

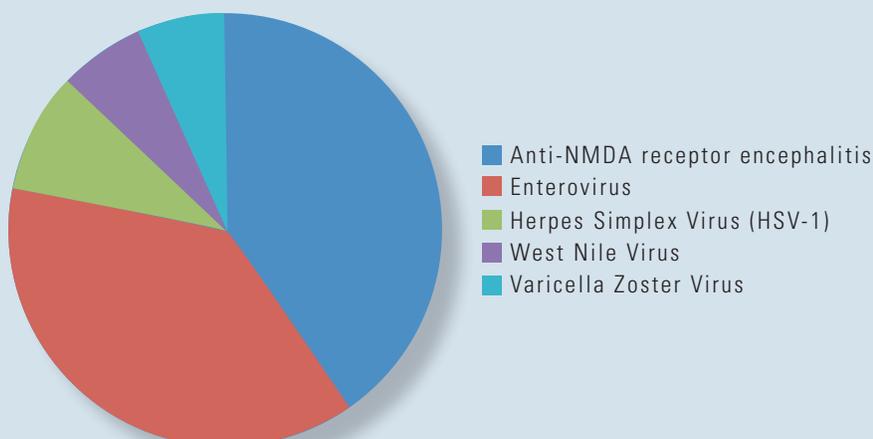
Diagnosing and Treating Anti-N-Methyl-D-Aspartate (NMDA) Receptor Encephalitis

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Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is an autoimmune condition in which the body produces antibodies that act against receptors in the brain, resulting in both neurologic and psychiatric symptoms. Common symptoms include personality change, psychosis, abnormal movements, seizures and autonomic dysfunction. The antibodies associated with this condition were first identified in 2005, and since then it has become recognized as one of the most common identifiable causes of encephalitis in children and young adults.

In the California Encephalitis Project, only 79 of 761 cases of encephalitis in individuals under age 30 had an identifiable etiology. Anti-NMDA receptor encephalitis accounted for 32 of those cases, and 65 percent of those patients were younger than 19. Additionally, the study showed that anti-NMDA receptor encephalitis may be more common than any single infectious cause of encephalitis, other than enterovirus.¹

Frequency of Identifiable Causes of Encephalitis
in the California Encephalitis Project



KEY INSIGHTS

- Anti-NMDA receptor encephalitis is a relatively common and treatable cause of encephalitis in pediatric patients.
- Common symptoms include personality change, abnormal movements, seizures and autonomic dysfunction.
- If these symptoms are present, an urgent child neurology evaluation is indicated and an evaluation for anti-NMDA receptor encephalitis should be initiated.
- Time-to-diagnosis and treatment of anti-NMDA receptor encephalitis have a significant impact on patient recovery and final outcome.

Clinical Presentation

Patients with anti-NMDA receptor encephalitis have a constellation of symptoms that are recognizable to providers familiar with the condition. However, comparisons of presentations among patients with this condition show significant variability. Most patients will exhibit multiple, but not all, possible symptoms of the condition. The order in which symptoms develop can vary from patient to patient, and not all symptoms may be present during the initial evaluation. Additionally, presentation varies by age group. Very young children present with symptoms that are distinct from those seen in teens and adults.

Psychiatric Symptoms

- The most common presenting symptoms in teenagers and adults include anxiety, insomnia, delusions, mania and paranoia.
- Young children tend to present with behavior changes, temper tantrums, hyperactivity and irritability, instead of overt psychotic symptoms.
- This initial phase is often followed by a stage with periods of alternating agitation and catatonia.
- Often the first provider to see the patient is a psychologist or psychiatrist.

Language Changes

- A reduction in spontaneous speech occurs in all age groups and may be a presenting symptom in pediatric patients.
- A progression to mutism is very common in pediatric patients and may also be seen in adults.

Movement Disorders

- Almost all patients will develop abnormal movements during the course of the disease.
- Oro-lingual-facial dyskinesias, such as chewing movements and tongue rolling, are the most characteristic movements.
- Abnormal movements of the trunk and extremities, including chorea, dystonia and rigidity, are also frequently seen.
- Young children may have ataxia or difficulty walking and may even lose the ability to walk.

