Autoimmune Movement Disorders in Children

A clinical approach.

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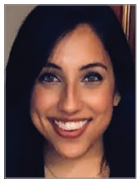
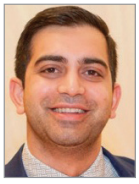


Recent advances in autoimmune neurology have led to increased recognition of autoimmune movement disorders in children. In this article, we discuss the pathophysiology, clinical approach, and management of these disorders and provide a brief overview of specific autoimmune movement disorders in children. Although there is overlap with autoimmune movement disorders in adults, many characteristics, including clinical presentation, antibody profiles, treatment responses, and differential diagnoses are different in children.

Pathophysiology

Autoantibodies can bind to extracellular or intracellular epitopes. Typically, antibodies that bind extracellularly to cell surface receptors, synaptic proteins, or ion channels are pathogenic. Antibodies that bind to intracellular targets may be biomarkers of disease but are usually not causative because there is no opportunity to bind to the target. Antibodies to extracellular targets can cause pathogenic effects via antibody-dependent cell-mediated cytotoxicity, direct agonist or antagonist effects, activation of the complement cascade, and antigen internalization (Figure 1).[1] To be pathogenic antibodies are typically immunoglobulin type G (IgG) that bind specific subunits of an extracellular protein in its natural conformation.[2]

Neural Circuits of Movement Disorders

Movement disorders are most often caused by dysfunction of motor circuits involving the basal ganglia and cerebellum (Figure 2).[3] The basal ganglia are a group of interconnected subcortical nuclei. Different areas of the basal ganglia receive afferent inputs or send efferent signals. The striatum (caudate and putamen) is the main input center, receiving afferents from the cortex, brainstem, and thalamus as well as the substantia nigra pars compacta (SNc), a part of the basal ganglia. The subthalamic nucleus (STN) also receives cortical input. Efferents in the striatum and STN send cortical input to the globus pallidus interna (GPi) and substantia nigra pars reticularis (SNr), which project

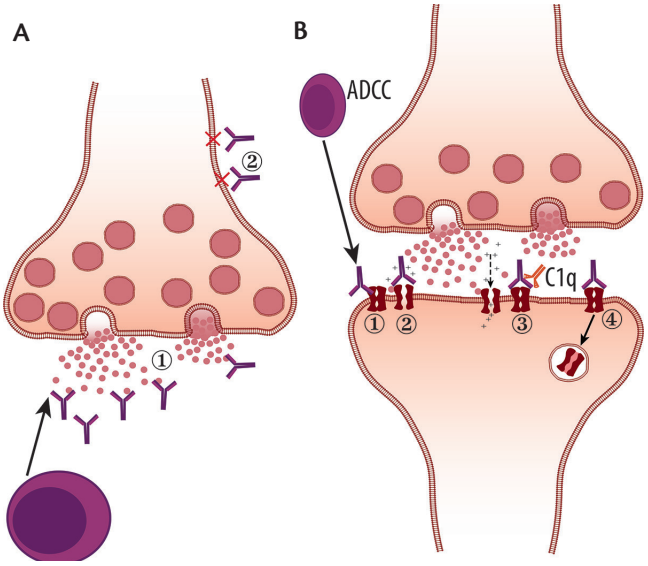

Figure 1. Pathophysiology of antibody mediated autoimmune diseases. A depicts intracellular-directed antibodies, which are most likely T-cell mediated (1) or may reach their targets when vesicles fuse and synaptic contents are then released. Intracellular antibodies generally are unable to reach their intracellular targets (2). However, neuronal surface antibodies (B) are pathogenic in a variety of mechanisms: 1) through antibody-dependent cellular cytotoxicity (ADCC); 2) directly binding to receptors and interfering with function; 3) antibody binding then triggers the complement cascade (C1q); or 4) antibody binding results in receptor internalization, which in turn interferes with function.

