with a younger age at onset, and their outcomes can be favorable with multidisciplinary treatment. ■

Legends to the Video

Video 1. Video of a woman aged 68 years with sudden onset tremor (elderly group, case 7). The video demonstrates entrainment and distractibility of a right hand jerky tremor with complete resolution on suggestion. The patients has associated functional gait with fluctuations of stance and gait and buckling of the knees. There is a tendency to hold on to surrounding objects.

Video 2. Video of a man aged 78 years with abrupt onset dystonia (elderly group, case 33). The video demonstrates the incongruous movements of face and upper limbs with variability and distractibility.

Video 3. This video demonstrates functional right hand and leg tremor accompanied by functional gait with uneconomic postures (identity masked).

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The Spectrum of Movement Disorders in Children With Anti-NMDA Receptor Encephalitis

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ABSTRACT

Background: Movement disorders are frequent but difficult to characterize in patients with anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis.

Methods: The phenomenology of movement disorders was characterized after a detailed examination of children with anti-NMDAR-encephalitis.

Results: We studied 9 children (5 females), ages 3–14 years, with confirmed anti-NMDAR-encephalitis. All patients presented with at least 1 movement disorder, including chorea (n=4), stereotypic movements (n=4), ataxia (n=3), limb dystonia (n=2), limb myorhythmia (n=2), oromandibular dystonia (n=2), facial myorhythmia, blepharospasm, opisthotonus, athetosis, and tremor (n=1, each). More than a single movement disorder was observed in 6 of these patients. Resolution of the abnormal movements was observed in all patients with immunotherapy; 1 patient improved with tetrabenazine.

Conclusions: A wide variety of movement disorders, often in combination, can be observed in children with anti-NMDAR encephalitis. Patients commonly present with more than a single movement disorder.

Key Words: anti-NMDAR encephalitis; stereotypies; chorea; dystonia; myorhythmia; autoimmune

Supporting Information may be found in the online version of this article.

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TABLE 1. Movement disorders observed in this case series

Case	Sex/age at onset	Myorhythmia (facial)	Myorhythmia (limb)	Chorea	Athetosis	Cranial dystonia	Opisthotonus	Limb dystonia	Stereotypic movements	Ataxia
1	F/13 years old	+	+			+[b]				+
2	M/8 years old								+	
3	M/3 years old			+		+[a]	+	+	+	
4	F/8 years old		+							
5	M/3 years old			+						+
6	M/11 years old			+	+					
7	F/5 years old			+					+	
8	F/14 years old								+	
9	F/10 years old[c]							+		+

[a]Blepharospasms
[b]orolingual and hemifacial dystonia
[c]fine upper limb postural tremor.

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis has received much attention in the last 5 years. The clinical syndrome usually follows a multistage course, often starting with behavioral manifestations and followed by an acute or subacute emergence of movement disorders. Although well characterized in adults,[1] the syndrome is more variable and atypical in children. Movement disorders typically appear after a period of prodromal and psychiatric manifestations in adults, but they may be the initial manifestation in children with anti-NMDAR encephalitis.[2,3] The phenomenology of these abnormal movements may be difficult to characterize, and patients may manifest more than a single one.

Patients and Methods

We aimed to characterize the movement disorders observed in a series of 9 children (4 males and 5 females, between 3 and 14 years old) with confirmed anti-NMDAR encephalitis referred to a tertiary-care center. All patients underwent extensive neurological evaluation and investigations searching for possible infectious, metabolic, and autoimmune causes of encephalitis. Parents or legal custodians signed informed consent for videotaping; the study was approved by the Institutional Review Board. All patients satisfied the following inclusion criteria: positive anti-NMDAR antibody titers (blood or cerebrospinal fluid [CSF]); and lack of evidence of other causes of encephalitis or movement disorders.

Results

All patients presented with at least 1 movement disorder: chorea (n=4), stereotypic movements (n=4), ataxia (n=3), limb dystonia (n=2), limb myorhythmia (n=2), oromandibular dystonia (n=2), facial myorhythmia, blepharospasm, opisthotonus, athetosis, and tremor (n=1, each). Orolingual dyskinesias frequently reported in this syndrome were observed in 2 patients and corresponded to myorhythmia and oromandibular dystonia. All patients had movement disorders involving their limbs, and 5 also had cranial involvement. One patient had 5 types of movement disorders, 1 patient had 4, 1 patient had 3, 3 patients had 2, and 3 patients had a single type (Table 1). No patient had an underlying tumor. We describe 6 representative cases.

