Anti-*N*-methyl-D-Aspartate-Receptor Encephalitis in a Four-Year-Old Girl

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Anti-*N*-methyl-D-aspartate-receptor encephalitis is a recently identified autoimmune disorder. We report on a 4-year-old girl presenting with seizures after nonspecific viral-like symptoms, progressing to severe aphasia, upper limb dyskinesias, fluctuation in consciousness, and inability to walk. Anti-*N*-methyl-D-aspartate-receptor encephalitis should be included in the differential diagnosis of acute/subacute encephalitis in children. *(J Pediatr 2010;156:332-4)*

Anti-*N*-methyl-D-aspartate-receptor (*N*MDAR) encephalitis is a recently identified disorder associated with antibodies against NR1-NR2 heteromers of the *N*MDAR resulting in a characteristic neuropsychiatric syndrome.[1,2] It was first described in female patients with ovarian teratoma but recently has been reported also in patients with non-paraneoplastic disorders.[2] Here, we report the first detailed clinical report of a 4-year-old girl with anti-*N*MDAR encephalitis without a detectable tumor.

Case Report

A 4-year-old girl was brought to the emergency department with a generalized seizure starting with clonic right arm movements. Four days before this a self-limiting illness developed with fever and cough. The patient was completely normal after diazepam administration. The result of the computed tomography scan was normal, but electroencephalography (EEG) showed left hemispheric slow spike and waves. One week later complex partial seizures developed, characterized by staring, mouth movements, and automatisms. Despite valproic acid therapy, the patient's neurologic condition worsened over the following days. She had development of an expressive dysphasia, upper limb dyskinesias, and fluctuation in consciousness; she also lost the ability to walk.

Thyroid-stimulating hormone, fT3, fT4, antithyroglobulin and anti-thyroid peroxidase antibodies, and urine organic acid values were normal. Serum immunoglobulin M for human herpes virus 6, adenovirus, rubella, measles, mumps, herpes virus 1-2, chickenpox, cytomegalovirus, Epstein Barr virus, Borrelia, and parvovirus B19 were negative. Blood and cerebrospinal fluid (CSF) 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 pneumoniae* were negative. Unmatched oligoclonal bands were present in CSF. Voltage-gated potassium channel and anti-glutamic acid decarboxylase antibodies were negative.

The EEG showed very slow background activity and high-voltage slow and sharp waves. The brain and spinal cord magnetic resonance imaging (MRI), 10 days after presentation, showed a small gadolinium-nonenhancing hyperintense area on T_2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences (**Figure**). The results of 2 additional magnetic resonance imaging examinations performed 1 and 2 months after presentation were unchanged.

With the presumptive diagnosis of autoimmune encephalopathy, intravenous immunoglobulin (IVIG; 400 mg/kg for 5 days) was administered 5 days after symptom onset, and oral prednisone (1.5 mg/kg/d) was started soon after the end of the first IVIG cycle. A second IVIG cycle was started 1 month after the end of the first one. The patient was soon able to walk without support, although cognitive impairment and aphasia persisted. EEG was essentially unchanged.

To rule out the presence of an occult tumor, abdominal and pelvic ultrasonography, whole body MRI, and guanidine scintigraphy were performed, and the results were normal. *N*MDAR antibodies were found to be positive in serum and CSF by binding to *N*MDAR-transfected cells.

In the subsequent 6 weeks, the patient had development of orofacial dyskinesias (jaw-opening dystonia and grimacing) and episodes of autonomic instability (labile blood pressure, bradycardia/tachycardia, and diaphoresis). Despite this, she was progressively able to walk but continued to have aphasia and was cognitively impaired. She demonstrated inability to concentrate and complete simple tasks, limited interest in social interaction, difficulty in verbal comprehension, purposeless and perseverative behaviors, with visual hallucinations and mood changes (**Video**; available at www.jpeds.com).

