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Clinical Observations

Anti–*N*-methyl-D-aspartate Receptor-Mediated Encephalitis in Infants and Toddlers: Case Report and Review of the Literature

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ABSTRACT

BACKGROUND: Anti-*N*-methyl-D-aspartate receptor encephalitis is an increasingly well-recognized inflammatory encephalitis in children and adults. **PATIENT:** We report a previously healthy 21-month-old girl who presented with behavioral change, self-mutilatory behavior, and echolalia. Over the ensuing weeks, symptoms progressed to include unilateral upper extremity dystonia, gait impairment, dysphagia, and mutism. Magnetic resonance imaging of the brain showed a tiny area of signal abnormality in the subcortical white matter, but was otherwise normal. Continuous video electroencephalography showed slowing of the background rhythm, but was without epileptiform discharges. Lumbar puncture showed a mild pleocytosis of mixed cellularity; bacterial culture and testing for various viral encephalitides were negative. Serum and cerebrospinal fluid was positive for autoantibodies directed against the *N*-methyl-D-aspartate receptor, and she was diagnosed with anti–*N*-methyl-D-aspartate receptor encephalitis. The patient was successfully treated with a regimen of immunotherapy that included dexamethasone, intravenous immunoglobulin, and rituximab. One year after initial presentation, the patient remained symptom-free. We further review the clinical characteristics, results of diagnostic studies, treatment, and outcome of infants and toddlers diagnosed with anti–*N*-methyl-D-aspartate receptor encephalitis that have been previously reported in the literature. **CONCLUSION:** Anti–*N*-methyl-D-aspartate receptor encephalitis is relatively common among infants and toddlers and often presents with a pattern of defining characteristics in this age group, particularly the absence of associated tumor.

Keywords: anti-NMDA receptor encephalitis, NMDA receptor, encephalitis, pediatric

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Introduction

Encephalitis mediated by autoantibodies directed against the *N*-methyl-D-aspartate receptor (anti-NMDA receptor encephalitis) is a now well-described clinical entity in children and adults[1-4] and constitutes one of the most common causes of encephalitis in children.[5] The syndrome is notable both for its often dramatic clinical presentation and for its typically favorable response to therapy. The syndrome of anti-NMDA receptor encephalitis includes some combination of neuropsychiatric symptoms, movement disorder, seizures, and/or autonomic dysfunction or vital sign instability, potentially progressing to coma and, in rare cases, death.[2-4] In children, symptoms of abnormal behavior, speech disturbance, seizures (including status epilepticus[6]), and movement disorder seem to predominate.[1,7]

Approximately 40% of all reported patients with anti-NMDA receptor encephalitis are children (i.e., age <18 years);[4] a recent study compiling more than 577

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patients with anti-NMDA receptor encephalitis found that 37% of them occurred in the pediatric age group.[7] However, few infants (<12 months) and toddlers (≥12 months and <36 month) had been reported previously.[2,3,8-10]

We describe a 21-month-old girl with anti-NMDA receptor encephalitis treated with first- and second-line immunotherapy who had recovered completely after a year. We also review the cases of anti-NMDA receptor encephalitis in infants and toddlers that have been published previously in the literature.

Case Report

The patient was a previously healthy, developmentally normal 21-month-old girl. She had received the 2011-2012 influenza vaccine, H1N1 vaccine, and immunization for hepatitis A approximately 2 weeks before presentation. Initial symptoms included unusual "temper tantrums," self-mutilatory behavior, and echolalia/echopraxia. She was evaluated by her primary care provider who began treatment for acute otitis media with amoxicillin.

Days later, she seemed to be using her left hand less than usual; she presented to an emergency room where she had what were described as choreiform movements of the left arm. She was admitted to the hospital. Results of a computed tomography scan of the head, lumbar puncture, magnetic resonance imaging (MRI) scan of the brain, and magnetic resonance angiogram of the head were read as normal. The patient was discharged home.