Case 1

A previously healthy 13-year-old African American female presented to the emergency room after a recent history of vague complaints of "heaviness" in the right leg, followed by unstable, ataxic gait. These manifestations were rapidly followed by altered mental status with perseverance, uncontrolled laughing, loud singing, and delusional religious thoughts. The patient was admitted to the intensive care unit because of hypoventilation, generalized seizures, and autonomic dysfunction with tachypnea and tachycardia. During that time she developed 1- to 2-Hz repetitive contractions of the procerus, corrugator, orbicularis oculi, and oromandibular muscles with tongue protrusion, along with slow leg tremor, consistent with facial and limb myorhythmia (Video 1) and cranial dystonia. A brain MRI was unremarkable. Marked improvement was observed after treatment with corticosteroids and intravenous immunoglobulins, followed by plasmapheresis and rituximab.

Case 2

An 8-year-old Hispanic boy presented with a 3-month history of agitation, insomnia, hallucinations, and generalized seizures, followed by social withdrawal and anorexia. He was found nonverbal and minimally interactive with the environment. Episodes of leftward gaze deviation were observed as well as stereotypic

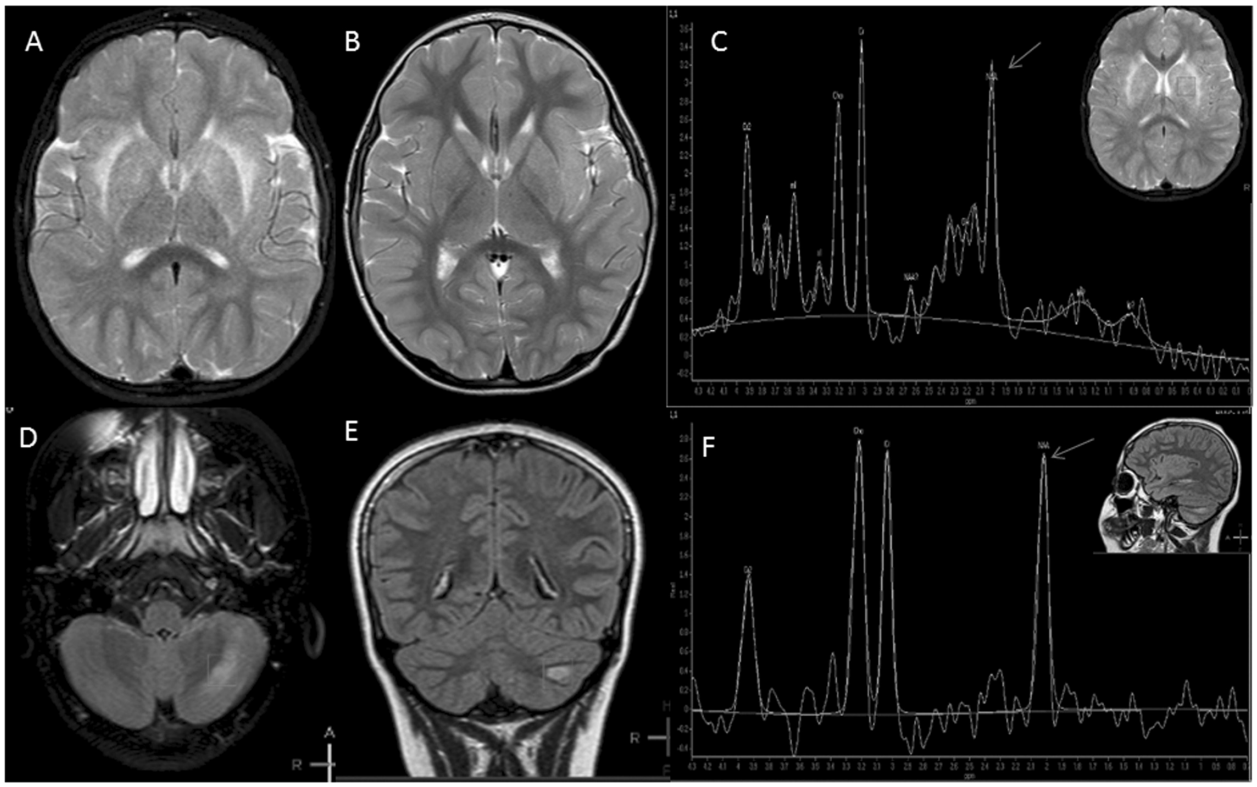

FIG. 1. A: Proton density MRI shows bilateral hyperintensities in the external and internal capsules—the lentiform "fork sign." **B:** The same hyperintensities were more subtle in the T2W sequence and FLAIR (not shown). **C:** MRS shows a decrease in the peak of *N*-acetyl aspartate with respect to choline and creatinine and an increase in myoinositol in the basal ganglia. **D, E:** Axial and coronal FLAIR shows a left cerebellar hyperintensity. **F:** MRS shows a fall in the peak of *N*-acetyl aspartate suggesting neuronal damage.

right and left arm flexion, elevation, and abduction (Video 2). When the right arm was restrained, he had purposeless left arm elevation. The electroencephalogram showed absence of an occipital dominant rhythm, multifocal sharp waves, most prominent in the left frontotemporal region, and diffuse slowing. A brain MRI was unremarkable. A 5-day trial of intravenous immunoglobulins did not provide symptomatic benefit. However, marked clinical improvement was observed after treatment with intravenous pulses of corticosteroids and 6 cycles of plasmapheresis. Seizures were controlled with levetiracetam.

