Gait Disturbance as the Presenting Symptom in Young Children With Anti-NMDA Receptor Encephalitis

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This case series demonstrates a novel clinical phenotype of gait disturbance as an initial symptom in children <3 years old with anti–N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis. Anti-NMDAR encephalitis is one of the most common causes of encephalitis in children, more common than any of the viral encephalitides and the second most common autoimmune cause after acute disseminated encephalomyelitis. Anti-NMDAR encephalitis in children often presents with disrupted speech and sleep patterns followed by progression to motor dysfunction, dyskinesias, and seizures. Because this condition can present initially with vague symptoms, diagnosis and treatment of anti-NMDAR encephalitis are often delayed. Although nearly 40% of all reported patients are <18 years old, few infants and toddlers have been reported with this disease. Four children <3 years old were diagnosed with anti-NMDAR encephalitis at our institution. Interestingly, each child presented initially with the chief concern of gait disturbance. One child presented with unsteady walking and slurred speech, suggestive of cerebellar ataxia, and 3 had inability to bear weight on a unilateral lower extremity, resulting in unsteady gait. Two of these children had seizures at the time of hospital presentation. All developed classic behavioral changes, insomnia, dyskinesias, or decreased speech immediately before or during hospitalization. When seen in the setting of other neurologic abnormalities, gait disturbance should raise the concern for anti-NMDAR encephalitis in young children. The differential diagnosis for gait disturbance in toddlers and key features suggestive of anti-NMDAR encephalitis are reviewed.

Anti–N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is one of the most common causes of encephalitis in children, more common than any of the viral encephalitides[1] and the second most common autoimmune cause after acute disseminated encephalomyelitis.[2] This neurologic disorder was first described in 2005 in young women who presented with psychiatric symptoms, seizures, encephalopathy, movement disorders, and autonomic instability and who were found to have ovarian teratomas.[3] Common antibodies that react against the NR1 subunit of the N-methyl-D-aspartate receptor were demonstrated to play a pathogenic role in this disease.[4]

Since that time, descriptions of symptom onset, treatment, and outcome in larger cohorts have been published, and the condition has become notable for its dramatic clinical presentation with typically favorable response to therapy. More recently, the heterogeneity

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of underlying etiologies and variability in natural history and presentation have been described, with striking differences noted in the pediatric population as compared with the more classic young adult population (Table 1). Adult patients typically present with acute behavioral changes or psychosis with progression of symptoms to include seizures, memory deficits, movement disorders, and autonomic dysregulation.[5] In contrast, children tend to present initially with seizures, movement disorders, and speech changes, and they are more likely to develop speech dysfunction, cerebellar ataxia, and hemiparesis.[6]

Although nearly 40% of all reported patients with anti-NMDAR encephalitis are <18 years old, few infants and toddlers have been reported with this disease.[7] We report on our clinical observations with 4 very young patients (≤3 years old) with anti-NMDAR encephalitis who presented with gait disturbance (Tables 2, 3, and 4). Gait disturbance, which is often difficult for parents to describe and may not be apparent to the provider, is nonspecific and can be seen in both benign, self-resolving entities and more worrisome ones. Therefore, we also review the differential diagnosis for gait disturbance in toddlers and identify key features that should raise concern for anti-NMDAR encephalitis.

TABLE 1 Clinical Features of Anti-NMDAR Encephalitis

	Adults	Children
Initial presenting symptoms	Changes in mood, behavior, and personality; psychosis	Seizures, movement disorders, changes in speech, disrupted sleep patterns
Symptoms at illness peak	Seizures, decreased consciousness, memory deficits, movement disorders	Seizures, movement disorders, behavioral changes
Manifestation of autonomic instability	Cardiac arrhythmias, central hypoventilation	Hypertension, tachycardia, hyperthermia
Classic etiology	Ovarian teratoma, other tumor, postinfection	Suspected postinfection