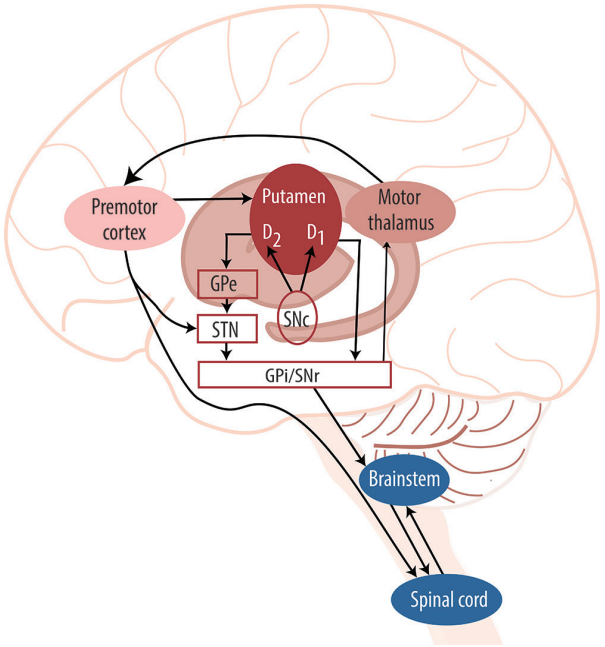

Figure 2. Structural representation of basal ganglia pathways including inputs and outputs. Abbreviations: D1, type 1 dopaminergic receptors; D2, type 2 dopaminergic receptors; GPe, globus pallidus externus; GPi, globus pallidus internus; SNc; substantia nigra pars compacta; SNr, substantia nigra pars reticularis; STN, subthalamic nucleus.

efferently to the thalamus and brainstem and back to the cortex in the cortico-striato-thalamic loop. Communication within the basal ganglia occurs via direct and indirect pathways that exert opposing effects. The direct pathway is monosynaptic and provides GABAergic input from the striatum to the output nuclei (GPi and SNr). The indirect pathway is polysynaptic and sends input from the striatum to the GPi/SNr via the globus pallidus pars externa (GPe) or via the GPe through the STN.[3]

Basal ganglia output exerts tonic inhibition of the thalamocortical pathway. Dopamine released from the SNc acts on dopamine type 1 (D_1) receptors to upregulate the activity of the direct pathway and via dopamine type 2 (D_2) receptors to downregulate indirect pathway activity. Direct pathway activation thus reduces the basal ganglia inhibition of the thalamocortical circuits allowing volitional movement, whereas indirect pathway activation inhibits movement. The type of movement disorder seen depends on which subcortical nucleus is affected and includes hypokinetic movements (ie, parkinsonism) or hyperkinetic movements (ie, chorea, athetosis, ballismus, myoclonus, tics, and dystonia).[3]

The cerebellum acts to control movement via the dentato-rubro-olivary loop and the cortico-cerebellar circuit.[2] In general, the cerebellum exerts tonic excitatory input to the cortex. Cerebellar dysfunction mostly is manifested as ataxia, although intention tremor and dystonia (rare) can also occur.

Clinical Approach

The clinical evaluation includes a detailed history, physical examination, and ancillary testing. A detailed history is critical, including collateral information from school teachers and other caregivers because sometimes symptom onset, especially when gradually progressive or situationally dependent, occurred when the child was away from their primary caregivers. Factors that provoke or lessen symptoms and family history are important to ascertain. Physical and neurologic examination provide additional information, including determining the type of movement disorder present.

Tics or dystonia alone are less likely to be autoimmune; prevalence of tics in children is common and often comorbid with obsessive-compulsive disorder (OCD) or attention-deficit/hyperactivity disorder (ADHD).[4] Dystonia can have multiple etiologies including cerebral palsy or genetic diseases.[5] If a new-onset movement disorder (within the past 3 months) is accompanied by other neurologic symptoms (eg, new-onset seizures, cognitive decline with prior normal development, speech changes, autonomic instability, or psychiatric symptoms), autoimmune causes should be considered. If there is a history of developmental delay or regression with illness, however, other diagnoses including genetic and metabolic disorders (eg, mitochondrial and inborn errors of metabolism) should be considered. Autoimmune causes are reported in up to 42% of children with acute movement disorders.[6] A negative family history does not remove the possibility of a genetic or metabolic disorder, because de novo mutations or autosomal recessive diseases can also cause movement disorders.