Case 3

A 3-year-old Hispanic male had subacute onset of myalgias, frontal headache, malaise, and vomiting, followed by mental confusion, insomnia, hallucinations, dysarthria, and motor aphasia. The patient was admitted to the hospital. During the hospitalization he developed generalized seizures, dysautonomia with brief episodes of apnea and complex abnormal movements with repetitive orofacial stereotypies, dystonic contractions of the left side of his face, blepharospasm, dystonic flexion of the right wrist and hand, opisthotonus, and chorea (Video 3). The electroencephalogram indicated epileptiform activity corresponding to the episodes of arm elevation. Marked improvement was observed with pulses of methylprednisolone and intravenous immunoglobulins; seizures responded to phenytoin and levetiracetam. The movement disorders (dystonia, chorea, and stereotypies) improved with tetrabenazine 25 mg 3 times a day. He had a relapse 5 months into his course, with further seizures and cognitive decline. Treatment with monthly intravenous immunoglobulins and mofetil mycophenolate 200 mg twice a day resulted in return to normal baseline.

Case 4

An 8-year-old Hispanic girl had sudden onset of generalized tonic-clonic seizures. During the hospitalization, she had a transient episode of right-sided hemiparesis on awakening, dysautonomic symptoms with episodic tachycardia, hypertension, fluctuating mental status, and abnormal movements consisting of slow, involuntary asynchronous (alternating flexion-extension) 1- to 2-Hz lower limb myorhythmia (Video 4). The electroencephalogram showed no occipital dominant rhythm with a diffusely slow background. Brain MRI was unremarkable. The CSF anti-NMDAR antibody was positive. The patient was treated with monthly intravenous immunoglobulins and pulses of

corticosteroids with initial response. However, she had a relapse 3 months later with generalized tonic-clonic seizures and tactile hallucinations; this time she required treatment with plasmapheresis. Seizures required treatment with multiple medications including zonisamide, fosphenytoin, levetiracetam, and lorazepam. Her serum NMDAR titers remained markedly elevated and she was maintained on mycophenolate for a year following this.

Case 5

This is a 3-year-old Hispanic boy who was brought to the hospital for evaluation of a 10-day history of progressive generalized movements. This presentation was followed by a wide-based, unsteady ataxic gait, limb ataxia with inability to feed himself, and dysarthria. The examination showed random, purposeless, involuntary, nonsuppressible movements corresponding to chorea (Video 5). The movements disappeared with sleep and worsened with excitement. Mild motor impersistence was also noticed. No seizures were observed. A brain MRI showed symmetric hyperintensities in the external and internal capsule resembling the "fork sign" (Fig. 1A,B). Magnetic resonance spectroscopy (MRS) showed a reduced peak of *N*-acetyl aspartate with increased levels of myoinositol in the basal ganglia (Fig. 1C). The patient showed marked improvement after intravenous pulses of methylprednisolone followed by oral corticosteroids. He had recurrence of his chorea 2 months later. Intravenous immunoglobulins followed by oral prednisone were reinitiated, with improvement in his movement disorder.

Case 6

An 11-year-old Hispanic male presented for evaluation of acutely altered mental status, irritability, agitation, restlessness, hallucinations, vomiting, and frequent crying, followed by generalized seizures. Examination showed generalized chorea and distal limb athetosis. The brain MRI showed a focal hyperintensity in the left cerebellar cortex without contrast enhancement (Fig. 1D,E) with reduction of the *N*-acetyl aspartate peak (Fig. 1F). The electroencephalogram showed slow occipital rhythm and delta activity in the frontal and occipital leads without epileptic discharges. Anti-NMDAR antibodies were negative in serum but positive in the CSF. Treatment with prednisone 3 mg/kg resulted in prominent neurological improvement. Oxcarbazepine was used to mitigate seizures. At follow-up he had no further seizures or abnormal movements but exhibited academic difficulties and anxiety. Further immunotherapy was discussed but not pursued.

