

Brainstem Lesions in Herpes Encephalitis

Herpes Ensefalitinde Beyin Sapı Lezyonu

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ÖZET

Herpes simpleks ensefaliti tipik olarak medial temporal ve inferior frontal lobları etkilemekte, beyin sapı lezyonları oldukça nadir olarak izlenmektedir. Burada, 42 yaşında deliryum tablosu ile başvuran ve herpes simpleks ensefaliti tanısı alan bir kadın hasta sunulmaktadır. Hastanın manyetik rezonans görüntülemesinde kontrast tutulumu gösteren inferior frontal ve pons lezyonları saptanmıştır. Hasta başarılı bir şekilde tedavi edilmiş ve nörolojik sekel kalmamıştır, ancak lezyonlardaki kontrast tutulumunun devam ettiği dikkati çekmiştir. Bu olgu herpes simpleks ensefalitinin de beyin sapı lezyonlarında ayırıcı tanıda araştırılmasını vurgulamaktadır. Ek olarak, kontrast tutulumunun klinik düzelme sonrasında birkaç ay daha sürebileceği akıldan tutulmalıdır.

Anahtar Kelimeler: Ensefalit, herpes simpleks, beyin sapı.

ABSTRACT

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Herpes simplex encephalitis typically involves the medial temporal and inferior frontal lobes; brainstem lesions are very unusual. We present a 42-year-old woman admitted with delirium and diagnosed as herpes simplex encephalitis. The patient had gadolinium-enhancing inferior frontal and pontine lesions on magnetic resonance imagings. The patient was successfully treated without any neurologic sequelae, though contrast-enhancement was still present. This case report emphasizes that herpes simplex encephalitis should be investigated in the differential diagnosis of brainstem lesions. Moreover, contrast-enhancement may persist for some months even after clinical improvement.

Key Words: Encephalitis, herpes simplex, brain stem.

INTRODUCTION

Herpes simplex virus (HSV) is the most commonly recognized cause of acute sporadic encephalitis in humans (1). Most cases are due to HSV type 1 (HSV-1); up to 10% may be caused by HSV type 2 (HSV-2) (2). HSV encephalitis (HSE) is postulated to occur as a consequence of the centripetal spread of the virus from sites of latent infection in the cranial nerve ganglia to the frontal or temporal lobes of the brain (3).

Herpes simplex encephalitis (HSE) responds well to specific antiviral drugs, but it has an extremely high mortality rate of about 70% if left untreated (4). Although the gold standard for diagnosing HSE was previously isolation of HSV from brain tissue, the risk of complications from a brain biopsy has led to replacement of this method with examination of cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) (1,5). Polymerase chain reaction (PCR) amplification of HSV sequences from the CSF offers a rapid, sensitive and inexpensive means to establish the initial diagnosis of HSE (6). The imaging method of choice for HSE is MRI because it provides the most sensitive method for detecting early lesions (1). Although HSE lesions have a characteristic predilection for the medial temporal and inferior frontal lobes, other unusual locations have been reported as well. In this case report, we present a patient diagnosed with HSE who had gadolinium-enhancing inferior frontal and pontine lesions on MRI.

CASE

A 42-year-old female patient was admitted to the hospital with fever, agitation and changes in consciousness. She was in a delirium state with prominent meningeal irritation signs and fever. On neurological examination, the pupils were isocoric and reactive to light. Deep tendon reflexes were normal, without pathological reflexes.

The leukocyte count ($10.000/\text{mm}^3$) and C-reactive protein (5.56 mg/dL) were increased. Lumbar puncture performed on the day of admission yielded leukocytosis with 90% lymphocytes. The initial CSF pressure was normal (250 mmHg). Cytological investigation of the CSF for atypical or malignant cells was normal. Glucose (67 mg/dL) and microprotein (30.7 mg/dL) were normal. PCR analysis of the CSF specimen was done twice following two lumbar punctures (on admission and 15 days later), and both were positive for DNA of HSV-1. The immunoglobulin (Ig) G level to HSV-1 was also positive (3.6 ISR) in enzyme-linked immunosorbent assay, while IgM for HSV-1 and IgG/M for HSV-2 were negative. PCR analysis for mycobacterium DNA and results of CSF culture were negative. Anti-HIV antibodies were negative. The electroencephalogram of the patient showed nonspecific diffuse generalized slowing over both hemispheres, without any lateralizing finding or epileptic focus.