Seizures

- New onset seizures are common and occur in 50 to 75 percent of patients.
- Common seizure types include focal seizures, motor seizures, complex partial seizures and generalized convulsions.
- Patients are at risk for status epilepticus—prolonged seizures lasting longer than 30 minutes.

Autonomic Dysfunction

- The most frequent autonomic manifestations include fever, tachycardia, hypertension, bradycardia and hypersalivation.
- A small percentage of patients develop hypoventilation, even when consciousness is preserved, and require respiratory support.
- Close monitoring of vital signs is recommended for all patients.

Differential Diagnosis

The differential diagnosis of anti-NMDA receptor encephalitis is broad and includes infectious causes of encephalitis, such as herpes simplex virus; acute disseminated encephalomyelitis (ADEM); inborn errors of metabolism, including urea cycle disorders; environmental toxins and medication overdoses; rheumatologic conditions, such as neuropsychiatric lupus; and primary psychiatric conditions, such as schizophrenia. Due to the extensive differential diagnosis, the diagnostic work-up of each patient must be individualized based on the presentation, and consultation with a child neurologist is recommended.

Diagnostic Tests

Cerebrospinal Fluid (CSF) Evaluation

- CSF will be abnormal in up to 90 percent of patients.
- More than 80 percent of patients will have positive oligoclonal bands, which are antibodies in the CSF that are not found in the serum.
- Up to 75 percent of patients will have elevated CSF white blood cell counts, usually with lymphocytic predominance, but neutrophilic predominance can also be seen.
- Approximately 10 to 15 percent of patients will have elevated protein concentrations.
- Anti-NMDA receptor antibodies can be found in the CSF as well as the serum.

MRI of the Brain

- For 50 percent of cases, MRIs will appear normal.
- The most common abnormal finding is nonspecific T2 hyperintense lesions involving the gray and/or white matter of the cortex, basal ganglia or brainstem; spine lesions are rare.
- The changes are usually mild and transient, but can occasionally be extensive.

- Occasionally, brain MRIs will show white matter lesions with associated enhancement after contrast that is consistent with demyelination. Patients with demyelinating lesions and confirmed anti-NMDA receptor encephalitis should be tested for anti-NMO antibodies, which have been found in this subset of patients.

Electroencephalogram (EEG)

- EEGs are used to assess the background activity and to evaluate for seizures.
- Most patients with anti-NMDA receptor encephalitis will have an abnormal EEG at some point in their disease course.
- 90 percent of patients will have slowing of background frequencies.
- 25 to 50 percent will have epileptic features, such as spike and wave discharges or captured seizures.

Infectious Disease Evaluation

- The evaluation for viral encephalitis is individualized, and depends on time of year and geographic location.
- Every patient should be tested for herpes simplex virus (HSV).
- The infectious disease team is often consulted to co-evaluate the patient.

Tumor Evaluation

- The first cases of anti-NMDA receptor encephalitis were described in young women with ovarian teratoma. In these patients, the body's immune response to this benign tumor resulted in production of the antibodies which cross-reacted with the patient's brain.
- Tumors, specifically teratoma, are found in less than half of adults with this condition and become increasingly rare in younger patients.
- Every patient with anti-NMDA receptor encephalitis should undergo a tumor evaluation.

Treatment

- Medications are used to decrease the circulating disease-causing anti-NMDA receptor antibodies and the body's overactive immune response.
- **Methylprednisolone** is an IV steroid that can be given at high doses and is often used with IV immunoglobulins (IVIG) as first-line therapy.
- **IVIG** are pooled antibodies, given by IV, that result in the body degrading circulating antibodies, including the anti-NMDA receptor antibodies that are disease-causing.
- **Rituximab** is a monoclonal antibody, given by IV, that targets the body's antibody producing cells and stops ongoing production of anti-NMDA receptor antibodies. It is often used as a second-line therapy for those patients whose recovery after receiving first-line treatments is inadequate.

- Other medications are often needed to treat specific symptoms, such as seizures, abnormal movements or psychosis.
- Rehabilitation programs, with intensive physical, occupational and speech therapy, are important to help patients regain function, and an inpatient admission to a specialized rehabilitation unit is often required.

