Anti-N-Methyl-D-Aspartate Receptor Encephalitis

Encephalitis caused by antibodies to the N-methyl-D-aspartate receptor causes symptoms of movement disorders, seizure, and psychiatric disturbances.

By Nidhiben Anadani, MD

The immune-mediated encephalitis associated with antibodies against the N-methyl-D-aspartate receptor (NMDAR) causes neurologic and psychiatric symptoms, including memory deficits, seizures, frequent dyskinesia, autonomic dysfunction, decreased consciousness and hypoventilation. The estimated incidence is 1.5 per million per year, and the California Encephalitis Project study showed that antiNMDAR encephalitis is more common than viral encephalitis. Occurrence in childhood is more frequent (median age 21 years) and girls and women are affected more often than men (8:2 female: male). The presence of antiNMDAR antibody is pathognomonic and causes a constellation of symptoms according to the stage of disease. A movement disorder with unique features is one of the common manifestations of antiNMDAR encephalitis and can raise suspicion for this readily treatable disease.

Pathophysiology

The NMDAR is a major mediator of excitotoxic neurotransmission by glutamate and glycine and plays a crucial role in synaptic transmission, dendritic sprouting, gene regulation, and synaptic remodeling. Misregulation of these receptors by glutamate, however, leads to apoptotic (cell death) signaling. Such excitotoxic damage by glutamate at the NMDAR is implicated in neurodegenerative diseases (eg, Parkinson disease, Huntington disease, epilepsy, and dementia).

AntiNMDAR antibodies target the NR2B heteromers on the extracellular regions of NMDAR, expressed in the hippocampus and forebrain. The antiNMDAR antibodies are thought to play a pathogenic role because titers decrease as neurologic symptoms improve. There is also a decrease NMDAR levels found in cultured cerebrospinal fluid (CSF) samples containing NMDAR antibody. Intoxication by drugs with antagonistic action to NMDAR (eg, phencyclidine and ketamine) resembles the neuropsychiatric symptoms of antiNMDAR encephalitis.

Complex movement disorder symptoms are thought to be caused by basal ganglia dysfunction and disinhibition of the brainstem central pattern generator, which produces rhythmic motion via reticulospinal projections to the spinal neurons. Under normal physiologic conditions, this central pattern generator is tonically inhibited by the supratentorial GABAergic system. A decrease in supratentorial NMDAR activity reduces the GABAergic corticostriatal input, thus releasing the brainstem central pattern generator from inhibitory control.

Etiology and Triggers

The 2 well-established triggers for developing antiNMDAR antibodies are tumors, most commonly teratomas, and herpes simplex encephalitis (HSE). Tumor-associated antiNMDAR encephalitis is more common in women and more typically occurs between age 12 and 45 years. A higher incidence has been observed in people with Asian or African ancestry compared with those of European or Hispanic descent. Compared with teratomas without associated antiNMDAR encephalitis, teratomas associated with antiNMDAR encephalitis show high infiltration of neuroglia and immune cells suggesting that glia may be involved in triggering autoimmune neurologic disease.

In a prospective study of 51 participants with HSE, 27% developed autoimmune encephalitis, usually within 2 months of treatment for HSE. AntiNMDAR antibodies were the most commonly identified antibody (64% of cases). A systematic review of HSE-associated antiNMDAR encephalitis cases found the latency between HSE and antiNMDAR encephalitis is significantly lower in children vs adults (24 days vs 40.5 days).

Rarely, antiNMDAR encephalitis co-occurs with demyelinating disorders associated with antibodies to aquaporin-4 or myelin oligodendrocyte glycoprotein (MOG). AntiNMDAR encephalitis should be suspected in cases of neuromyelitis optica and other demyelinating disorders if there are atypical symptoms of psychosis and dyskinesia.

