References


BRIEF COMMUNICATIONS

Delayed MRI Findings in Herpes simplex Encephalitis

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Herpes simplex encephalitis (HSE) is one of the most common forms of encephalitis, accounting for approximately 10% of all cases of encephalitis. Herpes simplex virus -1 (HSV) causes more than 90% of HSE cases in adults.

HSE is a life-threatening disease. Following the onset of neurological symptoms, most patients rapidly progress to confusion, delirium or coma within a few days. When initiated early, acyclovir treatment greatly benefits the prognosis, reducing the mortality rate from 70% to 25%.

Therefore, a rapid and reliable diagnostic tool is very important. Cerebral spinal fluid (CSF) analysis of viral DNA, using polymerase chain reaction (PCR), a technique highly sensitive and specific for the rapid diagnosis of HSE, appears positive for HSE between 3 and 12 days following the onset of neurological symptoms. The old standard is viral culture or brain biopsy, but that PCR, with its excellent sensitivity and feasibility, is considered diagnostic and definitive in most clinical settings. Brain magnetic resonance imaging (MRI) is also very sensitive in showing characteristic changes in temporal lobe, retrochiasmal lobe and occasionally in the medial temporal and gyri in HSE.

In most reported cases, MRI revealed brain abnormalities within one week after the onset of HSE.

The characteristic and sensitive findings of MRI help the early diagnosis of HSE. Here we report an atypical HSE case, which showed subacute clinical process and delayed MRI characteristic abnormalities.

Case Report

A 56-year-old previous healthy man was admitted to the Emergency Department shortly after a focal seizure of his left cheek and left arm accompanied by a transient loss of consciousness. He was nauseated and vomiting and complained of forehead pain. The patient had no fever and the neurological assessment was normal. Blood count revealed 11.24 x 10^5/L, white blood cells (WBC) with 58% neutrophils. The routine biochemical analyses were normal. The electroencephalogram showed poor adjustment of β wave amplitude. Brain MRI (Siemens, 1.5T) was normal (Figure A, B). There was no recurrence of seizure and the next day he was discharged from the hospital. He developed progressive memory deficits. On the 13th day, he felt pain in the upper back and shoulder concurrent with severe dizziness. He had a temperature of 37.6°C and was re-admitted into the hospital. He was very irritable with hallucinations and disorientation. The day of re-admission, the patient experienced three bouts of generalized tonic-clonic seizures. He rapidly progressed to lethargy. Electroencephalogram revealed single spike wave in the bilateral frontal and the left temporal regions with increased waves in the right occipital and temporal regions. The serum autoantibodies, including anti-nuclear antibodies, anti-dsDNA antibody, anti-histone antibodies and anticoagulants were negative and titers were in the normal range. On the 14th day, a lumbar puncture showed normal cell count with mildly increased protein content (687 mg/L). Cerebral spinal fluid HIV and HCV antibodies were negative, including HSV-1, HSV-2, and cytomegalovirus, were negative. The analysis of viral DNA PCR was not available in the first CSF test. Herpes simplex encephalitis was considered. He was treated with IV acyclovir and intravenous acyclovir 10mg/kg, every eight hours. On the 15th day, the fluid-attenuated inversion recovery (FLAIR) and T1-weighted MRI after administration of Gd-DTPA were performed and again, no abnormality was identified (Figure C). The patient continued to suffer from seizures three to four times/day. He deteriorated rapidly and on the 17th day, after three continuous seizures, he became comatose. He developed severe respiratory and cardiovascular failure and was placed on a ventilator. Brain CT revealed abnormal signals in both temporal lobes, mainly the left hippocampus, which displayed increased signal intensity on T2-weighted and diffusion-weighted images. The abnormal signal intensity was confirmed on FLAIR (Figure D). On the 27th day, lumbar puncture revealed 31 white blood cells/mm consisting of 79% polymorphonuclear cells and a protein level of 731 mg/L. Herpes simplex virus -1 PCR was positive, and CSF HSV-1 antibodies were also negative. The acyclovir treatment continued for three weeks. The patient gradually recovered and the seizures disappeared. He regained consciousness and orientation. A third lumbar puncture was performed on the 42nd day and CSF cell count returned to normal and HSV-1 IgG was determined to be positive, while other herpes viruses IgC and cytomegalovirus IgG were negative. Herpes simplex virus -1 PCR remained negative. The diagnosis of HSE-1 was confirmed. The patient continued to improve. The follow-up MRI was done on the 52nd day, and the abnormal signals in bilateral temporal lobes were present, but...
negative. Polymerase chain reaction of HSV was positive on the 5th day\(^2\). To exclude tumor and acute disseminated encephalomyelitis, we applied for the contrasted MRI, including FLAIR, 15 days after his first seizure. Fluid-attenuated inversion recovery is superior than T1 and T2 in detecting the early changes of HSE, and usually shows the lesions around a week after the onset of neurological symptoms\(^2\). The negative FLAIR findings 15 days after the first seizure indicated delayed abnormalities in brain MRI.

