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Case Report

Clinical Case of Anti-*N*-methyl-D-aspartate Receptor Encephalitis in an 8-Month-Old Patient With Hyperkinetic Movement Disorder

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ABSTRACT

This article describes an 8-month-old boy with the full clinical spectrum anti-*N*-methyl-D-aspartate receptor encephalitis. He was admitted to the hospital with involuntary orofacial head movements, behavioral changes, and fluctuation in consciousness. His examination showed tongue thrusting, decreased responsiveness, and hypotonia without fever. Analysis of the cerebrospinal fluid revealed increased protein levels (62 mg/dL). The next day he developed oral dyskinesia and choreoathetosis. Video-electroencephalogram polygraphy showed coreo-dystonic movements without electrographic correlation. A putative diagnosis of autoimmune encephalopathy was made, and treatment with intravenous immunoglobulin and methylprednisolone was started, with improvement in the abnormal movements. Antibodies to the *N*-methyl-D-aspartate receptor were identified in the cerebrospinal fluid and blood. He began receiving immunoglobulin once a month for a year. Two months after the treatment had started, the involuntary movement disappeared and his development has been normal. *N*-methyl-D-aspartate receptor encephalitis is a recently identified disorder. This is the youngest case reported. Prompt diagnosis and treatment are important to obtain full recovery.

Introduction

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis was first described in 2007 by Dalmau et al. [1]. Many of the individuals described in the literature are young women with an associated ovarian teratoma, but anti-NMDAR encephalitis is now being described more frequently in children. Despite this, paraneoplastic cases are less common in children than in adults. The differential diagnosis of acute or subacute encephalitis in children includes viral encephalitis. But anti-NMDAR encephalitis is a potentially reversible immune-mediated disorder, and because of that, early diagnosis is essential [2].

Here we report an 8-month-old boy with the clinical spectrum anti-NMDAR encephalitis (agitation, stupor, dysphagia, and relentless choreoathetoid movements).

Case Report

An 8-month-old boy was brought to the emergency room for evaluation of abnormal movements. Symptoms included abnormal head movements with rhythmic tongue thrusting, behavioral changes, fluctuation in consciousness, and hypotonia. Ten days before being admitted to the hospital, he had developed a self-limiting illness with fever, emesis, and diarrhea for 3 days, and the day before being admitted he had a fever of 39°C. At admission, the patient was not feverish, and the vital constants were normal. During 1 minute, the physical examination revealed a cluster of five short episodes of gaze, unconscious, and rhythmic tongue thrusting, similar to seizures. Cranial computerized tomography showed a chronic lesion in the left middle artery distribution. Complete blood count showed a white cell count of 3.480×10^3/uL (normal value 4.5 to 10×10^3/uL), and blood chemistry, C-reactive protein, and procalcitonin were normal. Cerebrospinal fluid evaluations yielded 4/mm^3 leukocytes, high protein level (62 mg/dL), with normal

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glucose (58 mg/dL) and lactate (17.9 md/dL). In the emergency room, he received treatment with acyclovir and phenytoin.

In the next few days, the patient quickly deteriorated, exhibiting orofacial dyskinesias and choreoathetoid movements, particularly in the upper extremities, no eye contact, and hypotonia. A nasogastric tube was required due to impaired oropharyngeal coordination. He did not have a fever or breathing problems. Magnetic resonance of the brain, including fluid-attenuated inversion recovery imaging and magnetic resonance spectroscopy, showed a pre- or perinatal hypoxic-ischemic injury in the left temporal lobe, with deposits of hemosiderin and gliosis. Video electroencephalography showed no electrographic correlation with involuntary movements, which persisted during wakefulness but not during sleep. Autoimmune and hypercoagulation biomarkers studies and investigations for inborn errors of metabolism were normal. Bacterial cultures from blood, urine, and cerebrospinal fluid samples were negative. Blood and cerebrospinal fluid polymerase chain reactions for DNA of adenovirus, cytomegalovirus, Epstein-Barr virus, human herpes virus-6, herpes simplex virus-1 and -2, parvovirus B19, and mycoplasma pneumonia were normal. Analysis of cerebrospinal fluid and blood obtained at admission revealed, approximately 10 days after he was hospitalized, antibodies compatible with anti-NMDAR specificity. Before this last result, administration of piracetam, tetrabenazine, levetiracetam, and valproic acid had minimal effect on his movement disorder.

