# Emergency Department Presentations of Anti–*N*-Methyl-D-Aspartate Receptor Encephalitis

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**Abstract:** Anti–*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an acute autoimmune neurological disorder that presents with acute to subacute psychiatric and/or neurological complaints including new onset behavioral changes that may evolve to psychosis and catatonia, cognitive decline, new onset seizures, progressive encephalopathy, and/or movement disorders. Female teens and adults often have an associated ovarian teratoma as an underlying etiology, but most pediatric patients do not have an identifiable associated neoplasm. The diagnosis requires confirmatory serum and/or cerebrospinal fluid analysis findings of anti-NMDAR antibody titers. It can be misdiagnosed as a psychiatric condition or a viral encephalitis. The clinical features that distinguish anti-NMDAR encephalitis from a primary psychiatric disorder are the acute onset of the mood and behavioral changes with no prior history, the waxing and waning of consciousness (delirium/encephalopathy), and primary neurological features such as seizures and abnormal involuntary movements, including dyskinesias and dystonias. The prognosis is improved with earlier recognition and prompt immunotherapy treatment, making this an important diagnosis for emergency physicians.

**Key Words:** NMDA receptor, NMDAR, anti-NMDAR encephalitis, encephalitis, dyskinesia, seizures, teratoma, paraneoplasia, psychosis, neuroautoimmune syndrome, paranoia, hallucinations, agitation, mutism

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## TARGET AUDIENCE

This CME article is intended for pediatric emergency medicine physicians, emergency medicine physicians, pediatricians, nurse practitioners, nurses, physician assistants, respiratory therapists, and any other medical personnel involved in the care of children presenting with acute care conditions that could present with neurological or psychiatric symptoms.

## LEARNING OBJECTIVES

After completion of this CME article, readers should have improved their knowledge of and enhanced their competence to:

1. Clinically describe the diagnosis of anti-NMDAR encephalitis
2. Interpret laboratory testing pertinent to confirming anti-NMDAR encephalitis
3. Distinguish a primary psychiatric problem from an anti-NMDAR encephalitis.

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The authors have disclosed that the U.S. Food and Drug Administration has not approved the use of the drugs and IVIG described in this article for the treatment of anti-NMDAR encephalitis due to the rarity of this condition. Please consult the products' labeling for approved information.

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## Case 1

A 10-year-old Pacific Islander boy presented to the emergency department (ED) with a new onset seizure disorder. Despite anticonvulsants, he later returned to the ED for status epilepticus and again for a breakthrough seizure. Seventeen days after his initial seizure, he developed agitation, paranoid ideation, as well as auditory and visual hallucinations. Four days after this, he returned to the ED with altered mental status, agitation, and confusion. His past and family histories were negative for psychiatric disease. His cerebrospinal fluid (CSF) analysis showed 56 white blood cells (90% lymphocytes) and 108 red blood cells per microliter, protein at 116 mg/dL (elevated), and glucose at 75 mg/dL. Cerebrospinal fluid oligoclonal bands were positive. Cerebrospinal fluid anti–*N*-methyl-D-aspartate receptor (anti-NMDAR) titer was positive. Imaging result was negative for tumors. Initial combativeness and agitation were refractory to infusions of dexmedetomidine, midazolam, and ketamine. He eventually was treated with risperidone, intravenous immune globulin (IVIG), and high-dose corticosteroids. He was discharged home after 10 weeks nearly back to his baseline function. He was subsequently continuing in mainstream middle school without academic difficulties. There were mild behavioral difficulties that were likely present before his illness.

## Case 2

A 15-year-old girl of mixed Polynesian ethnicity presented with vertigo to her primary care physician (PCP) who prescribed meclizine. She presented to the ED the next day and the next day again with headaches, dizziness, and nausea. She then presented to her PCP with blurred vision. The result of a computed tomographic scan of her brain was normal. Thirteen days after her initial vertigo, her family noted increased emotional lability. Two days later, she was brought to the ED with altered mental status, severe agitation, combative behavior, paranoia, and memory deficits. Her past and family histories were negative for psychiatric disease. Her combative behavior and agitation were controlled with intramuscular olanzapine. The results of her electroencephalogram (EEG) and brain magnetic resonance imaging (MRI) scan were normal. Cerebrospinal fluid showed 9 white blood cells (95% lymphocytes), and less than 1 red blood cells per microliter, protein at 41 mg/dL, and glucose at 71 mg/dL. Oligoclonal bands were negative. Anti-NMDA CSF titer was positive. A pelvic ultrasound demonstrated a right adnexal mass. The mass was removed, which proved to be a mature cystic teratoma with significant neuroglial tissue with multiple lymphoid aggregates. She was treated with plasmapheresis, IVIG, corticosteroids, and olanzapine. She was discharged after 3 weeks of hospitalization. She returned to her baseline neurocognitive state.