CSF	Cerebrospinal fluid
EEG	Electroencephalography
FLAIR	Fluid-attenuated inversion recovery
IVIG	Intravenous immunoglobulin
MRI	Magnetic resonance imaging
*N*MDAR	*N*-methyl-D-aspartate-receptor

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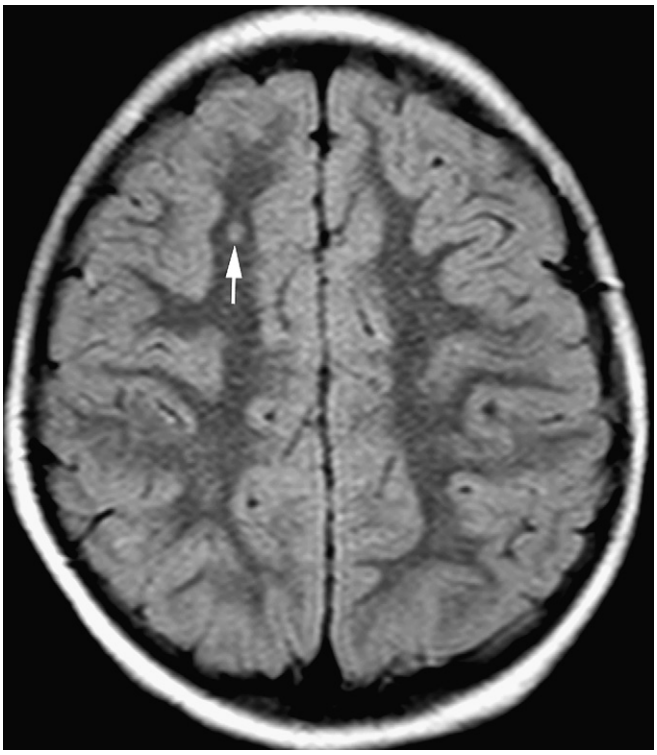

Figure. Brain MRI: axial FLAIR MRI shows small hyperintense area in the subcortical white matter of the right frontal lobe *(arrow)*.

Three months after the onset of symptoms, she was able to walk and pronounce many words and sentences, although she still appeared confused and perseverative. At the last clinical evaluation, 5 months after the onset, her social interaction and behavior further improved.

Discussion

This patient with *N*MDAR encephalitis has no evidence of an ovarian tumor and has made a relatively good recovery after immunotherapy. Anti-*N*MDAR encephalitis is a recently-described autoimmune encephalitis associated with antibodies that bind to the *N*MDAR. The characteristic clinical picture in adulthood is a neuropsychiatric syndrome including confusion, paranoid or delusional thoughts, seizures, episodes of autonomic instability, and orofacial-limb dyskinesias. Brain MRI may show areas of increased signal on FLAIR or T_2 sequences involving the medial temporal lobes, corpus callosum, and brainstem, but often the result of MRI is normal. EEG usually reveals diffuse delta activity, often without paroxysmal discharges. The CSF may reveal lymphocytic pleocytosis, increased protein concentration, and presence of oligoclonal bands, suggesting that the immune response is taking place partly within the central nervous system compartment. *N*MDAR antibodies can be found in both serum and CSF, or in the CSF only, depending on the techniques used. In primary cultures of hippocampal neurons, Dalmau et al[2] showed that patients' CSF immunoglobulin G produces a selective and reversible decrease of *N*MDAR clusters, suggesting that the antibodies are pathogenic.

