CASE REPORT

Post Herpetic Anti-NMDA- Receptor Encephalitis in an 18-month-old Infant

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Hossein ESLAMIYEH MD[1]

Reihane RANJBAR JAMALABADI MD[1]

Mohsen ASKARBIOKI MD[2]

1. Department of Pediatrics, Shahid Sadoughi University of Medical Science, Yazd, Iran

2. Nuclear Science and Technology Research Institute, Atomic Energy Organization, Tehran, Iran

Corresponding Author

Ranjbar Jamalabadi R. MD
Department of Pediatrics, Shahid Sadoughi University of Medical Science, Yazd, Iran

Email: Ranjbar3414@gmail.com

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Abstract

Herpes simplex encephalitis (HSE), caused by herpes simplex virus type 1 (HSV-1), is the most common cause of severe sporadic encephalitis worldwide.

HSE is occasionally accompanied by the recurrence of clinical symptoms that usually occur a few weeks following the initial infection. According to recent studies, the recurrence can be due to a secondary autoimmune mechanism rather than the virus invasion. One of the most common etiologies for autoimmunity is Anti-N-Methyl-D-Aspartate receptor encephalitis. This disorder is a treatable autoimmune encephalitis manifesting as movement disorder or neuropsychological involvement.

Case presentation

The article pertains to the presentation of an 18-month-old infant with a primary diagnosis of herpetic encephalitis who was re-admitted to the hospital shortly after discharge with restlessness, speech disorder, and abnormal movements. The movements were predominantly choreiform and disappeared during sleep. Brain MRI revealed abnormal predominance in the left temporoparietal regions with encephalomalacic changes in some areas in favor of sequella of previous encephalitis in addition to recent right temporal involvement of sequella of previous encephalitis. The polymerase chain reaction test of cerebrospinal fluid for herpes simplex infection was negative. Therefore, the possibility of autoimmune encephalitis was raised. More laboratory examinations revealed that the Anti-N-Methyl-D-Aspartate receptor antibody level was significantly elevated in cerebrospinal fluid. Thus, the diagnosis of Anti-N-Methyl-D-Aspartate receptor encephalitis was established.

Conclusion

Relapsing symptoms after herpes simplex virus encephalitis, especially with movement disorders, should raise a high clinical suspicion of Anti-N-Methyl-D-Aspartate receptor encephalitis in children. Therefore, clinicians should be cautious of its occurrence in infants; despite its rarity in that age group.

Keywords: Anti-N-Methyl-D-Aspartate Receptor Encephalitis; Infant; Herpetic Encephalitis

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Introduction

Herpes simplex encephalitis (HSE) caused by herpes simplex virus type 1 (HSV-1) is the most common cause of severe sporadic encephalitis worldwide (1, 2). HSV-1 is more prevalent in children and adults, while HSV-2 is more common in infants (3).

HSE is an acute or subacute disease that causes focal and generalized neurological disorders (4). In addition, it is one of the neurological emergencies associated with high morbidity and mortality (5).

Early symptoms in children and adults include fever, headache, vomiting, seizures, confusion, loss of consciousness, and focal neurologic signs (3, 6-8).

HSE-induced complications can exacerbate the conditions in children (9). It is occasionally complicated by the recurrence of clinical symptoms that usually occur a few weeks after the initial infection and sometimes during the initial treatment. The recurrence is assumed to happen due to a secondary immune mechanism rather than the virus. According to recent studies, the Anti-N-Methyl-D-Aspartate receptor encephalitis is the most prevalent autoimmunity associated with these recurrences (10).

Case presentation

An 18-month-old boy was referred to our center for the first time because of fever, lethargy, repeated seizures, and vomiting since two days ago. During hospitalization, he experienced three focal clonic seizures affecting the right side of his body with orofacial automatism. Seizures were ultimately controlled with phenytoin, phenobarbital, and levetiracetam, followed by clonazepam.

The infant had no nuchal rigidity on physical examinations with negative Kernig and Brudzinski's signs. No sign of organomegaly was detected either. On neurological examinations, cranial nerves were intact. His muscle tone and deep tendon reflexes were slightly decreased, but the Babinski sign was seen in his right foot.

He was the first child of non-consanguineous parents born through Cesarean –section. He had no history of asphyxia at birth and no history of previous seizures or medication consumption. He had normal development before starting the disease.

Due to fever, loss of consciousness, and seizures, Electroencephalography (EEG) and brain Magnetic Resonance Imaging (MRI) were requested. MRI revealed diffuse involvement of the left fronto-parieto-temporal regions and the left thalamus.

EEG showed periodic lateralized epileptiform discharges (PLEDs) in the left hemisphere (Figure 1).

A lumbar puncture was requested to rule out herpetic encephalitis, which indicated red blood cell=1000 / mm^3 and white blood cell=100 / mm^3 (60% neutrophils and 40% lymphocytes). Glucose and protein levels were in the normal range. Cerebrospinal fluid PCR for herpes simplex virus was also requested. According to imaging and CSF findings, the patient's treatment started with ceftriaxone and acyclovir, with a presumptive diagnosis of herpetic encephalitis. After three days, HSV -PCR of CSF showed a positive result for HSV 1, and treatment was continued with acyclovir.