Clinical Presentation

A group of symptoms develop and progress according to stages of disease in antiNMDAR encephalitis. Initially, there is a
prodromal illness followed by psychiatric manifestations and prominent neurologic manifestations, including movement disorders, seizures, autonomic dysfunction, and impaired consciousness. Next, there is a long recovery stage (Figure) with persistent neurologic symptoms. Adults and children have different symptomatology; an observational study of 577 people with antiNMDAR encephalitis showed 65% of adults presented with behavior problems, whereas 50% of children under age 12 years presented with seizures or a movement disorder. Within the first 4 weeks of presentation, symptoms were similar across all ages, although movement disorders were still more common in children under age 12 years, and memory deficits and hypoventilation occurred more often in adults.10

Movement Disorder

Complex abnormal movements, sometimes hard to describe, associated with antiNMDAR encephalitis, occurred in 86% of people in a series of 100 cases. Movement disorders during antiNMDAR encephalitis are more frequent in children vs adults (87% vs 40%).13 There is no specific movement disorder phenotype of antiNMDAR encephalitis, however. Orofacial dyskinesias, choreoathetosis, and dystonia are among the most common, and athetosis, stereotypies, posturing, myoclonus, abnormal eye movements (eg, nystagmus, ocular dipping, and eye deviation), tremor, hemiballismus, and ballismus also occur.2,4 In an expert-rated video study, 7 experts rated 76 videos from 34 participants with antiNMDAR encephalitis and reported that movement disorder was an early presenting symptom and lasted for a median 112.5 days. Dystonia, chorea, and stereotypes were among the most common movement disorders, and 97% and 76% of participants had 2 or 3 of these, respectively.13 The presence of mixed movement disorders can help differentiate antiNMDAR encephalitis from other neurologic disorders in which the coexistence of dystonia, chorea, and stereotypes is uncommon.

Orofacial dyskinesia associated with antiNMDAR encephalitis is also different from that seen in other disorders. In antiNMDAR encephalitis, dyskinesias have a slower frequency (<3-6 Hz), are more widespread, and often persist in sleep and unresponsive states, causing self-injury.8

Presence of a movement disorder can help differentiate an HSE relapse from antiNMDAR encephalitis induced by HSE. In a retrospective analysis those with antiNMDAR encephalitis were more likely to have movement disorder symptoms and less likely to have seizure compared with those who had an HSE relapse.13

There is evidence that the duration and type of movement disorder associated with antiNMDAR encephalitis differs with age. In a retrospective analysis study of 28 individuals with antiNMDAR encephalitis, hyperkinetic movements (eg, choreoathetosis) were more common in children under age 10 years vs those age 10 years or more (14%). In contrast, hypokinetic movements (eg, catatonia and bradykinesia) were more common in those over age 10 years, whereas no person in this study under age 10 years had bradykinesia or ballismus. Although orofacial-lingual dyskinesia was equally present at all ages, it tended to last longer in those over age 10 years. Differences in type of movement disorder may relate to age-dependent differences in receptor distribution or sensitivity, dysfunction of different parts of the basal ganglia, or dopamine receptors.16

Stereotypies are often common in young children and range simple movements (eg, cycling of leg, thrashing movement of limb, repetitive flexion-extension of trunk, or head nodding) or complex (eg, raising and lowering of the arm, finger wiggling, learned movements of playing piano or harp, dance figures, or rolling-pills).7 Perseveration of a motor task (eg, moving hair behind the ear or scratching the nose) has been observed. Stereotypies may be difficult to differentiate from psychiatric symptoms or seizures, and prolonged clinical observation and videoEEG may help in defining symptoms clearly and guiding treatment appropriately.17

Oligosymptomatic presentation is a rare phenotype of antiNMDAR encephalitis, seen in 1% of cases and characterized by the presence of only 1 neurologic symptom, rather than the typical multiple neurologic and psychiatric symptoms. Because antiNMDAR can present with predominant movement disorder symptoms without major psychiatric or epileptic manifestations, antiNMDAR antibody testing should be considered in a new-onset, unexplained movement disorder in an appropriate clinical setting.18
Seizure
Seizure is a common symptom in the acute phase of anti-NMDAR encephalitis, occurring in 57% to 82% of cases. In a case series of 109 patients, there were recurrent seizures (30.7%), nonrefractory status epilepticus (25%), a single seizure (19.3%), refractory status epilepticus (14.8%), and super refractory status epilepticus (10.2%). The most common seizure type was generalized seizure (45.5%) followed by combined focal and generalized seizure (31.8%), and then focal seizure (22.7%). All individuals in this study were seizure free 2 years after participating without the need for long-term antiseizure medications. The presence of tumor, status epilepticus, coma, and intensive care unit (ICU) admission were predictive factors for recurrence of seizure after the acute phase.