TABLE 2 Cases: Clinical Characteristics

	Case 1	Case 2	Case 3	Case 4
Age at symptom onset, mo	39	25	36	17
Sex	Female	Male	Male	Female
Clinical symptoms at presentation				
Ataxia	Yes	No	No	No
Unilateral refusal to bear wt	No	Yes	Yes	Yes
Sleep disturbance	Yes	No	Yes	No
Behavior or personality change	Yes	No	Yes	Yes
Seizure	Yes	No	Yes	No
Chorea or orofacial dyskinesia	No	No	No	Yes
Speech disturbance or arrest	Yes	No	Yes	No
Recent preceding illness	Yes	Yes	No	No
Clinical symptoms subsequently developed				
Ataxia	Yes	No	No	No
Unilateral refusal to bear wt	No	Yes	Yes	Yes
Sleep disturbance	Yes	Yes	Yes	Yes
Behavior or personality change	Yes	Yes	Yes	Yes
Seizure	Yes	No	Yes	No
Chorea or orofacial dyskinesia	No	Yes	Yes	Yes
Speech disturbance or arrest	Yes	Yes	Yes	Yes

CASE SUMMARIES

Case 1

A 3-year-old healthy African American girl presented with 1 week of somnolence and an episode of unresponsiveness, slurred speech, and unsteady gait followed by a focal seizure. On examination, she exhibited extremes of temperament fluctuating between somnolence and agitation, paucity of speech, and gait ataxia. EEG revealed decreased activity over the left hemisphere. Brain MRI showed multifocal nonenhancing cortical T2 hyperintensities consistent with either postseizure signal abnormalities or encephalitis (Fig 1A). Given the patient's return to baseline by hospital day 2, lumbar puncture was deferred. She was discharged on levetiracetam for seizure prophylaxis.

Six days later, she returned with aggression, insomnia, and another focal seizure. Cerebrospinal fluid (CSF) analysis showed a mild lymphocytic pleocytosis. By the next day, she was at baseline. Anti-NMDAR antibodies were detected in the CSF, but given her spontaneous marked improvement, immune therapy was not pursued.

Case 2

A 2-year-old healthy African American boy presented with refusal to bear weight on the left leg, which progressed to complete inability to walk over 4 weeks. He received an initial diagnosis of toxic synovitis and then postinfectious cerebellar ataxia. He then developed inability to sit, dysarthria, paucity of speech, constipation, insomnia, and decreased movement on the left. On examination, he had choreiform movements and facial dyskinesias. A brain MRI from his previous hospitalization showed subtle T2 hyperintensities, which persisted on subsequent MRI (Fig 1B). CSF studies revealed a mild lymphocytic pleocytosis. Because of concern for autoimmune encephalitis, he was treated empirically with intravenous immunoglobulin (IVIg). Given lack of improvement, he subsequently received high-dose intravenous (IV) methylprednisolone followed by

TABLE 3 Cases: Diagnostic Findings

	Case 1	Case 2	Case 3	Case 4
MRI brain (region of abnormalities)	Cingulate, dentate, parahippocampal	Right frontal, cingulate	Normal	Normal
Magnetic resonance spectroscopy brain	Not done	Normal	Normal	Not done
MRI spine	Not done	Normal	Not done	Normal (cervical)
Malignancy evaluation	Abdominal ultrasound and computed tomography of the chest, abdomen, pelvis normal	Abdominal and scrotal ultrasound normal	Not done	Abdominal ultrasound and MRI pelvis normal
EEG	Focal slowing	Normal	Focal slowing and focal seizures	Bilateral slowing
CSF studies				
White blood cells/mm^3	10	1	21	4
Glucose, mg/dL	51	73	53	56
Protein, mg/dL	18	13	16	21
IgG index[a]	Not done	0.9	1.2	0.5
Oligoclonal bands[b]	Pattern 2	Pattern 2	Pattern 2	Pattern 1
Bacterial or viral testing	Negative	Negative	Negative	Negative
Paraneoplastic panel	Negative	Not done	Negative	Negative
NMDAR Antibody	Positive	Not done	Positive	Positive
Serum studies				
Paraneoplastic panel	Negative	Negative	Negative	Negative
NMDAR Antibody	Not done	Positive	Positive	Positive

[a] Normal immunoglobulin G (IgG) index ≤0.8.