On the day of admission, MRI performed on a 1.5 T MR unit showed corticosubcortical, non-hemorrhagic contrast-enhancing, hyperintense signal changes in the left inferomedial frontal gyrus and gyrus recti and right pons (Figure 1A,B). The frontal lesion extended into the left superior frontal gyrus and the anterior part of the lentiform nucleus. Both lesions were hyperintense in diffusion-weighted MRI, and had lower apparent diffusion coefficient values, supporting the presence of vasogenic edema.

The patient was diagnosed with HSE caused by HSV-1. Four days after the treatment, she was in her pre-illness state with normal neurological examination. She completed a three-week acyclovir treatment. A follow-up cranial MRI performed five months later demonstrated that the lesions in the inferior frontal gyrus and right inferior pons were still minimally contrast-enhancing (Figure 2A,B).

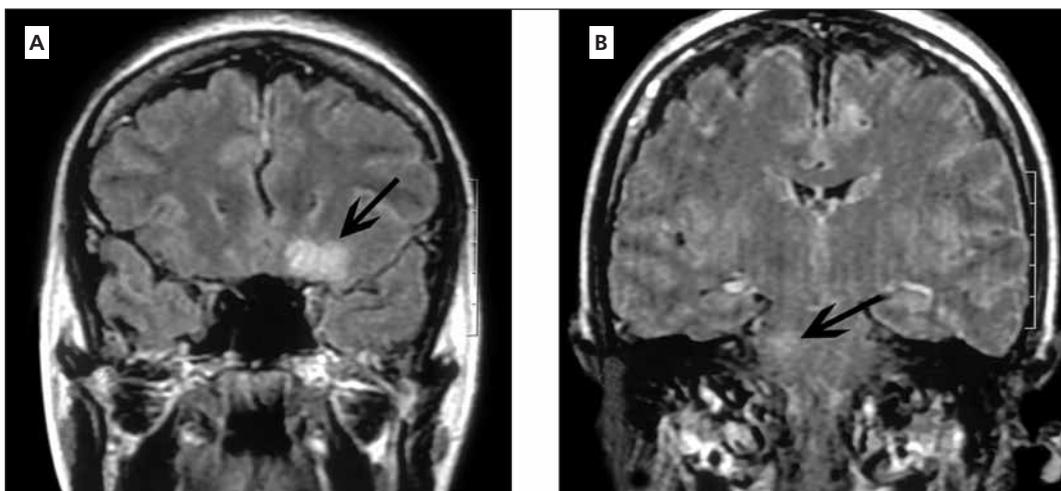


Figure 1A,B. Coronal FLAIR images show hyperintense corticosubcortical signal changes in the left inferomedial frontal gyrus, gyrus recti and right basis pontis.

