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Autoimmune post-herpes simplex encephalitis. A pediatric clinical case report

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ABSTRACT

Herpes simplex virus (HSV) encephalitis is a common cause of severe and potentially fatal encephalitis. Autoimmune post-herpes simplex encephalitis (AIPHSE) affects a percentage of patients who developed herpes simplex encephalitis (HSE) and is characterized by the onset of new neurological/psychiatric symptoms and/or worsening of deficits acquired during the herpes infection within a predictable time frame. It is caused by a mechanism not related to HSV, but by autoimmune conditions, and is susceptible to treatment with immunomodulators.

Here we describe the case of a 5-year-old boy with AIPHSE who required first- and second-line immunomodulatory treatment, with an adequate course and remission of symptoms.

Keywords: *herpes simplex; encephalitis; autoimmune disorders of the nervous system; N-methyl-D-aspartate receptor encephalitis; immunomodulators.*

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INTRODUCTION

Herpes simplex virus (HSV) encephalitis is a common cause of severe and potentially fatal encephalitis in pediatrics.[1] Despite a successful completion of antiviral therapy, up to 27% of patients with herpes simplex encephalitis (HSE) develop new neurological and/or psychiatric symptoms within 3 months of completing the therapy.[2,3] Initially interpreted as a relapse, most of these patients have immune-mediated encephalitis with antineuronal antibodies directed against the GluN1 subunit of the N-methyl-D-aspartate (NMDA) receptor[3,4] in the cerebrospinal fluid (CSF).

Here we describe the case of a boy diagnosed with AIPHSE due to anti-NMDA receptor antibodies.

CASE REPORT

This was a previously healthy 5-year-old boy who started with vomiting and fever 3 days before being referred to our hospital. Twenty-four hours later, he had a focal seizure on the right side of the body with subsequent generalization and progression to generalized convulsive status epilepticus, which was controlled with intravenous lorazepam. The CT of the brain was normal.

He was transferred to the intensive care unit of our hospital; upon admission, he had low-grade fever and somnolence, with no other positive findings on his physical examination.

His lumbar puncture showed clear, colorless CSF, CSF glucose levels: 88 mg/dL (43% of blood glucose levels), CSF protein levels: 22 mg/dL, lactate: 1.7 mg/dL, chloride: 115 mEq/L, cells: 105/mL (93% mononuclear, 7% polymorphonuclear). He received ceftriaxone 100 mg/kg/day and acyclovir 60 mg/kg/day.

He had repeated generalized tonic-clonic seizures, which were controlled with loading doses of diphenylhydantoin.

The electroencephalogram (EEG) showed a disorganized and diffusely slow basal pattern. The CT of the brain (10 days after the onset of his clinical condition) showed a left temporal cortico-subcortical hypodense area with edematous appearance, partial collapse of the anterior horn of the left ventricle, and slight midline deviation (*Figure 1*).

The virological test of the CSF by polymerase chain reaction (PCR) was positive for HSV type 1 and negative for enterovirus and adenovirus.

The MRI of the brain (13 days after onset) showed an extensive image of hyperintensity in the left frontal-temporal-occipital-insular cortico-subcortical area (with involvement of the limbic system in T2 and FLAIR sequences), hyperintensity in the left perithalamic insular cortex and right perisylvian area, and facilitation in diffusion sequence, compatible with encephalitis.

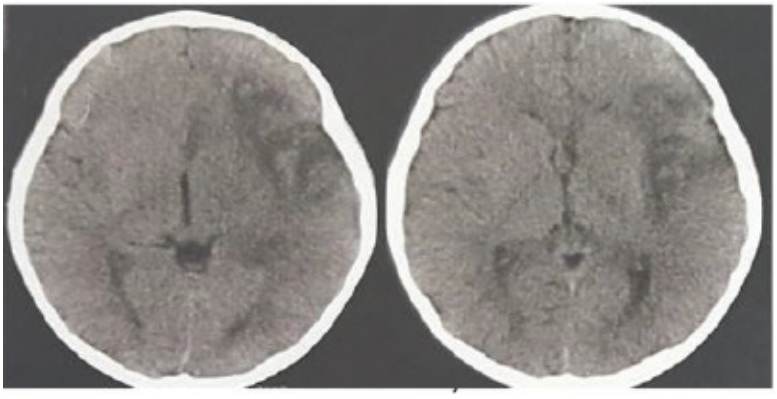
He was diagnosed with HSE and received acyclovir for 21 days.