During hospitalization, the patient regained consciousness, his fever recessed, and the seizures did not recur. After a twenty-one-day course of acyclovir, the patient was discharged while phenytoin, phenobarbital, and clonazepam were prescribed for him.

One week after being discharged, the patient returned with restlessness, speech difficulties, and choreic movement, especially in the upper extremities. For better evaluation, he was re-admitted, and brain imaging was performed. A brain MRI revealed abnormal high signals in his left fronto-parieto-temporal regions with encephalomalacic changes due to sequella of previous infection and recent right temporal involvement

No leukocytosis was reported in his initial tests. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were normal. Organic acids in blood and urine samples and serum ammonia and lactate levels were tested for metabolic disorders; all were in the normal range. CSF- PCR for herpes simplex was requested again to rule out relapsing herpetic encephalitis, and its result was negative. The history and extrapyramidal signs, including choreic movements, raised the possibility of autoimmune encephalitis. Therefore, serum and CSF were analyzed for autoimmune disorders. The Anti-N-Methyl-D-Aspartate receptor antibody test was positive in the autoimmune panel investigation in CSF, and the diagnosis of Anti-N-Methyl-D-Aspartate receptor autoimmune encephalitis was confirmed. The patient was treated with five-day methylprednisolone pulse therapy, followed by intravenous immunoglobulin (IVIG) for three days and aripiprazole. After three months, the patient's speaking, behavior, and restlessness improved, and his choreic movement resolved.

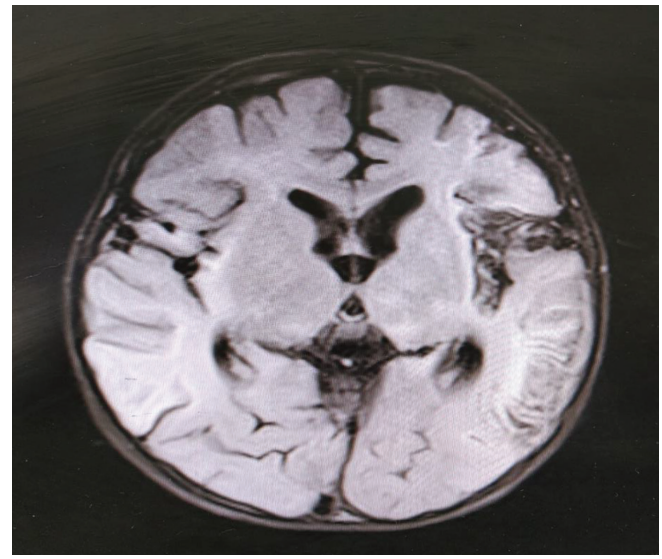

Figure 1. *Fluid attenuated inversion recovery (FLAIR) sequence showed high intensity signals in right fronto-parieto-temporal and left temporal regions and encephalomalic changes in right side.*

Discussion

Herpes simplex encephalitis is the most common worldwide cause of severe sporadic encephalitis (1,2). It is a neurological emergency associated with high morbidity and mortality (5).

Some patients have recurrent clinical symptoms a few weeks following the initial infection. In the

past, reinfection was thought to be a major cause of the recurrence of symptoms, although today, we know auto-immunity has a prominent role in relapse (11, 12). Autoimmune encephalitis and reinfection are two principal differential diagnoses in patients with relapsing symptoms.

According to recent studies, the Anti-N-Methyl-D-Aspartate receptor antibody is the main autoimmune component associated with these recurrences and the most common etiology of autoimmune-related encephalitis in children (10,11). The infection is assumed to trigger the immune system to produce antibodies to cross the blood-brain barrier and interact with the N-Methyl-D-Aspartate receptor. The critical point is that Anti-N-Methyl-D-Aspartate receptor encephalitis is a treatable autoimmune disease manifested as neuropsychological involvement in children (13).

Behavioral and movement disorders are often the first signs of autoimmune encephalitis in infants and are difficult to diagnose (10). In addition to mentioned symptoms, seizures and seizure-like episodes should be considered suspicious, and prompt and aggressive treatments should be initiated based on clinical symptoms before the CSF result is confirmed (8,11,12).

Epidemiological studies have shown the highest prevalence of HSE among young patients with a mean age of twenty-one. However, it can also occur in infants younger than two months and adults older than eighty-five (13). Autoimmune encephalitis can occur at any age. However, clinical symptoms can be different in children from those in adults. Symptoms are mainly described as neurological involvement, especially choreoathetoid movements in children such as our case, but it is more psychological in adults.

In Conclusion

Recurrence of symptoms after herpes simplex virus encephalitis, especially with a movement disorder, should raise high clinical suspicion for Anti-N-Methyl-D-Aspartate receptor encephalitis in children. Therefore, clinicians should be aware of this condition, which can occur at any age.

Considering that Anti NMDA receptor encephalitis is rare in infants such as our case, rapid diagnosis and initiation of treatment will result in a better prognosis and minimal neurological complications (5).

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Author's contribution

Definite diagnosis of the case and critical revision of the manuscript for important intellectual content: Hossein Eslamiyeh contributed to case management and writing the article, Reihane Ranjbar Jamalabadi studied related scientific texts and contributed to manuscript writing and Mohsen Askarbioki.

Conflict of Interest

The authors declare that there is no conflict of interest.

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