[b] Oligoclonal bands pattern 1: No oligoclonal IgG bands present in CSF or serum. Oligoclonal bands pattern 2: Two or more oligoclonal IgG bands identified in CSF only (indicative of intrathecal synthesis of IgG).

TABLE 4 Cases: Treatments and Outcomes

	Case 1	Case 2	Case 3	Case 4
Seizure treatment	Levetiracetam → valproic acid	None	Levetiracetam → oxcarbazepine	None
Insomnia treatment	Clonidine	Clonidine	None	Clonidine
Attention treatment	None	None	Methylphenidate	None
Chorea treatment	None	Carbamazepine	None	None
Immune therapy				
IVIg	Not administered	2 g/kg divided over 5 days	2 g/kg divided over 5 days	2 g/kg divided over 3 days, then monthly for 6 months
IV methylprednisolone	Not administered	30 mg/kg per day for 5 days	30 mg/kg per day for 5 days	30 mg/kg per days for 5 days
Rituximab	Not administered	Not administered	Not administered	375 mg/m^2 weekly for 4 weeks
Posthospitalization disposition	Home	Inpatient rehabilitation	Inpatient rehabilitation	Inpatient rehabilitation
Follow-up				
1 mo	Seizure-free, mild behavior and sleep problems	Able to stand independently, residual gait disturbance	Baseline mobility, mild language and attention problems	Poor oral intake, mobility symmetric, unable to sit, lack of verbalization
3 mo	Not available	Improved insomnia and chorea, clonidine and carbamazepine weaned off	Baseline mobility and attention, mild language delay	Able to sit but unable to bear weight, insomnia, lack of verbalization
6 mo	At baseline	At baseline	Not available	Stands unassisted, chorea resolved, full oral diet, minimal verbalization
8 mo	Not available	Not available	Not available	Walks unassisted, clonidine weaned off, minimal verbalization

an oral corticosteroid taper. CSF anti-NMDAR antibodies later resulted positive. By 6 months, he had returned completely to baseline.

Case 3

A 3-year-old Hispanic American boy with mild attention deficit symptoms presented with 10 days of daily vomiting associated with a 1- to 2-minute episode of decreased responsiveness. He then developed intermittent right leg pain and refusal to bear weight and had a focal

seizure. His neurologic examination upon admission was normal. An EEG showed multiple brief seizures originating from the left hemisphere. Brain MRI was normal. He was discharged on levetiracetam.

Three days later, he was readmitted for agitation, insomnia, and paucity of speech. His examination was notable for restlessness, inattention, choreiform movements, tongue-thrusting, and facial dyskinesias. Repeat brain MRI was normal. CSF analysis revealed a mild lymphocytic pleocytosis. He was treated empirically with IVIg, followed by high-dose IV methylprednisolone and subsequent oral corticosteroid taper because of incomplete improvement. CSF anti-NMDAR antibodies later resulted positive. Three months later, he was nearly at baseline.

Case 4

A 17-month-old healthy Hispanic American girl presented with decreased movement of the right arm and abnormal gait preceded by 1 week of fussiness and decreased activity. Her examination was notable for decreased spontaneous movement of the right arm, subtle choreiform movements of the right hand, facial dyskinesias, and a circumducting gait. She then developed insomnia, poor oral intake, progressive loss of speech, and refusal to bear weight on the right. Brain MRI and CSF studies were unremarkable. She was treated empirically with IVIg with some improvement. CSF anti-NMDAR antibodies later resulted positive.

Over the next 3 weeks, she had weight loss due to poor oral intake, persistent loss of speech, inability to sit, and worsening weakness. She was readmitted and received high-dose IV methylprednisolone followed by an oral corticosteroid taper and a second course of IVIg. She had clinical improvement but, because of persistent symptoms, needed a gastrostomy tube, 1 course of rituximab, and monthly IVIg for 6 months. She has since recovered significantly but with persistent expressive language deficits.