## Case 3

A normal 3-year-old girl was noted to have increased sleep restlessness and bed wetting multiple times per night. Approximately 2 weeks later, she developed limping with ataxia, intermittent involuntary movements, and wanted to be carried more. Four

days later, she was hospitalized when she developed hyperkinetic movements and difficulties sitting up on her own, and she was not interested in playing with other children. An evaluation showed a normal CSF profile, a normal MRI brain scan result, and elevated streptococcal serologies, suggesting the possibility of Sydenham chorea. On day 5 of hospitalization, she became more somnolent and had a seizure. A follow-up CSF profile showed a pleocytosis and an elevated protein. She was empirically started on IVIG for suspected anti-NMDAR encephalitis. By this time, the anti-NMDAR assay on the initial CSF sample returned as positive. The second CSF sample had a rising anti-NMDAR titer as the patient became more encephalopathic. She had a 6-month hospitalization with multiple courses of IVIG, high-dose corticosteroids, plasmapheresis, rituximab, and cyclophosphamide. At discharge, she required gastrostomy tube feeding, she was nonverbal, and she had very limited purposeful motor activity with spasticity and clonus, requiring a wheelchair. She continued on monthly Cyclophosphamide and IVIG treatments. Two years after her initial presentation, she eventually made a complete functional recovery and was back in mainstream schooling but had no recollection of her previous hospitalization.

### Brief Case 4

A child was admitted to a psychiatric hospital for a new onset psychosis. After several days, the psychiatry staff suspected anti-NMDAR encephalitis and transferred the patient to a children's hospital where the diagnosis was confirmed and treatment was successful.

### Brief Case 5

A patient with a refractory encephalopathy of unknown cause was doing poorly. Medical support was about to be withdrawn. An anti-NMDAR test returned positive. The patient recovered after immunotherapy.

## INTRODUCTION

What condition should be considered in pediatric patients presenting with a variety of acute new onset neurological and/or psychiatric symptoms including psychosis, mutism, encephalopathy, movement disorders, and/or seizures? The discovery and increased understanding of anti-NMDAR encephalitis have changed the diagnostic approach to a variety of clinical problems such as acute psychosis, catatonia, subacute memory disturbance, new onset seizures, dyskinesias, and limbic encephalitis.[1] With increased awareness of this disorder, the disease is also being more frequently recognized in younger teenagers and children. Prompt recognition and treatment with immune therapy and tumor removal (in paraneoplastic cases) have the potential to improve prognosis and long-term outcome.[2,3]

Anti-NMDAR encephalitis is an acute autoimmune neurological disorder first described in adults in 2005,[4] the majority of whom had ovarian teratomas.[2–4] Subsequently, the target antigen for this paraneoplastic condition was identified as the NMDAR.[2,3] Children were subsequently described with anti-NMDAR encephalitis, although the majority did not have an associated neoplastic condition.[5]

The NMDARs are glutamate receptors and ligand-gated cation channels with crucial and complex roles in synaptic transmission and plasticity of neural networks.[3,6–8] The NMDAR is composed of subunits known as NR1 and NR2. NR1 subunits and varying types of NR2 subunits combine (most commonly as tetramers) to form varying NMDAR subtypes with distinct neurological function, pharmacological properties, anatomical distribution, and interactions with other receptors and intracellular messengers.[3,8,9] NR1 and NR2 are also known as GluN1 and GluN2 (newer terminology). The density and type of NMDAR vary with brain location and age. The NMDARs are widely distributed throughout the brain including the limbic system with involvement in learning, memory, and emotion. *N*-methyl-D-aspartate receptors in the prefrontal cortex and frontostriatal structures play an essential role in executive functioning, including the ability to plan and organize behaviors, sustain attention, and regulating behavior and emotion.