During the course of his disease, he had new focal seizures which affected his consciousness, so treatment with levetiracetam was started.

At discharge, after 26 days of hospitalization, the patient presented expressive language disorder and right hemiparesis, and required assistance to walk.

He was readmitted 4 days later due to somnolence, swallowing disorder, and abnormal movements (orolingual dyskinesia and segmental

Figure 1. Computed tomography of the brain



Signs of diffuse cerebral edema. Area of left temporal and frontobasal cortico-subcortical hypodensity.

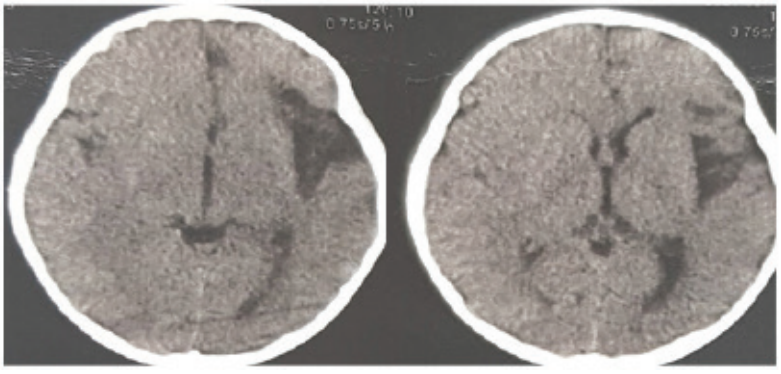
choreoathetosis) which persisted while he was awake, in addition to his previous neurological condition.

A new CT showed left temporal and frontobasal sequelae hypodensity and a new right frontobasal edematous area (*Figure 2*).

The video-EEG showed a severe disorganized basal pattern, left fronto-temporal spikes, and abnormal movements (chorea and dyskinesia) while awake, without electroencephalographic correlation.

AIPHSE was suspected, so a new lumbar puncture was performed, which showed a clear, colorless CSF, normal CSF glucose levels and CSF protein levels: 66 mg/dL, 5 cells/mm^3. CSF was negative for HSV, enterovirus, herpes 6,

Figure 2. Computed tomography of the brain



Left temporal and frontobasal hypodense sequelae area. New right frontobasal edematous area.

varicella-zoster (by PCR), and anti-AMPA-R1, AMPA-R2, CASPR2, LGI1, GABA-R antibodies by cell-based assay (CBA). CSF was positive for anti-NMDA receptor antibodies (CBA). The test for serum anti-MOG antibodies was negative (CBA).

The MRI of the brain (5 days after rehospitalization) showed hyperintensity in the left cortico-subcortical frontal-parietal-temporal-insular regions (with areas of encephalomalacia) and right frontal-temporal-insular regions of the T2 and FLAIR sequences. Gyriform enhancement was observed in the left hemisphere (*Figure 3*).

He received intravenous gamma globulin 2 g/kg, distributed over 2 consecutive days, on 2 occasions, and methylprednisolone 30 mg/kg/day for 3 days, with slight improvement of the level of consciousness and a decrease of abnormal movements. He also received 4 doses of rituximab 375 mg/m^2 weekly, with recovery of the level of consciousness, remission of abnormal movements, and progressive restoration of his clinical condition to the deficits prior to the immune-mediated process.