Psychiatric Manifestations
Psychiatric symptoms are seen more commonly in adults than children (90% vs 42%). Although no specific psychiatric symptoms of anti-NMDAR encephalitis have been identified, a cohort study of 111 cases showed psychiatric symptoms were present in 59% and approximately 40% had been admitted to a psychiatric institution. The most common psychiatric manifestation in this cohort was visual and auditory hallucinations (40%) followed by depression (23%), acute schizoaffective episode (23%), mania (8%), and eating disorder or addiction (6%). Antipsychotic intolerance occurred in 47% of these individuals, requiring admission to ICU due to rhabdomyolysis, high temperature, muscle rigidity, mutism, and coma—some of which are also seen with anti-NMDAR encephalitis disease itself. In a meta-analysis that included 544 cases, agitation (59%) and psychosis (54%) were the most common psychiatric manifestations. Agitation was commonly seen in children, whereas psychosis was more common in adults.

Diagnosis
The clinical presentation and finding of anti-NMDAR antibodies in serum or CSF is highly suggestive of the diagnosis. Further aids to diagnosis include brain MRI, CSF analysis, and EEG. In a large cohort of individuals with anti-NMDAR encephalitis abnormal findings on EEG, CSF, or MRI were present in 90%, 79%, and 33% of cases respectively. In another series of 100 cases, 95 individuals had abnormal CSF findings, including lymphocytic pleocytosis, elevated protein concentration, and oligoclonal bands. Findings on EEG were abnormal and included generalized or frontotemporal slow activity and epileptic activity in 92 of the 92 persons who had EEG. Brain MRI in 55 cases using fluid-attenuated inversion recovery (FLAIR) sequence showed increased signal in various locations, including the medial temporal lobe, cerebral cortex, cerebellum, brainstem, and basal ganglia along with contrast enhancement in the cortex, meninges, and basal ganglia. Tumor screening showed the presence of teratoma in 58 of 98 individuals, 56 of whom were women. It is important to test CSF for anti-NMDAR because the CSF antibody assay is more sensitive than serum.

In 2016, a group of experts proposed diagnostic criteria for anti-NMDAR encephalitis, which includes a constellation of clinical, MRI, laboratory, and CSF findings along with tumor screening (Table). The proposed criteria have high sensitivity (90%) and specificity (96%) and provide a tool for early diagnosis of anti-NMDAR encephalitis within 2 weeks of first symptom onset.

**TABLE. ANTI-N-METHYL-D-ASPARTATE RECEPTOR ANTIBODY-ASSOCIATED ENCEPHALITIS DIAGNOSTIC CRITERIA**

<table>
<thead>
<tr>
<th>Probable</th>
<th>Definite</th>
</tr>
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<tbody>
<tr>
<td>Rapid$^a$ onset of 4 of 6 core symptoms listed below</td>
<td>Rapid onset of 1 of 6 core symptoms listed below</td>
</tr>
<tr>
<td>WITH laboratory findings of either</td>
<td>WITH findings of anti-NMDAR antibodies in CSF or serum</td>
</tr>
<tr>
<td>1. EEG: focal or diffuse slow or disorganized activity, epileptic activity, or extreme delta brush OR</td>
<td>If only serum is available, confirmatory tests must be done (eg, live neurons, tissue histoimmunochemistry, or cell-based assay)</td>
</tr>
<tr>
<td>2. Pleocytosis or oligoclonal bands in CSF analysis</td>
<td></td>
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<tr>
<td>OR rapid onset of 3 core symptoms plus systemic teratoma</td>
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</tbody>
</table>