One month after initial presentation, she exhibited progressive speech disturbance, gait impairment, dysphagia, and weight loss. She was brought to a local tertiary care medical center. Repeat brain MRI showed a tiny area of T2/fluid attenuation inversion recovery hyperintensity in the subcortical white matter of the left superior frontal gyrus (Fig) deemed nonspecific in etiology. A repeat lumbar puncture was performed, and standard tests were sent, along with polymerase chain reaction (PCR) testing for herpes simplex virus and testing for antibodies to the NMDA receptor. Based on the combination of abnormal behavior, speech dysfunction, and dyskinesia, the clinical presentation was deemed suggestive of anti-NMDA receptor encephalitis. Presumptive treatment was initiated.

The patient was treated with intravenous immunoglobulin 400 mg/kg per day for 5 days followed by Solu-Medrol 30 mg/kg per day for 5 days. Cerebrospinal fluid (CSF) and serum was positive for autoantibodies to the NMDA receptor. The patient was transferred to our institution for subsequent management.

On initial examination by the authors, the child was awake with poor eye contact, minimal spontaneous vocalizations, and absent comprehensible speech. She exhibited orobuccal dyskinesias and choreoathetosis most prominently involving the left upper extremity. Strength was normal. There was decreased axial tone. Sensation was intact. Reflexes were 2+; toes were upgoing bilaterally. She was nonambulatory and exhibited mild dysmetria and titubation.

Reanalysis of CSF drawn at the referring institution revealed anti-NMDA receptor antibodies at a titer of 1:10. Repeat lumbar puncture (performed 2 weeks after the prior lumbar puncture) revealed a white blood cell count of 5 per high powered field, glucose of 56 mg/dL, and protein of 17 mg/dL; there were three CSF-specific oligoclonal bands; anti-NMDA receptor antibodies were now present at a titer of 1:100. Continuous video electroencephalography showed slowing of the background rhythm, but not epileptiform discharges. Neuroimaging performed during the second admission to the outside institution was reviewed by the authors and by a pediatric neuroradiologist at the authors' institution, confirming the initial interpretation. MRI of the chest, abdomen, and pelvis with and without gadolinium contrast enhancement was normal, with no evidence of ovarian neoplasm, although the left ovary was not clearly identified; this latter finding is common at this age because of the small size of the ovaries in girls younger than age 2.[11] Alfa-fetoprotein level was 2.61 ng/mL (normal range, 0.6-11.1); beta-human chorionic gonadotropin level was <1.0 mIU/mL (these markers can be elevated in cases of mature ovarian teratoma depending on the tissue elements present, although such testing is not a required component of the workup of anti-NMDA receptor encephalitis[12]). The patient was treated with rituximab 375 mg/m^2 per day weekly for 4 weeks, and monthly courses of intravenous immunoglobulin (1 g/kg body weight) and dexamethasone (10 mg/m^2 per dose twice daily for 3 days) were continued for 2 additional months to complete a 3-month total treatment course. The patient was transferred to acute inpatient rehabilitation after the first treatment and was discharged home after 3 weeks of inpatient rehabilitation in stable condition.