Diagnostic Testing

Suggested ancillary testing is outlined in Table 1. Positive findings supportive of a diagnosis of autoimmune movement disorders can include cerebrospinal fluid (CSF) pleocytosis, elevated IgG index, or positive oligoclonal bands along with MRI evidence of inflammation. Antibody testing is also helpful, but interpretation of positive results should be made cautiously depending on the antibody. Imaging features are variable and range from normal to T2 lesions and enhancement (Table 2).

Treatment and Follow-Up

Treatment includes disease-modifying immunotherapy and symptomatic treatment. Steroids and intravenous immunoglobulin (IVIG) are first-line immunotherapy and plasmapheresis is also considered, especially in severe or refractory cases. Determining whether any identified antibody has an extracellular vs intracellular target can guide the choice of second-line agents, which include rituximab, cyclophosphamide, or mycophenolate mofetil.[7] Neuropsychologic testing can also identify underlying

TABLE 1. EVALUATION FOR SUSPECTED AUTOIMMUNE MOVEMENT DISORDER

Imaging	• Brain MRI with and without contrast ◦ If positive antibody on autoimmune encephalopathy panel,[a] then whole body imaging, usually MRI or CT for tumor evaluation ◦ Ovarian or testicular ultrasound (can be more sensitive than MRI/CT)
EEG	• Consider EEG (ideally 24-hour study, if possible in patients with encephalopathy)
Cerebrospinal fluid (CSF)	• Cell count, protein, glucose, IgG index, oligoclonal bands, neopterin, autoimmune encephalopathy panel • Also consider CSF neurotransmitters, lactate, pyruvate, amino acids
Serum autoimmune studies	• Antinuclear antibody with reflex titers for other antibodies • Thyroid peroxidase, thyroglobulin antibodies • Serum autoimmune encephalopathy panel
Genetic or metabolic	• Chromosomal microarray, whole exome/genome sequencing, targeted gene panels, mitochondrial genetic panels • Serum amino acids, urine organic acids, lactate, pyruvate, ammonia

[a]Certain antibodies can have a low level false positive; GAD65 antibodies is a common positive finding and so the level should be verified with the laboratory of whether the titer is of neurologic significance. For example, whereas the cutoff for GAD65 on the Mayo encephalopathy panel is >0.02 nmol/L, neurologic symptoms are attributed when antibody levels are >20 nmol/L.[31]

cognitive issues. Treatment duration varies and generally our practice has been to give 2 years of immunotherapy for children who recover. Relapses can occur and some individuals may require longer treatment immunotherapy or have a poor response to immunotherapy, especially when the identified antibodies have intracellular targets.

Specific Antibody-Associated Disorders

Anti-NMDAR Encephalitis

Characterized by neuropsychiatric symptoms, catatonia, speech dysfunction, seizures, memory deficits, dysautonomia, and central hypoventilation, anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is caused by antibodies to the NMDAR. Children are more likely than adults to develop movement disorders in the first month of symptoms.[8] Movement disorders include chorea, dystonia, stereotypies, myorhythmia, and cerebellar ataxia, are generally refractory to symptomatic treatment,[9] and improve as disease recovery occurs after immunotherapy (see *Anti-NMDAR Encephalitis* in this issue).