Cerebral spinal fluid PCR-test of HSV-1 in the gold standard in the diagnosis of HSE. It is reported that the PCR-positive period for HSE is from Day 3 to Day 15\(\text{a}^1\). Polymerase chain reaction can be negative within two days of HSE onset\(\text{a}^1\). The negative finding of CSF PCR in our patient could be due to the two weeks acyclovir treatment\(\text{a}^1\). Positive PCR appeared in the acute stage and intrathecal IgG could be measured in the postictal stage. Intrathecal IgM/IgG were detectable 14 days after onset of the disease and persisted for several years. Generally, PCR is negative in the cases with detectable intrathecal IgG\(\text{a}^1\). The sensitivity and specificity values of specific HSV-1 IgG assay are about 89%\(\text{a}^1\). The false positive mainly arises from the cross-reaction with varicella zoster antibodies\(\text{a}^1\).

In our patient, the CSF varicella zoster virus IgG was negative in the three tested time points. The specific HSV-1 IgG in CSF in our patient turned from negative on Day 14 and 27 to positive on Day 42, confirming the diagnosis of HSE. The etiological diagnosis of HSE is very important because other causes of limbic encephalitis, such as connective tissue disorders, paraneoplastic and voltage gated potassium channel associated limbic encephalitis, also selectively involve the hippocampus and other limbic structures\(\text{a}^1\).

The reason for delayed MRI findings in our HSE patient is unclear. This patient had no seizures, previously. He had a subacute onset of HSE. After the first seizure, he had a plateau phase of 11 days, and then his condition worsened rapidly. The second negative MRI was taken on the 3rd day after the deterioration. On the 11th day after the deterioration, MRI revealed characteristic medial temporal lobe lesions. The increase of CSF WBC occurred in parallel to the positive MRI findings. We propose that the subacute onset of HSE may account for the delayed MRI findings in this patient.

Hemps simplex encephalitis is a severe disease. The combination of MRI and CSF PCR-test promotes the early diagnosis of HSE. However, the assessment of CSF-PCR and brain MRI at the onset of neurological symptoms can be negative. For those patients with clinically suspected HSE and negative initial findings in CSF and MRI, serial, repeated tests of CSF PCR, CSF IgM and IgG tests and MRI are required to confirm the diagnosis of HSE.

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Figure: Serial cranial MRI scans of the HSE patient. On the second day following the first seizure, MRI ventrotemporal (A: Diffusion, B: FLAIR). On the 15th day, the contrast-enhanced T1 weighted image (C) and FLAIR (D) did not reveal apparent abnormality, either. On the 23rd day, abnormal signal was seen on both lateral ventral temporal lobe, mainly in the left hippocampus with a small lesion in the right hippocampus, which displayed hyperintensity in Diffusion (E) and FLAIR (F).

Discussion

This patient was diagnosed with HSE by intrathecal synthesis of antibodies against HSV-1. The case was characterized by several uncommon features. First, the initiation of HSE in this patient was subacute. WBC had a delay of 11 days after the first seizure, followed by apparent neurological and psychological manifestations, and then he deteriorated quickly. Second, he had a late increase of WBC in the CSF with polyneuropsychic cell predominance. Third, he had delayed positive MRI findings. This patient underwent serial MRI scans following the first seizure and apparent abnormality appeared on the 23rd day, but not on the 15th. To our knowledge, negative MRI findings more than 15 days after the onset of neurological symptoms of HSE have not been reported previously. Holinger et al reported normal MRI findings in a PCR confirmed HSE patient, where the patient was followed for 14 months. However, during the acute phase, the last MRI was taken on Day 6. Our results indicate that abnormal MRI findings in HSE can occur as late as two to three weeks, and the cases with normal MRI findings in early stage must be followed more closely within the first month.

Magnetic resonance imaging is very sensitive in the detection of morphological abnormalities in acute HSE cases. Positive brain MRI is generally documented within one week of the HSE onset. Magnetic resonance imaging clearly shows the typical HSE lesions in the unilateral or bilateral temporal lobes, insular cortex, frontal lobes, which display hyperintensity in T1, and hyperintensity in T2, Diffusion and FLAIR images. It is of note that the Diffusion and FLAIR are the most sensitive radiographic methods in detecting HSE. In an immunodecient patient, the abnormal MRI findings were found to occur earlier than PCR DNA tests in this patient. The MRI Diffusion revealed hyperintensity in the insular lobe on the 2nd day after neurological symptoms appeared, where PCR of HSV was still negative. Polymerase chain reaction of HSV was positive on the 5th day. To exclude tumor and acute disseminated encephalomyelitis, we applied for the contrast MRI including FLAIR, 15 days after his first seizure. Fluid-attenuated inversion recovery is superior than T1 and T2 in detecting the early changes of HSE, and usually shows the lesions around one week after the onset of neurological symptoms. The negative FLAIR findings 15 days after the first seizure indicated delayed abnormalities in brain MRI.

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