity and 90% specificity,¹ although false-negative results have been reported.⁵ CSF HSV PCR has been seen to be negative in patients later proven to have HSV encephalitis when CSF analysis was performed early on in the disease progression or less than 4 days from symptom onset.^{6,7} This patient presented with 2 weeks of the generalised malaise but with worsening of symptoms within the 2 days prior to presentation, which makes it possible that his initial CSF evaluation was negative because he was early on in his disease process. Furthermore, it is possible that his CSF evaluation on day 9 was negative for HSV by means of PCR because the patient had been treated with

intravenous acyclovir for 5 days prior to the CSF collection on day 9. Another reason suggested for the possibly negative CSF HSV PCR is a low viral level in CSF because major viral replication occurs in the brain and only few viral particles may be present in the CSF.⁷

Typical CSF findings in a patient with HSE include lymphocytic pleocytosis, mildly elevated protein level and normal glucose level. A normal CSF cell count is seen in less than 5% of immunocompetent adults.^{6 8–10} A CSF glucose concentration of less than 50% of the serum glucose is seen in less than 5% of patients with HSE.⁶ Both the CSF WCC and CSF protein become elevated as the disease progresses. The average CSF WCC is 100 cells/ μ L.² Our patient had a CSF cell count with predominance of lymphocytes; however, the CSF cell count was only slightly increased without significant proteinorraquia. Previous studies have shown that the presence of fewer than 10 leucocytes/mm³ in CSF has been associated with a higher likelihood of a negative CSF HSV PCR result.⁶ Approximately 80% of treated patients will have a negative CSF PCR result at greater than 14 days of illness.⁶ Our patient was treated with intravenous acyclovir for 5 days only. However, it is possible that this contributed to a negative HSV PCR result.

Neuroimaging plays an important role in the diagnosis of HSV with MRI being the procedure of choice in patients with suspected HSE.⁶ More than 90% of PCR-proven HSV encephalitis cases have abnormal MRI findings including increased T2 and decreased T1 signals in the temporal lobes.⁶ More specific MRI findings in patients with HSE include involvement of the medial temporal cortex with a later bilateral spread along the limbic cortex to the orbital frontal lobes and insular cortex; later in the disease, there may be involvement of further structures such as the parietal, occipital lobes, cingulate gyrus and brain stem.^{4 11–14}

Along with the typical clinical presentation of HSV encephalitis being acute, progressive onset of fever in 90% of cases as well as headache (80%), motor deficit (30–40%) and seizure (40–67%) being key pieces to diagnosis of HSV, radiological studies in the diagnosis of HSE also have a role. MRI is more sensitive and specific compared to CT and abnormalities appear earlier on MRI; therefore, MRI is the imaging modality of choice to help diagnose HSV.⁶ A typical presentation on MRI involves a mass-like and infiltrative abnormality in the medial temporal lobes, insula, cingulate gyri and inferior frontal lobes.⁴ This case is unusual because an initial MRI of the brain revealed an isolated increased T2 signal in the left cingulate and medial frontal lobe without involvement of the temporal lobes. The typical presentation on MRI did not occur in this case until day 24 with right temporal lobe involvement. Previous studies reported the concomitant presence of extratemporal involvements in 55% of HSE cases with only 15% demonstrating pure extratemporal lesions.^{4 11–14} It has been postulated that neuronal transmission is the mechanism in HSV-1 encephalitis. There is probably intracranial transmission via the meningeal branches of the trigeminal nerve.¹⁵ The cingulate gyrus can be affected via the efferent connections of the hippocampus. However, the pathophysiology for selective HSV-1 transmission into the cingulate and medial frontal lobe without involvement of other limbic structures remains unclear.

In conclusion, this case of HSE was very atypical with slightly abnormal CSF studies, negative HSV PCRs as well as an

unusual presentation on the MRI with only frontal lobe involvement until late in the course of disease when classic temporal lobe involvement appeared.

Learning points

- ▶ A high index of suspicion is needed to diagnose herpes simplex encephalitis (HSE) when encountering a patient with fever, encephalopathy and focal neurological deficits despite atypical imaging and cerebrospinal fluid (CSF) analysis.
- ▶ A low threshold to treat for HSE is necessary for a patient with signs of encephalitis despite negative PCR because of the possibility of a false negative and a high mortality rate without early and effective treatment.
- ▶ It has been postulated that negative herpes simplex virus PCR may be possible when the CSF cell count is only slightly increased like in this case.

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