Discussion

Our patients illustrated the broad spectrum of hyperkinetic movement disorders associated with anti-NMDAR encephalitis.[3] Movement disorders have been reported in 86% of adults and 84% of children and include orofacial dyskinesias; chorea; choreoathetosis; facial, limb, and trunk dystonia; myoclonus; tremor; opsoclonus-myoclonus; and ataxia.[1–3] In a series of 32 children and adolescents with anti-NMDAR encephalitis, stereotyped movements and orofacial dyskinesias were the most common movement disorders, with 85% and 45%, respectively.[2] In addition to chorea, dystonia, and athetosis, the other type of hyperkinetic movements observed in cases 1 and 4 was myorhythmia. The term *myorhythmia* was coined by Hertz[4] to describe a rest tremor usually associated with brain stem lesions and distinguishable from parkinsonian tremor by slower (1–3 Hz) and more irregular frequency. The movement is typically seen in patients with Whipple's disease and other types of encephalitis.[5–7] Myorhythmia can be differentiated from parkinsonian tremor by its lower frequency, lack of parkinsonian signs, and absent response to levodopa and can be distinguished from stereotypies by the characteristic features it is lacking, most importantly, patterned, repetitive, coordinated movement.[8]

Cases 3, 5, 6, and 7 (the 4 youngest children) showed features of chorea. Chorea is particularly dominant in younger children and anti-NMDAR chorea should be considered in the differential diagnosis of all childhood choreas, including Sydenham's chorea. Case 5 showed decreased levels of *N*-acetyl aspartate in the MRS, suggesting neuronal damage of the basal ganglia, with hyperintensities in the external and internal capsule resembling the lentiform "fork sign" described in patients with renal impairment and metabolic acidosis.[9] Nevertheless, our patient did not have evidence of any of these conditions.

Orofacial dystonia was observed in case 3. Different types of oromandibular-lingual "dyskinesias" have been described in patients with anti-NMDAR and infectious encephalitis,[10] but careful observation usually allows differentiation of these dyskinesias into orofacial stereotypy, dystonia, or myorhythmia.

In conclusion, the phenomenology of movement disorders in children affected with anti-NMDAR encephalitis may be difficult to characterize,[11] and patients often present with more than a single abnormal movement, further complicating the classification of the movement disorders. These hyperkinetic movements usually improve with immunosuppressive therapy or tetrabenazine, a monoamine depleter of the central nervous system.[12]

Legends to the Videos

Video 1. This is a 13-year-old female with repetitive facial, tongue protrusion, and lower limb movements corresponding to myorhythmia.

Video 2. This is an 8-year-old male with repetitive stereotypic left arm flexion, elevation, and abduction.

Video 3. This is a 3-year-old male with orolingual stereotypic movements, blepharospasm, dystonic left facial contractions, and stereotypic movements of the left arm.

Video 4. This is an 8-year-old female with slow alternating movement of the lower limbs corresponding to myorhythmia.

Video 5. This is a 3-year-old male with generalized chorea and motor impersistence.

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Validation of Parkinsonian Disease-Related Metabolic Brain Patterns

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ABSTRACT

Background: The objective of this study was to validate disease-related metabolic brain patterns for Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy.

Methods: The study included 20 patients with Parkinson's disease, 21 with multiple system atrophy, and 17 with progressive supranuclear palsy, all of whom had undergone a clinically motivated [18F]-fluoro-deoxyglucose positron emission tomography scan at an early stage of their disease. At a follow-up time after the scan of 2–4 years, a clinical diagnosis was made according to established clinical research criteria. Patient groups were compared with 18 healthy controls using a multivariate covariance image analysis technique called scaled subprofile model/principal component analysis.

Results: Disease-related metabolic brain patterns for these parkinsonian disorders were identified. Validation showed that these patterns were highly discriminative of the 3 disorders.

Conclusions: Early diagnosis of parkinsonian disorders is feasible when the expression of disease-related metabolic brain patterns is quantified at a single-subject level. © 2013 *Movement* Disorder Society

Key Words: Parkinson's disease; FDG-PET imaging; disease-specific metabolic brain patterns; differential diagnosis; multivariate statistical analysis technique

Visual examination of [^{18}F]-fluoro-deoxyglucose positron emission tomography (FDG-PET) scans may guide the differential diagnosis of parkinsonian syndromes. Nevertheless, interpretation of both clinical symptoms and FDG-PET scans can be difficult. Previously, univariate methods such as statistical parametric mapping (SPM) have been used to identify group differences between parkinsonian patients and controls.[1–3] However, scaled subprofile modeling/principal component analysis (SSM/PCA), a multivariate method, not only identifies group differences, but also shows relationships in metabolic activity between different brain regions in combined samples of patients and control scans.[4,5] A Parkinson's disease–related metabolic pattern was

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