The clinical constellation in this 4-year-old child was consistent with the description of anti-*N*MDAR encephalitis, with seizures, episodes of autonomic instability and orofacial-limb dyskinesias. In addition, she showed cognitive impairment, with severe aphasia, purposeless and perseverative behaviors, limited social interaction, and inability to walk in the acute stage, with a slow recovery during follow-up. Despite the striking clinical picture, it is important in children to exclude bacterial or viral infection of the central nervous system or acute disseminated encephalomyelitis[3,4]; we also excluded Hashimoto encephalopathy[5] and subacute encephalopathy related to voltage-gated potassium channel antibodies.[6]

*N*MDAR are ligand-gated cation channels with crucial roles in synaptic transmission and plasticity. Overactivity of *N*MDAR is a proposed underlying mechanism for epilepsy and dementia and may contribute to the neurodegeneration in stroke, whereas reduced activity produces symptoms of schizophrenia.[2] Treatment for anti-*N*MDAR encephalitis, as in other antibody-mediated disorders, includes consideration of corticosteroids, intravenous immunoglobulins, plasma exchange, cyclophosphamide, azathioprine, and rituximab,[1,2] with 75% of patients making a substantial recovery, and only 25% dying or have sequelae of severe deficits.[2]

Our patient appears to have a non-paraneoplastic form of anti-*N*MDAR encephalitis, preceded by a nonspecific viral illness. A high incidence of prodromal viral-like symptoms has been described,[2,7] but it is not clear whether these form part of an early immune activation or result from a nonspecific infection that facilitates crossing of the blood-brain barrier by the immune molecules.[8]

The differential diagnosis of acute/subacute encephalitis in children should include this novel and potentially reversible immune-mediated disorder, and further studies are needed to define the range of clinical presentations in children, especially because the evaluation of psychiatric symptoms may be challenging in the pediatric population. ■

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50 Years Ago in THE JOURNAL OF PEDIATRICS

Recent Experience in the Treatment of Diarrhea in Infants

Darrow DC, Welsh JS. J Pediatr 1960;56:204-10

One of the greatest opportunities of the pediatrician is to save the life of a baby with dehydration. A step back into history allows *The Journal of Pediatrics* to honor the man for whom an early intravenous rehydration solution was named: Daniel C. Darrow. Darrow carefully recorded the electrolyte and water balances of infants with diarrhea while working at Johns Hopkins in the 1940s. By 1960, one may imagine him rounding at the Children's Mercy Hospital in Kansas City, with scores of crying, dehydrated, and/or malnourished babies housed in a large room, purging on cloth diapers, slowly advancing dilute feedings. None would have the advantage of a central line, parenteral nutrition, nasogastric tube, or amino acid formula.

This case series (n = 307 with dehydration in a 2-year period) describes a large number of infants with electrolyte abnormalities (n = 105). The authors recorded the percentage of infants with hypernatremia (>160 mEq/L), 10%; hypokalemia (>3 mEq/L), 5%; and acidosis (HCO_3 < 15), 50%. Darrow and Welsh also emphasized risk factors for hypernatremia including oral Na^+ supplementation and the use of evaporated milk. They pointed out that cerebral complications, specifically convulsions, associated with hypernatremia seldom developed unless the initial Na^+ concentration was >150 mEq/L with a rapid decline in level.

The modern reader may almost overlook the composition of oral Lytren. At that time, Lytren replaced Na^+, K^+, and Cl^-, without providing any glucose to couple with Na^+ entry across the brush border. This oral rehydration solution (ORS) would have been a much poorer therapy than the glucose-ORS formulated during the next decade. The new ORS contained closely-matched Na^+: glucose ratios, on the basis of human perfusion studies in the late 1960s performed in East Pakistan (Bangladesh) and reported by Nalin et al and Pierce et al.[1,2] Also, the new solution, unlike Lytren, contained bicarbonate, just as modern ORS contains citrate, to reverse metabolic acidosis.

Length of stay was much different in those days: the authors boast that 69 of 105 infants were discharged at 2 weeks! Senior pediatricians often remark that in 2009, the entity protracted diarrhea of infancy is much less prevalent than it was in the 1960s. Interestingly, Darrow and Welsh describe what may be one of the earliest observations that a casein hydrolysate rescued an infant that could not tolerate refeeding of cow's milk formula after rehydration.

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