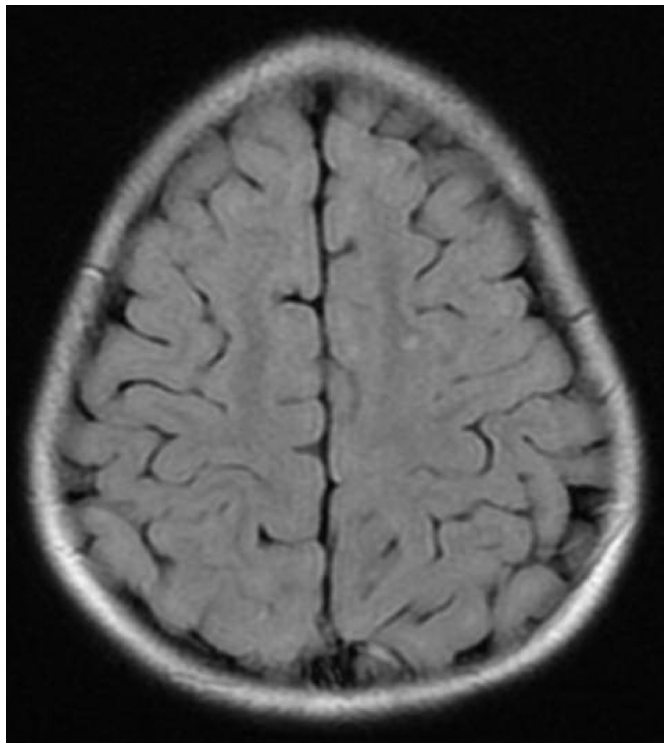

FIGURE.
Magnetic resonance imaging of the brain showed a tiny area of left frontal signal abnormality on T2 fluid-attenuated inversion recovery sequences, but was otherwise normal.

One month after completion of therapy, she had improved greatly, but was not back to neurological baseline. The patient had recovered 100+ words and could combine words into two- to three-word phrases. She walked unassisted without gait impairment and climbed stairs unassisted. The patient did exhibit residual sleep disturbance, which was managed medically. The patient received an additional three courses of monthly dexamethasone and intravenous immunoglobulin for these residual symptoms.

One month subsequent, approximately 6 months after initial presentation, the patient had returned to neurological baseline, with no apparent residual deficits. Repeat MRI of the brain was normal; MRI of the abdomen and pelvis was normal. Repeat lumbar puncture showed a white blood cell count of 4, glucose of 40, and protein of 16; oligoclonal bands were now absent; CSF anti-NMDA receptor antibody titer remained weakly positive at 1:10.

One year after initial presentation, the patient is symptom-free and is a developmentally normal 3-year-old girl according to parental report and informal physician assessment.

Discussion

Anti-NMDA receptor encephalitis is an increasingly recognized neurological syndrome in children and adults. However, there are few reports in the literature of cases involving infants and toddlers (Table).[2,3,8-10,13] We present

TABLE.
Prior Reports of Anti-NMDA Receptor Encephalitis in Infants and Toddlers

Reference	Age	Sex	Symptoms	Treatment	Tumor	Outcome
Florance et al.[2]	23 mo	F	B, MD, AD	Solu-Medrol, IVIG	N	Recovery
	3 yr	F	B, MD, AD	Solu-Medrol, IVIG	N	Recovery
Irani et al.[3]	2 yr	F			N	
Wong-Kisiel et al.[9]	20 mo	M	B, Sp, MD, AD, Sz	Prednisone, IVIG	N	Residual speech
				Solu-Medrol, ritux	N	Apraxia
Gable et al.[8]	2 yr					
Kashyape et al.[11]	27 mo	F	B, Sp, MD	Steroids, IVIG, ritux	N	Seizures; speech, memory issues
	27 mo	F	B, Sp	Steroids, IVIG, Solu-Medrol	N	Recovery
Goldberg et al.	23 mo	F	B, Sp, MD	Solu-Medrol, IVIG, dex, ritux	N	Recovery
TOTAL	83%	F	B, 100% MD, 83% Sp, 67% AD, 50% Sz, 17%	Solu-Medrol, 100% IVIG, 100% ritux, 33%	0%	Recovery, 67% Deficits, 33% Death, 0%

Abbreviations:
AD = Autonomic dysfunction
B = Behavioral
F = Female
IVIG = Intravenous immunoglobulin
M = Male
MD = Movement disorder
Ritux = Rituximab
Sp = Speech abnormality
Sz = Seizure
Here, pediatric is defined as age ≤18 years; infant, age >2 months and ≤1 year; toddler, age >12 months and ≤36 months. Time to diagnosis is listed, when known. Note that some cases come from larger series including adults.

an illustrative case of a 21-month-old female toddler with anti-NMDA receptor encephalitis who exhibited a complete response to second-line immunotherapy.

Florance et al.[2] reported the first case series of pediatric patients (age <18 years) with anti-NMDA receptor encephalitis. They described 32 children, 8 of whom were age 6 years or younger and 2 of whom were younger than age 3 years, including a 23-month-old girl. Irani et al.[4] reported a case series of 44 patients with anti-NMDA receptor encephalitis that included one toddler, a 2-year-old girl. The youngest known patient with anti-NMDA receptor encephalitis was 8 months old at diagnosis.[10]

There have been a number of reports of anti-NMDA receptor encephalitis during pregnancy,[14] but we found no reports of newborns with acquired anti-NMDA receptor encephalitis via transplacental transfer of autoantibodies, although this remains a theoretical possibility.