Three days after his admission, with the presumptive diagnosis of autoimmune encephalopathy, he was given intravenous immunoglobulin (400 mg/kg for 5 days) with pulse methylprednisolone (30 mg/kg/day) for 5 days. Oral prednisone (1.5 mg/kg/day) therapy was started after methylprednisolone administration ended and lasted for 6 weeks. After the antibody anti-NMDAR was identified, a second intravenous immunoglobulin cycle was started 15 days after the end of the first one. To rule out the presence of an undiagnosed tumor, abdominal, testicular, and pelvic ultrasonography was performed and the results were negative. There was an improvement in the patient's condition with the second cycle of intravenous immunoglobulin. He recovered motor functions and started to eat by mouth.

One month later, he had no involuntary movement. He was in the hospital for 22 days and finished treatment with prednisone and tetrabenazine. He has been receiving intravenous immunoglobulin once a month for 1 year. At the last clinical evaluation, 20 months after the onset, he was stable without treatment and his development was normal, but he was on speech therapy for apraxia.

Discussion

The clinical symptoms presented in this 8-month-old patient were suggestive of anti-NMDAR encephalitis. We believe that this case is different from those previously described in the literature because, to our knowledge, this is the youngest patient with anti-NMDAR encephalitis yet described. Twenty-five percent to 40% of patients with anti-NMDAR encephalitis are younger than 18 years old [2]. The youngest patient described so far was 20 months old [3].

The pathogenesis of this disease is not clear, and different possibilities have been suggested. Some authors suggest that a tumor or a viral infection triggers the immunological response [4-7]. Anti-NMDAR produces a decrease of glutamate receptor NMDA with less γ-amino-butyric acid and excess glutamate in prefrontal and subcortical areas. This produces psychosis and dyskinesias similar to schizophrenia [7-9].

This disease in children is slightly different from that in adults [4]. It is more common as a viral-like syndrome (fever, headache, cough) [8], and the first symptoms are neuropsychiatric symptoms (changes in behavior, tantrums, restlessness, and aggressiveness) [4]. Seizures and abnormal movements such as dyskinesias, chorea, dystonic episodes, or catatonia [10] are the first symptoms. After that, language deterioration, encephalopathy, autonomic instability, and hypoventilation are observed; these are less frequent in children [4]. Somnolence is a common early symptom, but insomnia appears later [2,9].

The cerebrospinal fluid may reveal lymphocytic pleocytosis and increased protein concentration in the beginning, and a presence of oligoclonal bands are revealed later during the course of the disease [9,11,12]. The electroencephalogram analysis reveals epileptiform activity [13], and later, theta or delta activity is observed. The magnetic resonance cranial is normal in 50% of the cases, in the rest there is nonspecific hyperintensity in T2 or fluid-attenuated inversion recovery imaging of cortical or subcortical areas [12]. Anti-NMDAR can be diagnosed by a blood or cerebrospinal fluid test. The study of anti-NMDA in cerebrospinal fluid, at different time points, can be useful to monitor the treatment [12]. It is important to look for a teratoma of the ovary or germ cell tumor of the testis.

Seventy-five percent of patients make a substantial recovery. This disease has a mortality rate of about 4% and relapse may occur in 20-25% [4,7,11]. The optimal treatment for this condition, after the removal of the tumor, is immunotherapy. Early treatment decreases the number of antibodies, which means a better prognosis and fewer relapses [11]. There is no established protocol for the management of anti-NMDAR encephalitis. First-line options are corticoids or immunoglobulin [5,9]. A second step includes an aggressive regimen with plasma exchange, cyclophosphamide, azathioprine, and rituximab [2,3,14-16].

The present case highlights the importance of including this autoimmune disease as a differential diagnosis in children with unexplained encephalopathies associated with movement disorders, regardless of whether the patient is a young child or baby. Early immunomodulatory therapy should be considered in such cases, as it may improve recovery.

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