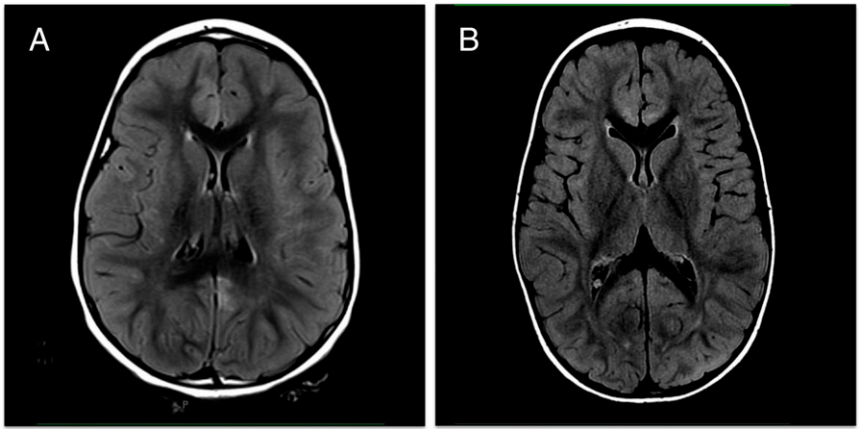

FIGURE 1
Brain MRI, Cases 1 and 2. T2 fluid-attenuated inversion recovery images for Case 1 (A) and Case 2 (B) showing multifocal nonenhancing cortical T2 hyperintensities consistent with either postseizure signal abnormalities or encephalitis.

DISCUSSION

Anti-NMDAR Encephalitis

Alteration of cognition and behavior, abnormal movements, and gait disturbance should prompt consideration of anti-NMDAR encephalitis, even in young children in whom this clinical entity has been infrequently reported. Given the nonspecific presentation, higher incidence of particular mimics, difficulty of neurologic examination in toddlers, and potential for improvement without treatment (as in Case 1), it is likely that anti-NMDAR encephalitis is underrecognized in this population.

Despite a classic clinical picture, abnormalities on MRI, EEG, and routine CSF analysis are inconsistent between patients and therefore may not provide definitive diagnosis. Previous studies suggest that only 55% of patients with this disease have abnormal MRI of the brain, typically nonspecific T2 fluid-attenuated inversion recovery signal hyperintensities and contrast enhancement in the hippocampus, cerebellum, frontal cortex, basal ganglia, and brainstem.[4] MRI abnormalities were seen in 2 out of 4 of our patients. Similarly, EEG findings are nonspecific. Electroclinical seizures can be noted, although subclinical seizures and abnormal movements with no EEG correlate are also reported.[5] Two of our patients had seizures, and focal or generalized slowing was noted in 3 of our 4 patients. In previous studies, 95% of patients had abnormal CSF as defined by lymphocytic pleocytosis, increased protein concentration, or positive oligoclonal bands.[4,8] Three out of 4 of our patients had CSF abnormalities, including pleocytosis and oligoclonal bands. Definitive diagnosis is made by detection of autoantibodies directed against the N-methyl-D-aspartate receptor in the serum or CSF, which was seen in all of our patients.

Differentiating Between Anti-NMDAR Encephalitis and Other Pediatric Disorders

In this age group, a number of other neurologic and systemic conditions can present with gait disturbance or ataxia, similar to anti-NMDAR encephalitis (Table 5). Acute postinfectious cerebellar ataxia, thought to also be autoimmune, typically presents after a febrile illness or immunization with ataxia with or without nystagmus. Unlike anti-NMDAR encephalitis, it is a benign and self-limited, typically