AntiMOG-Associated Movement Disorders

Antimyelin oligodendrocyte glycoprotein (antiMOG) antibodies can cause neuroinflammatory diseases including demyelinating diseases and autoimmune encephalitis.[10] Movement disorders have been described in 7 people with antiMOG-associated illness who also had antiNMDAR antibodies.[11] In 1 case report, a child age 2 years presented with antiMOG-related acute disseminated encephalomyelitis (ADEM).[12]

AntiLGI-1– and AntiCaspr2-Associated Disorders

Children can also develop autoantibodies to voltage-gated potassium channel-associated proteins, including leucine-rich glioma inactivated 1 (LGI-1) and contactin-associated protein-related 2 (Caspr2), which both cause movement disorders.[13] Clinical syndromes primarily include encephalitis, new-onset seizures, and neuropsychiatric symptoms but also a peripheral component (eg, Morvan syndrome, which is more common with antiCaspr2). Autonomic symptoms, including hypertension, sweating, and weight loss can also occur. Chorea, parkinsonism, myoclonus, and limb dystonia occur in both but are more common with antiLGI-1.[14] Neuromuscular symptoms are common with both antiLGI-1 and antiCaspr-2 and can include neuromyotonia, cramps, and generalized weakness. Multiple seizure types have been identified including faciobrachial dystonic seizures (FBDS), focal tonic or clonic seizures, and generalized tonic-clonic seizures. Primarily seen in LGI-1, FBDS can be easily mistaken for a movement disorder and is poorly responsive to antiseizure medications (ASMs) but improves with immunosuppressants. Serum testing for antiLGI-1 and antiCaspr2 is highly sensitive but greater sensitivity is reached by testing both serum and CSF.[15] Tumors have not been reported with antiLGI-1 and antiCaspr2 in children, although antibody-negative limbic encephalitis has been associated with Hodgkin lymphoma.[16] Imaging findings can be highly variable and nonspecific (Table 2).

Hashimoto Encephalopathy

Hashimoto encephalopathy (HE), also known as *steroid-responsive encephalopathy associated with autoimmune thyroiditis*, is characterized by neurologic and psychiatric symptoms with increased levels of antithyroid antibodies (eg, antithyroid peroxidase [antiTPO] or antithyroid globulin).[17] In 10% of people with antiTPO antibodies, however, there are no neurologic symptoms; other autoimmune causes should thus also be considered.[13] Children with HE can experience cognitive and language decline, seizures including new-onset refractory status epilepticus,[18] insomnia, and psychiatric symptoms (eg, depression, psychosis, anxiety, hallucinations and mania).[18] Movement disorders include tremors, dystonia, ataxia, and hyperkinetic behaviors, including tics and myoclonus.[19] Nonspecific abnormalities may be seen on MRI but are more typically normal. Findings on EEG are typically abnormal.[19]