In a cohort of 577 patients with anti-NMDA receptor encephalitis, 81% of patients were girls and 38% had an underlying tumor.[7] The likelihood of detecting a tumor appears to depend on sex and age, with this being more common in girls and in adults. Forty-six of all girls with anti-NMDA receptor encephalitis had an underlying tumor, but only 6% of males[7,15]; among females, almost 60% of women (age ≥18 years) had a tumor, but only 16% of girls ≤12 years and none ≤6 years.[15] The youngest known patient with anti-NMDA receptor encephalitis found to have an underlying tumor was age 7 years at presentation.[7] Although infants and toddlers with anti-NMDA receptor encephalitis appear to be at decreased risk for occult neoplasm, it is reasonable to perform an initial screening with contrast-enhanced MRI of the abdomen and pelvis. The role for surveillance imaging after successful treatment in this age group is not clear, but repeat imaging should be considered in patients who remain symptomatic after treatment and in the case of neurological relapse.

The most common presenting symptoms of anti-NMDA receptor encephalitis in adults include psychiatric symptoms and memory impairment, whereas in children the syndrome more typically includes abnormal behavior, movement disorders, and seizures.[7] Although only representing a small number of patients, the reported cases of anti-NMDA receptor encephalitis among infants and toddlers presented most commonly with behavioral abnormalities, movement disorders, and speech arrest, with seizures being less commonly reported. All patients were polysymptomatic. No patients were found to have an underlying tumor. Two thirds of all patients made a complete recovery.

In our patient, treatment was begun presumptively given the highly suggestive clinical presentation before receiving the results of confirmatory testing. The differential diagnosis of anti-NMDA receptor encephalitis is broad.[5] In an infant or toddler, the differential includes: viral encephalitis, acute disseminated encephalomyelitis or other post- or parainfectious autoimmune or inflammatory encephalitis, drug intoxication, or neuroleptic malignant syndrome. A series of 100 patients (adults and children) with anti-NMDA receptor encephalitis found that more than three fourths of all patients initially presented to psychiatrists or psychiatric institutions.[15] However, new-onset psychosis would be

much less likely in infants and toddlers, which may contribute to the speed with which patients were diagnosed despite the diagnostic challenges posed by this age group.

Accumulating data suggest that rituximab is an effective treatment for anti-NMDA receptor encephalitis, including in children.[9,16] Among patients with anti-NMDA receptor encephalitis not responding to first-line therapy (i.e., steroids and/or intravenous immunoglobulin), those receiving second-line immunotherapy (rituximab and/or cyclophosphamide) showed better outcome relative to patients not receiving second-line agents; patients receiving second-line immunotherapy also experienced fewer relapses relative to those not receiving such therapy.[7] For general pediatricians and pediatric neurologists without experience with these agents, a multidisciplinary treatment approach involving the expertise of rheumatology or oncology is recommended. The treatment regimen formulated by the oncology group at the authors' institution is contained in this article and is modified from an existing protocol developed for the treatment of opsoclonus myoclonus ataxia syndrome, another severe autoimmune disease of the central nervous system with paraneoplastic and idiopathic forms.[17]

The patient in the present report did have continued presence of anti-NMDA receptor antibodies in the CSF at 1-year follow-up, as is observed in some children who have achieved a full recovery.[5]

In summary, we present a 21-month-old girl with anti-NMDA receptor encephalitis and review the literature on this condition in infants and toddlers. Our analysis suggests that anti-NMDA receptor encephalitis is not uncommon in this relative to other age groups. However, there are no reports of underlying ovarian teratoma or other occult malignancy in the now nine reported infants and toddlers with anti-NMDA receptor encephalitis. This diagnosis should be considered in young children with some combination of acute-onset behavioral abnormalities, speech dysfunction, movement disorder, and seizures.

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