**Must rule out other possible causes for probable or definite diagnosis**

<table>
<thead>
<tr>
<th>Core symptoms</th>
<th>Probable</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Abnormal (psychiatric) behavior or cognitive dysfunction</td>
</tr>
<tr>
<td>2</td>
<td>Speech dysfunction (pressured speech, verbal reduction, mutism)</td>
</tr>
<tr>
<td>3</td>
<td>Seizures</td>
</tr>
<tr>
<td>4</td>
<td>Movement disorder, dyskinesias, or rigidity/abnormal postures</td>
</tr>
<tr>
<td>5</td>
<td>Decreased level of consciousness</td>
</tr>
<tr>
<td>6</td>
<td>Autonomic dysfunction or central hypoventilation</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; NMDAR, N-methyl-D-aspartate receptor. $^a$Rapid onset defined as within a 3-month period
**Treatment and Prognosis**

Immunotherapy and tumor removal (if applicable) are the mainstay of treatment. In a large cohort of 577 people with anti-NMDAR encephalitis, 81% had good neurologic outcome at 24 months with first-line immunotherapy (ie, steroids, intravenous immunoglobulin [IVIG], or plasma exchange) and tumor removal if present. The risk of relapse is low (12% in this study) and most relapses were less severe than the initial presentation and often monosymptomatic. Risk of relapse is lower with the initiation of first-line immunotherapy during the acute phase of disease and further reduced by second-line immunotherapy (ie, rituximab, cyclophosphamide, or a combination of both) when used during a relapse. The factors associated with good outcome include not being admitted to the ICU, early treatment initiation, and low severity of disease in first 4 weeks of presentation. Abnormal movements typically respond well to immunotherapy, but tetrabenazine can be considered for uncontrolled hyperkinetic movements.

The Anti-NMDAR Encephalitis One-Year Functions Status (NEOS) score predicts neurologic outcome accurately at 1 year using various clinical and ancillary data. The NEOS score includes 5 independent risk factors for poor prognosis: 1) need for ICU admission, 2) no treatment within 4 weeks of symptom onset, 3) lack of clinical improvement in 4 weeks after starting therapy, 4) abnormal brain MRI, and 5) CSF white blood cell (WBC) count higher than 20 cells/L. The score ranges from 0 to 5, with 1 point assigned to each of these factors. A higher score is associated with higher modified Rankin scale score at 1 year.

**Conclusion**

Anti-NMDAR encephalitis is a commonly recognized and well-described type of autoimmune encephalitis affecting mostly young girls and women. The syndrome is initiated by teratoma or history of previous HSE. Clinical presentation is complex and includes a prodromal illness, psychiatric manifestations, neurologic symptoms (ie, movement disorder, epilepsy, or coma), and dysautonomia. Movement disorders are a common presentation that can often be complex and difficult to describe and persist during sleep or a comatose state and be self-injurious. Hyperkinetic movements are more common in children, whereas hypokinetic movement and catatonia are more common in teenagers and adults. Early-onset movement disorders can help differentiate anti-NMDAR encephalitis induced by HSE from a relapse of HSE.

Diagnosis is based on clinical presentation along with the use of ancillary tests especially CSF and serum assay for anti-NMDAR antibodies. Early initiation of immunotherapy within 4 weeks of treatment and tumor removal (if applicable) significantly improve long-term neurologic outcome. Admission to the ICU, a poor response to immunotherapy, abnormal brain MRI brain, and CSF pleocytosis indicate poor prognosis for neurologic recovery. Movement disorder symptoms improve with immunotherapy, although drugs (eg, tetrabenazine) can be used for refractory orofacial dyskinesia. Persons under age 50 with new-onset movement disorders with multiple abnormal movements should have testing for serum and CSF anti-NMDAR antibodies because early diagnosis and treatment improves long-term neurologic outcomes.

**Disclosures**

**NA reports no disclosures**