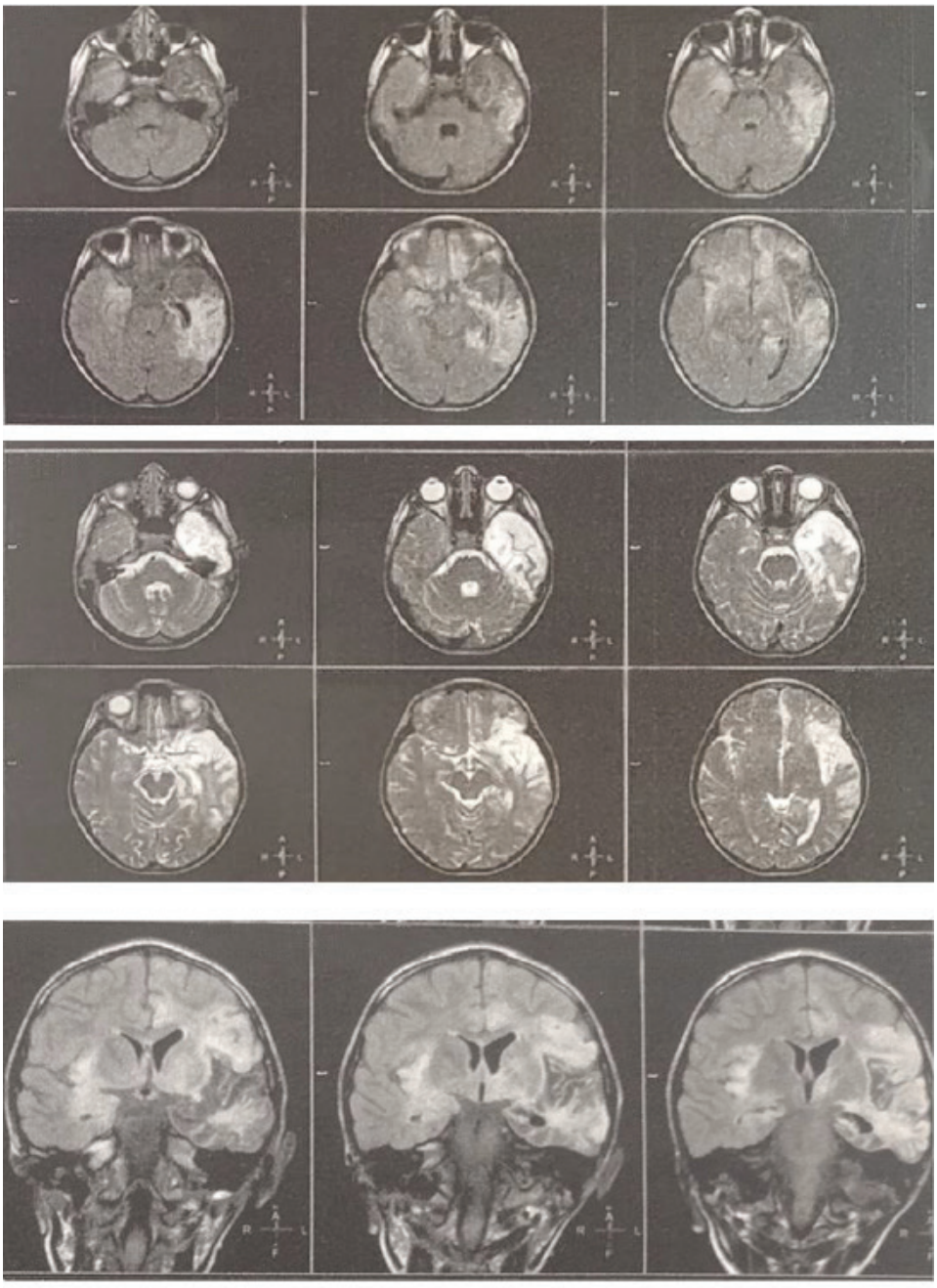
DISCUSSION

The course of HSE is usually monophasic and has a bimodal age presentation, and most frequently affects the pediatric and elderly populations.[1] In recent decades, reports have been made of patients who, having completed antiviral therapy, developed new neurological/psychiatric symptoms[2–5] within 3 months of completing the treatment.[2,3,5–9] Initially interpreted as a relapse,[2–5] the negative CSF test for HSV and the lack of response to antiviral therapy suggested other pathogenic mechanisms.[3–5,7,8]