TABLE 2. ANTIBODIES ASSOCIATED WITH AUTOIMMUNE MOVEMENT DISORDERS IN CHILDREN

Antigen	Movement disorder	Other neurologic symptoms	Associated tumor	Imaging features
$GABA_AR$[24]	Dystonic tongue movements, chorea, opsoclonus, ataxia, orofacial dyskinesias	Confusion, lethargy, complex partial seizures, status epilepticus	Hodgkin lymphoma 10 months prior	Multifocal T2-FLAIR cortical-subcortical lesions involving temporal (95%) and frontal (65%) lobes, also basal ganglia, cerebellum and brainstem
$GABA_BR$[25,32]	Opsoclonus, ataxia, chorea	Encephalopathy, refractory status epilepticus	None	Brainstem, basal ganglia, and hippocampi; mesial temporal lobe (adults)
GAD65[33]	SPS, PERM, ataxia, myoclonus, and parkinsonism	Limbic encephalitis, temporal lobe epilepsy, dysarthria, memory, or behavioral disturbances	Rare, none reported in children	Usually normal; can have T2-FLAIR lesions in hippocampus
GlyR[34]	SPS, PERM, progressive dyskinesias	Explosive-onset epileptic encephalopathy; limbic encephalitis, demyelinating optic neuropathy, and focal seizures	Rare, none reported in children	Usually normal; can have T2-FLAIR lesions in hippocampus or elsewhere in brain; rarely, spinal cord lesion
NMDAR[9]	Chorea, dystonia, stereotypies, myorhythmia, cerebellar ataxia	Psychiatric symptoms, speech dysfunction, seizures, memory deficits, dysautonomia, central hypoventilation	Ovarian teratoma	Normal in 50%; T2 lesions in multiple regions in brain
LGI-1[14,15]	Chorea, parkinsonism, limb dystonia	FBDS, new-onset GTC/focal seizures, encephalopathy, neuropsychiatric disturbances, neuromyotonia	Adults with SCLC, thymoma, ovarian, renal, & skin tumors	Mesiotemporal T2 hyperintensities, T1 hyperintensity basal ganglia, PET: bilateral hypometabolism in striatum
CASPR2[14]	Orthostatic myoclonus	Weakness, sleep dysregulation, dysautonomia, encephalopathy, neuropathic pain, neuromyotonia	Adults with thymoma, prostate, skin and thyroid tumors	Brain atrophy, posterior white matter change with contrast enhancement, T2-weighted WM hyperintensities
D_2[22]	Generalized dystonia, parkinsonism, oculogyric crisis, chorea, hemidystonia, and ocular flutter	Psychiatric symptoms, seizures, lethargy, disorganized speech	No known association	T2-FLAIR hyperintensities within the basal ganglia
DPPX[13,21]	Tremor, myoclonus, stiff-person-like syndrome with ataxia, nystagmus, periodic limb movements	Seizures, diarrhea	B-cell lymphoma	Can be normal; some with nonspecific T2-FLAIR hyperintensities, one with temporal lobe atrophy
Hashimoto encephlopahy[18,19]	Tremor, dystonia, myoclonus, ataxia, chorea	Stroke-like episodes, new onset seizures including status epilepticus, psychiatric symptoms, headache, amnesia	None	Typically normal or nonspecific white matter changes
AQP4[28]	Tonic spasms	Paresthesias, vomiting, quadriparesis, bilateral optic neuritis	None	Optic neuritis, transverse myelitis; tonic spasms are usually associated with cervical spine lesions
MOG[12]	Dystonia, orofacial dyskinesias	Aphasia, seizures, encephalopathy	None	Bilateral asymmetrical lesions in deep white matter, brainstem, cortex

Abbreviations: AQP4, aquaporin-4; CASPR2, contactin-associated protein-related 2; D_2, dopamine receptor type 2; DPPX, dipeptidyl-peptdase-like protein 6: GABA, γ-aminobutyric acid; GAD; glutamic acid decarboxylase; GlyR, glycine receptor; GTC, generalized tonic-clonic seizure; LGI-1, leucine-rich glioma inactivated 1; MOG, myelin oligodendrocyte protein; NMDA; *N*-methyl-D-aspartate; PERM; progressive encephalomyelitis with rigidity and myoclonus; SPS, stiff-person syndrome; T2-FLAIR, T2-weighted fluid-attenuated inversion recovery; WM, white matter.

Although a majority of cases have been steroid responsive, 25% require additional immunotherapy including IVIG, rituximab, and mycophenolate mofetil.[20]

AntiDPPX-Associated Movement Disorders

The presentation of antidipeptidyl-peptidase-like protein 6 (DPPX) antibody-associated encephalitis includes tremor, myoclonus, ataxia, cerebellar ocular movement abnormalities, periodic limb movements of sleep, and seizures.[13] Stiff-person syndrome (SPS) and progressive encephalomyelitis with rigidity and myoclonus (PERM) can occur with antiDPPX-associated disease and antibodies to DPPX have been associated with B-cell lymphoma.[21] Diagnosis can be difficult because there is insidious onset, and symptoms can be preceded by diarrhea or unintentional weight loss. No abnormal imaging findings have been reported in children with DPPX-antibody–associated encephalitis.[13]