Outcomes

At least 75 percent of patients will have substantial recovery. The rate and degree of recovery appear to be related to how quickly a diagnosis is made and treatment is begun using appropriate immunomodulating agents. There is limited information about cognitive and psychological outcomes in these patients; however, my experience suggests that these problems are under-recognized in patients with otherwise excellent neurologic recovery.

Conclusion

Anti-NMDA receptor encephalitis is a relatively common and treatable cause of encephalitis in pediatric patients. Any child presenting with personality change or psychiatric symptoms should be evaluated for co-existing neurological symptoms such as abnormal movements or new seizures. If these symptoms are present, an urgent child neurology evaluation is indicated and an evaluation for anti-NMDA receptor encephalitis should be initiated. Time-to-diagnosis and treatment of anti-NMDA receptor encephalitis have a significant impact on patient recovery and final outcome. We welcome your questions and referrals.

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¹ Gable MS, Sheriff H, Dalmau J, Tilley DH, Glaser CA. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 2012;54:899-904.

Additional Resources

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Author PROFILES



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Pediatric neurologist Amanda Moen, M.D., treats children who have epilepsy and other neurological conditions. She received an M.D. from the University of Iowa's Carver College of Medicine in Iowa City, Iowa, and completed a pediatric residency and a child neurology residency at The Children's Hospital Colorado in Denver. Her professional interests include anti-NMDA receptor encephalitis, neuroimmunology, leukodystrophies and other metabolic and genetic neurological disorders.



Young Child With Anti-NMDA Receptor Encephalitis

History: The mother of a 4-year-old girl brought her daughter to the emergency room because of a change in behavior. She reported that the girl had seemed sad and unlike herself for one week. She first noticed her daughter having frequent episodes of crying for no apparent reason. During the preceding week, the girl also seemed more tired than normal, and she had low grade fevers to 100.1 F. Four days earlier, her mother observed that her daughter seemed to be constantly playing with her tongue, chewing on it and running it over her teeth. She also noticed that the girl seemed to be fidgeting with her hands more, “like she was anxious and couldn’t keep them still.” The patient was seen by her pediatrician and a psychologist and they felt she was depressed. Over the next two days, she stopped speaking, began sleeping very little and developed an unsteady gait. Shortly after admission to the hospital, she had a new spell that consisted of stiffening her right arm and staring.

Evaluation: On neurologic examination, the child had continuous oro-lingual dyskinesias, chorea of her upper extremities and was unable to walk. She was mute but attentive. She underwent blood work and a spinal tap. Her spinal fluid showed nine white blood cells. An extensive infectious workup was negative. MRI of the brain with and without contrast was normal. Her serum was positive for anti-NMDA receptor antibodies. An EEG was done to evaluate the episodes of staring and arm stiffening and confirmed that these events were seizures.

Treatment: She had the classic clinical presentation for a young child with anti-NMDA receptor encephalitis. Specifically, she was a young child whose change in mood/personality was accompanied by multiple neurologic symptoms including a movement disorder, mutism and seizures. Due to the clinical picture, treatment with IV methylprednisolone and IV immunoglobulins (IVIg) was initiated after CSF cultures were negative for 24 hours. She was started on oxcarbazepine for seizure control.

Outcome: She required a 10-day admission to the inpatient rehabilitation unit. At discharge, she walked independently and was able to say a few words with prompting. One month after discharge, her mother reported that the girl is still less talkative than before her illness, but this is the only remaining symptom.

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New Physician Joins Gillette

Joy Taber, M.D., is board-certified in physical medicine and rehabilitation. She cares for adult patients who have cerebral palsy, spina bifida and other childhood-onset conditions. She received a medical degree and completed her residency in physical medicine and rehabilitation at the University of Minnesota School of Medicine in Minneapolis. In addition, she served as a U.S. Air Force flight surgeon. She is a member of the American Academy of Physical Medicine and Rehabilitation, American Medical Association and Minnesota Medical Association. She sees patients at Gillette Lifetime Specialty Healthcare.