The presence of antibodies against the GluN1 subunit of the NMDA receptor in the CSF, typical of anti-NMDA receptor encephalitis, raised the possibility of an autoimmune mechanism responsible for the clinical manifestations observed.[3–8]

The NMDA receptor is a neuronal membrane receptor with roles in synaptic transmission and neural plasticity.[8,10] The processes underlying the synthesis of anti-NMDA receptor antibodies are unknown. The proposed mechanisms suggest that HSV infection would determine, by direct cell destruction, the exposure of neuronal antigens

Figure 3. Magnetic resonance imaging of the brain



Axial and coronal sections showing hyperintensity in T2 and FLAIR sequences of left cortico-subcortical frontal-parietal-temporal-insular areas and right temporal-insular and frontobasal areas.

to the systemic immune system.[6,8,9] Other possibilities involve non-specific B-cell activation and molecular mimicry by epitopes shared by HSV and the NMDA receptor.[6,8,9] The role of predisposing genetic factors is still unknown, although in some cases it could be related to deficiencies in innate immunity mediated by the Toll-like receptor 3 (TLR3).[11]

The presence of anti-NMDA receptor antibodies[3,8,9,12,13] alters its expression on the surface of the neuronal membrane and affects the function of other synaptic proteins.[6]

Typically, patients with AIPHSE caused by anti-NMDA receptor antibodies have completed

antiviral therapy, have a negative PCR for HSV in CSF, and symptoms cannot be explained by other complications (e.g., internal *milleu* disturbance, drug toxicity, or stroke) or by residual deficits caused by the HSV infection (e.g., epilepsy).[9]

It may affect patients of any age and involves 10–27% of patients with HSE.[3,5,7–9] Symptoms are usually subacute and occur over days or weeks, with an average time interval between HSV infection and the onset of the first symptoms of 32 days (range: 7–61 days).[8,9] In children under 4 years of age, the time interval described by Armangue et al., was shorter (mean: 26 days, range: 24–32 days) than in those older than 4 years of age (mean: 43 days, range: 25–54 days).[9]

The clinical manifestations in children often differ from those in adolescents and adults. In younger children (under 4 years of age), abnormal movements (most frequently choreoathetosis and orofacial dyskinesia), seizures, and alterations in the level of consciousness predominate.[3,4,8,9,12] In adolescents and adults, behavioral changes, psychiatric alterations (psychosis), and cognitive deficits are the most frequent manifestations, in some cases accompanied by seizures.[3,5,8,9]

The CSF test is negative for HSV 1 and 2 in all cases, and may show mild pleocytosis and high CSF protein levels.[3,8,9]

The MRI images show contrast-enhanced areas, suggesting a breakdown of the blood-brain barrier, which would allow complement and proinflammatory molecules,[13] comparable to those found during viral encephalitis, to enter the central compartment. In the follow-up MRI performed 4 months later, patients with AIPHSE had a higher frequency of necrosis with cystic lesions.[9]

The prognosis is substantially worse than that described in forms of anti-NMDA receptor encephalitis that do not follow a herpes simplex infection, possibly due to the presence of clinical or subclinical deficits related to the preceding viral infection[9] in addition to other mechanisms, such as complement-mediated or T-cell-mediated cytotoxicity, which do not seem to play a relevant role in classical immune-mediated encephalitis and could be more relevant in cases of AIPHSE. Further studies are still required.[9]

An early and timely recognition of this complication is critical for the adequate and early treatment of AIPHSE with immunomodulators,[8,9] which are effective in reducing immune-mediated deficits and improving the patients' quality of life.[9,14,15] The management of immunotherapy in AIPHSE is similar to that of anti-NMDA receptor encephalitis that does not follow a herpes simplex infection.[15] First-line immunomodulation includes corticosteroids, gamma globulin, or plasmapheresis; while second-line immunomodulation includes rituximab and cyclophosphamide, among others.[12,14,15]

The current evidence suggests that, in patients who have had HSE, it is necessary to maintain a high level of suspicion for a manageable immune-mediated complication, such as AIPHSE due to anti-NMDA receptor antibodies, at the onset of new symptoms.[15] ■

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