AntiD_2-Associated Movement Disorders

Antibodies to D_2 are seen in basal ganglia encephalitis and less commonly in Sydenham chorea and Tourette syndrome.[2] AntiD_2 can result in hypokinetic and hyperkinetic movement disorders.[13] Individuals with antiD_2-associated movement disorders most commonly had generalized dystonia and parkinsonism (ie, bradykinesia and akinesia). Chorea, tremor, and oculogyric crisis were also seen. Other symptoms included lethargy, sleep disturbances, seizures, and psychiatric symptoms. Hyperintense T2 MRI lesions were seen in the basal ganglia in 50% of cases, and EEG findings were either normal or demonstrated encephalopathy. Most cases had a monophasic course with accelerated recovery after intravenous steroids and IVIG, but nearly half of individuals were left with motor abnormalities, cognitive impairments, and psychiatric diagnoses.[22,23]

AntiGlyR- and AntiGAD65-Associated Movement Disorders

Characterized by progressive muscle stiffness and painful spasms with exaggerated startle, stiffness, and spasms of lower spine and proximal legs, childhood-onset SPS has phenotypic variability.[13] The SPS spectrum includes PERM, which may present with respiratory and autonomic dysfunction along with brainstem and long-tract signs. Clinical features may fluctuate or progress and can include limb and truncal rigidity, painful muscle spasms, segmental dystonia, hyperekplexia, and brainstem involvement (eg, ocular motor disturbance, hemifacial spasm, trismus, blepharospasm, dysphagia, and dysarthria). Life-threatening respiratory failure may occur.[2]

Both SPS and PERM have been associated with antibodies to glutamic acid decarboxylase (GAD) and glycine receptors (GlyR).[13] AntiGlyR antibodies are also associated with explosive-onset epileptic encephalopathy (without rigidity and myoclonus), limbic encephalitis, demyelinating optic neuropathies and focal seizures with progressive dyskinesia.[13] AntiGAD antibodies are also associated with ataxia, myoclonus, and parkinsonism.[2] Brain MRI and CSF studies are usually normal. Diazepam or baclofen is used for symptomatic treatment along with immunotherapy (see *Stiff-Person Syndrome* in this issue).[13]

AntiGABAR-Associated Movement Disorders

Disease associated with antibodies to γ-aminobutyric acid type A receptor ($GABA_AR$) usually has a presentation with seizures and multifocal cortical and subcortical T2 lesions on MRI.[24] Children are more likely to develop a movement disorder with anti$GABA_AR$-associated disease than adults. Of 11 children with known cases, 7 developed orofacial dyskinesias, dystonic postures, or generalized choreoathetosis. Anti$GABA_AR$ antibodies are also, rarely, associated with SPS.[13] Anti$GABA_BR$ encephalitis is rare in children; a single case has been reported in a boy age 3, who presented with encephalopathy, seizures, and a mixed movement disorder including opsoclonus, ataxia, and chorea.[25]

Demyelinating Diseases

Movement disorders can occur in demyelinating diseases (eg, multiple sclerosis [MS] and neuromyelitis optica spectrum disorders [NMOSD]). Although it is rare, paroxysmal ataxia-dysarthria can occur in MS,[26] including children in the authors' experience. Brief recurrent stereotyped tonic spasms without loss of awareness occur, are often painful, can involve 1 or more limbs, and are triggered by sudden movement or stress. Tonic spasms can also occur in pediatric MS[27] and, in the authors' experience, in NMOSD.[28] Oxcarbazepine is most effective for symptomatic management.

Other Presumed Autoimmune Movement Disorders

OMAS. Associated with antiglutamate dehydrogenase type 2 (GluD2), opsoclonus myoclonus ataxia syndrome (OMAS) is a syndrome characterized by opsoclonus, nonepileptic myoclonus, ataxia, behavioral and sleep disturbances, and, sometimes, cognitive decline.[13] Neuroblastoma is detected in 50% of cases; OMAS occurs in 3% of children with neuroblastoma.[13] Brain MRI in the acute phase is generally normal. Antibodies to surface-expressed GluD2 and antiHu have been associated with OMAS.[13,29] In 75% of cases there is a chronic relapsing course and permanent neurologic sequelae, including cognitive and behavioral disorders.[13]