TABLE 5 Features of Anti-NMDAR Encephalitis and Its Mimics in Young Children

	Pathophysiology	Clinical Features in Addition to Gait Dysfunction	Diagnostic Studies
Anti-NMDAR encephalitis	Postinfectious autoimmune	Altered cognition, speech dysfunction, ataxia, sleep disturbance, autonomic instability, seizures, movement disorder	Anti-NMDAR antibodies in serum or CSF; CSF may have mild pleocytosis; MRI normal or nonspecific.
Acute postinfectious cerebellar ataxia	Postinfectious autoimmune	Ataxia with or without nystagmus	CSF may have mild pleocytosis; MRI normal or nonspecific.
Acute cerebellitis	Direct cerebellar infection	Altered cognition, elevated intracranial pressure, ataxia, fever, systemic symptoms	CSF pleocytosis; imaging may show cerebellar edema.
Toxic ingestion	Injury to Purkinje cells	Altered cognition, seizures, ataxia, clinical presentation depends on toxin	Urine and serum toxicology screens.
Opsoclonus–myoclonus–ataxia syndrome	Paraneoplastic autoimmune	Developmental regression, opsoclonus, myoclonus, ataxia	Metaiodobenzylguanidine scan, computed tomography or MRI of chest or pelvis.
Acute disseminated encephalomyelitis	Postinfectious autoimmune	Altered cognition, seizures, ataxia, cranial neuropathies, focal neurologic deficits, myelopathy	CSF may show pleocytosis and elevated protein; MRI shows white matter T2 hyperintense lesions, usually with contrast enhancement.
Cerebellar stroke	Vascular	Dizziness, nausea, vomiting, gait disturbance, headache	MRI shows diffusion restriction in affected vascular territory.
Inner ear disease	Infectious	Vertigo, nystagmus, sensorineural hearing loss, tinnitus, fever, aural fullness	MRI may show contrast enhancement of the labyrinth.
Benign paroxysmal vertigo	May be migraine precursor	Brief spells of vertigo and ataxia lasting a few minutes with no alteration of cognition; normal between spells	Imaging and CSF studies normal.
Guillain–Barré syndrome	Postinfectious autoimmune	Ascending weakness, ataxia, areflexia	CSF shows albuminocytologic dissociation, electromyogram and nerve conduction studies consistent with demyelination.

resolving within 2 weeks.[9] Acute cerebellitis, the direct result of cerebellar infection, leads to more significant cerebellar inflammation and can be distinguished clinically from postinfectious cerebellar ataxia by altered mental status, elevated intracranial pressure, and systemic symptoms such as fever and nuchal rigidity.[10] Imaging may reveal cerebellar edema, which may prompt closer monitoring.

Opsoclonus–myoclonus–ataxia syndrome, a paraneoplastic process typically related to neuroblastoma in this age group, can also mimic anti-NMDAR encephalitis when ataxia precedes the other symptoms. Ataxia in opsoclonus–myoclonus–ataxia syndrome can be accompanied by developmental regression and irritability, similar to anti-NMDAR encephalitis.[10] Acute disseminated encephalomyelitis may also be considered when a child presents with encephalopathy and gait disturbance after a viral illness or immunization. Unlike in anti-NMDAR encephalitis, imaging shows T2 hyperintense and contrast-enhancing white matter lesions.[11] About half of patients with cerebellar strokes present with gait disturbance,[12] making vascular pathology another consideration.

Any child presenting with ataxia should also be evaluated for toxic ingestion, as cerebellar Purkinje cells are highly susceptible to injury from toxins.[10] Inner ear disease can result in vertigo that also may manifest as gait abnormalities. Guillain–Barré syndrome can present with gait disturbance due to leg weakness. As in other autoimmune processes, preceding infection is common, but areflexia distinguishes Guillain–Barré syndrome from central etiologies.[13]

Although many entities can present with gait disturbance in toddlers, evidence for accompanying encephalopathy, seizures, focal neurologic deficits, or inflammation should raise suspicion for anti-NMDAR encephalitis. Because much of the initial diagnostic evaluation may be unremarkable or nonspecific, strong consideration should be given when the clinical picture is not consistent with more benign or systemic etiologies. Management of anti-NMDAR encephalitis focuses on immunotherapy, seizure control, and tumor detection and removal. Outcome is generally thought to be favorable, particularly with aggressive and early therapy, which leads to more rapid recovery and reduced morbidity.[14,15] One of our patients experienced spontaneous improvement, 2 returned to baseline by about 3 months after hospitalization, and 1 patient has persistent language delay 16 months after hospitalization. However, significant morbidity and mortality have been reported, particularly in patients who need intensive care. Therefore, timely recognition of this condition and differentiation from its mimics may have definite implications for the treatment plan and eventual prognosis.

ABBREVIATIONS

anti-NMDAR: anti–N-methyl-D-aspartate receptor
CSF: cerebrospinal fluid
IV: intravenous
IVIg: intravenous immunoglobulin

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