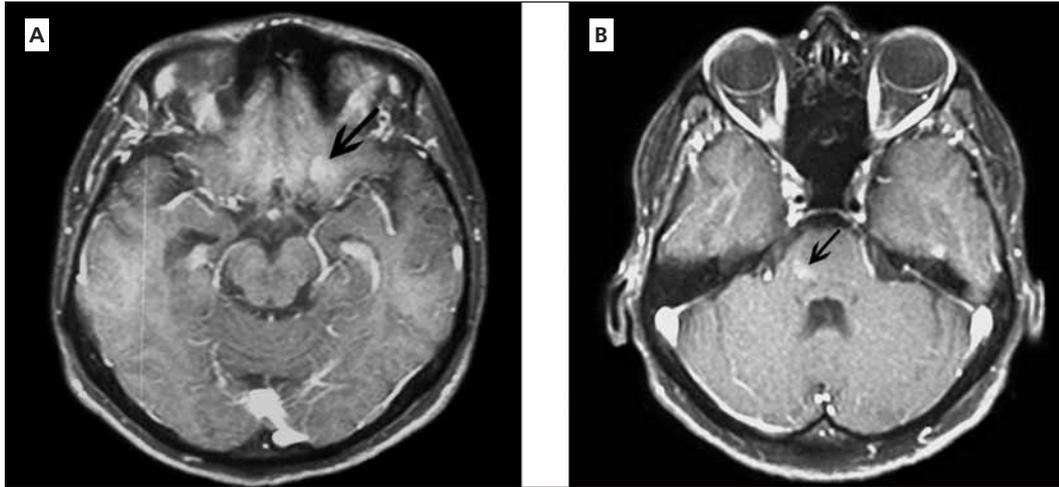


Figure 2A,B. Cranial MRI performed five months after the initiation of treatment demonstrates the presence of mild homogeneous contrast enhancement in lesions in the left inferior frontal gyrus and right basis pontis in contrast-enhanced T1WI.

DISCUSSION

Early diagnosis is essential in HSE, as the prognosis is largely dependent on early treatment (7). A CSF exam generally demonstrates elevations in protein concentrations and lymphocytic pleocytosis (4). The application of PCR to detect HSV DNA in the CSF is a very sensitive method for the diagnosis of HSE (1). In our patient, lymphocytic pleocytosis and positive results for HSV-1 were shown.

MRI has an important role in the diagnosis and differential diagnosis of HSE (7). The lesions of HSE caused by HSV-1 have a characteristic predilection in the brain for the medial temporal and inferior frontal lobes, and occasionally for the insular cortex and cingulate gyrus (8). The role of "conventional" MR sequences in the diagnosis and differential diagnosis of HSE has been summarized in the literature (9). Recently, diffusion-weighted imaging (DWI) was shown to be useful for early diagnosis (5,7,10).

Although typical localizations of HSE facilitate the diagnosis, some atypical localizations of HSE have been reported as well. Two reports documented two children with HSE with cerebellar involvement, and another study showed cerebellar lesions on T2WI, T1WI, FLAIR, and DWI, with similar intensity to cerebral lesions, indicating that the cerebellum was similarly involved in the pathology of HSE (11-13). MR findings in a patient with acquired immunodeficiency syndrome (AIDS) revealed necrosis of both cingulate gyri and cerebellar involvement, with the sparing of the hippocampi and limbic cortices (14). Another case report demonstrated subcortical, bilateral opercular and bilateral thalamic lesions, with the sparing of temporal and inferior frontal lobes (15). Scattered lesions in bilateral hemispheres were also shown to be caused by HSV in a case of neonatal encephalitis (16).

Herpetic brainstem encephalitis is another rare atypical presentation of HSE. High-signal intensities in the right pontine tegmentum, right cerebellar peduncle and vermis on fluid-attenuated inversion recovery imaging were demonstrated in a case report, and 35 cases with herpetic brainstem encephalitis were reviewed in a study by Yoshidome et al. (17). They suggested involvement of the brainstem due to HSV-1 with possible infection via the right trigeminal nerve. In our case, pontine lesions were present in addition to an inferior frontal lesion.

The presence of increased signal intensity on T2W-MRI was also reported in patients with HSE in contrast to clinical improvement and the disappearance of signal abnormalities on DWI (18,19). However, these reports had a fairly limited follow-up (8-10 days). In another case report, on the other hand, the high signal intense lesions on T1W-MRI were detected in the left medial temporal lobe, right insula, and straight gyrus after three months, although the clinical symptoms had improved significantly (20). Another feature in our patient was the persistence of contrast enhancement in imaging findings after about five months, as the patient responded very well to the treatment, becoming symptom-free. The consequence of persistent inflammation in the development of chronic brain lesions, the neuroanatomical location of inflammatory cells and the long-term effects on neural systems affected by HSV-1 remain unknown. However, a recent study by Armien et al. has shown that the predominant macrophage/neutrophil infiltration in the acute stage evolved into a largely lymphocytic infiltrate in the subacute stage and was sustained over a month (21). Interestingly, the appearance of plasma cells was a distinct feature observed only during the chronic phase of the infection. The presence of activated microglia was also shown to be sustained in damaged areas during the chronic pha-

se of the infection. The role of cytokines in mediating the long-term neurological damage observed during HSV-1 encephalitis is currently unknown.

In light of this information, we aimed to emphasize that HSV infection should be kept in mind in the etiology of even atypical brain lesions. The resolution of imaging findings can occur later than the clinical improvement, with persistent contrast enhancement.

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