Poststreptococcal Movement Disorders. The most common cause for acute isolated chorea in children is Sydenham chorea (SC), which is poststreptococcal and considered immune-mediated, although no specific antibodies have been identified. Psychiatric symptoms can occur along with motor impersistence (eg, milkmaid sign, tongue darting, and pronator signs) and dysarthria.[2]

Pediatric autoimmune neuropsychiatric disorder associated with a streptococcal infection (PANDAS) and pediatric acute-onset neuropsychiatric symptoms (PANS) continue to be controversial diagnoses. Diagnostic criteria include an explosive onset of symptoms including movement disorders (eg, tics and chorea) and neuropsychiatric symptoms with a proposed immune-mediated mechanism. Validation of biomarkers and treatments, however, have been variable and require further investigation.[2]

SLE- and APS-Associated Movement Disorders. Systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) are complex autoimmune disorders that may present with several neurologic manifestations, including movement disorders.[9] Chorea is the most common movement disorder in SLE and also occurs more commonly in people diagnosed with APL in childhood (before age 15 years).[9] Parkinsonism is well described in SLE and dystonia is occasionally described in both conditions.[13] Up to 92% of people with SLE-associated chorea are seropositive for antiphospholipid (aPL) antibodies.[13] Other movement disorders in APL include hemidystonia, ataxia, and tics.[9] Improvement has been reported with haloperidol, tetrabenazine, valproic acid, clonidine, corticosteroids, aspirin, and D_2 antagonists (See *Movement Disorders in Antiphospholipid Syndrome and Systemic Lupus Erythematosus* in this issue). Plasmapheresis or IVIg has been used for refractory cases[9]; long-term immunosuppression with mycophenolate, cyclophosphamide, and rituximab has been used.[6]

Antibody-Negative Autoimmune Movement Disorder

Although it is difficult to make a diagnosis of an autoimmune disorder as the cause of neurologic symptoms without a positive laboratory test (Table 3), this is not unique to autoimmune disorders. For example, a negative finding on genetic testing does not rule out a genetic etiology because clinical genomic sequencing (genome or exome sequencing) has an average 33% yield even in targeted populations with presumed genetic etiologies. Yield of exome sequencing is 34.4% in dystonia, with a higher yield in complex dystonia or intellectual disabilities.[5] Consideration of an antibody-negative autoimmune movement disorder follows guidelines of antibody-negative autoimmune encephalitis, which includes clinical and paraclinical evidence of neuroinflammation (ie, CSF pleocytosis or CSF-specific oligoclonal bands and MRI features of encephalitis).[17,30] The majority of PANDAS/PANS patients would not meet the proposed criteria for pediatric autoimmune encephalitis.

Conclusion

As the field of autoimmune neurology expands, increased understanding of autoimmune causes for movement disorders will develop. In conjunction with genetic and metabolic evaluations, autoimmune evaluation should be considered in children with new-onset movement disorders, especially if accompanied by other neurologic symptoms. ■

TABLE 3. CRITERIA FOR AUTOANTIBODY-NEGATIVE BUT PROBABLE AUTOIMMUNE ENCEPHALITIS

In the absence of well-recognized autoantibodies in serum and CSF, there must be:

Onset	Rule Out	Diagnostic tests
Rapid (<3 months)	Well-defined auto-immune encephalitis syndromes (eg, typical limbic encephalitis, Bickerstaff's brainstem encephalitis, or ADEM)	MRI abnormalities suggestive of diagnosis
		OR
		CSF pleocytosis, CSF-specific oligoclonal bands or elevated CSF IgG index
AND	AND	OR
Includes working memory deficits, altered mental status, or other psychiatric symptoms	Reasonable exclusion of other causes	Brain biopsy showing inflammatory infiltrates and excluding other diagnoses (eg, tumor)

Abbreviations: ADEM, acute disseminated encephalomyelitis

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