Suffice it to say that NMDAR activity is highly complex but critically important to normal behavior and cognitive function. To better understand the complexities of the NMDAR, we can look at the manner in which phencyclidine (PCP) antagonizes NMDARs resulting in prominent psychiatric symptoms ranging from acute psychosis, paranoia, and agitation to catatonia resembling symptoms seen in schizophrenia.[10] *N*-methyl-D-aspartate receptors are present on presynaptic gamma-aminobutyric acid (GABA) neurons, and antagonizing these NMDARs leads to disinhibition.[10] Ethanol and dextromethorphan affect the NMDARs, leading to hallucinogenic effects. The anesthetic effects of the drugs ketamine and nitrous oxide are partially caused by their effects on NMDARs leading to dissociative effects. The hyperactivation of NMDARs has been shown to cause excitotoxicity to mediate acute neuronal death and chronic neurodegeneration and is a proposed underlying mechanism for epilepsy, dementia, and stroke.[11–14] In contrast, the hypoactivation of NMDARs is involved in the development of psychiatric states and may produce symptoms of schizophrenia.[12–16]

Anti-NMDAR encephalitis research demonstrated that the target antigen of patients was the NR1 subunit of the NMDAR.[3] The "anti-NMDAR antibody" is actually an anti-NR1 antibody, although rare cases of anti-NR2 encephalitis have been described.[10] Despite the severity of the disorder, patients often recovered after tumor removal and immunotherapy, suggesting a reversible immune-mediated pathogenesis.[3] Application of NMDAR antibodies into cultures of hippocampal neurons resulted in a concentration-dependent reduction of postsynaptic dendritic NMDAR clusters that reversed after antibody removal.[3,17,18] Similarly, antibodies in CSF from patients with anti-NMDAR encephalitis led to the loss of surface NMDARs and reduced NMDAR function.[1,18]

Female patients (12–45 years of age) with anti-NMDAR encephalitis often have associated ovarian teratomas[2,3,19,20] that express NR1 antigens that stimulate antibodies.[3,5] Other tumors associated with anti-NMDAR encephalitis include sex-cord stromal tumor, neuroendocrine tumor, teratoma of the mediastinum, small cell lung cancer, and lymphoma.[3,5,21,22] Cases in children are less likely to have tumors.[5] Although most pediatric patients with tumors also had teratomas, a case with neuroblastoma and another with Hodgkin lymphoma have been reported.[23,24]

Because the majority of pediatric patients with anti-NMDAR encephalitis do not have coexisting tumors identified, other unknown immunological triggers are presumed to be involved. Although an infectious cause might be suspected given the high frequency of a viral type of prodrome, a consistent pathogen has not been identified despite extensive testing on many patients. There are a few isolated and uncommon case reports of anti-NMDAR encephalitis in association with mycoplasma, human herpes virus 6, and herpes simplex virus.[22,25–27]

A possible mechanism underlying the development and progression of anti-NMDAR has been suggested. At the acute stage, intrathecal production of anti-NMDAR antibodies induces the internalization of NMDARs, reducing the density of neuronal surface NMDARs, resulting in neuronal hypoactivity with associated psychiatric and/or neurological symptoms. At the chronic/recovery stage after the level of anti-NMDAR antibodies subsides

and the blood-brain barrier is restored, the level of anti-NMDAR antibodies in the CSF decreases. Then as the NMDARs are expressed on the neuronal surface again, neuronal function recovers with improvement/resolution of associated psychiatric and/or neurological symptoms.[28]

Anti-NMDAR encephalitis is a newly described entity, but it is only part of a spectrum of neuroautoimmune syndromes that have been identified by the discovery of other new autoimmune antibodies. Autoantibodies to the multitude of receptors and other important central nervous system antigens result in encephalopathies related to the dysfunction of these specific receptors/molecules. Examples include anti-LGI1 (leucine-rich glioma inactivated 1, previously known as the voltage-gated potassium channel, VGKC), anti-NMO (neuromyelitis optica), anti-AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid), anti–GABA-B (gamma-amino butyric acid-B), anti-CASPR2 (contractin-associated protein-like 2), ANNA-1 (type 1 antineuronal nuclear antibody, also known as anti-Hu), anti-Ma2 (no spell out), and anti-GAD65 (65-kd variant of glutamic acid decarboxylase).[29–31]

All drugs and IVIG described in this article are off-label uses because of the rarity of this condition.

## Epidemiology

Anti-NMDAR encephalitis commonly occurs in young females but has been reported in males and females of all ages (from 8 months to 85 years).[1,3,19,21] Epidemiological studies suggest that anti-NMDAR encephalitis is among the most common causes of known antibody-associated autoimmune encephalitis. A multicenter population-based study of causes of encephalitis in the United Kingdom showed that 4% of patients had anti-NMDAR encephalitis, which was the second most common immune-mediated cause, after acute disseminated encephalomyelitis (ADEM).[32] In a center that is focused in the study of encephalitis of unclear etiology (California Encephalitis Project), the frequency of anti-NMDAR encephalitis was 4% (32 confirmed cases of 761 cases of encephalitis of uncertain etiology), which was more common than herpes, West Nile virus, and enteroviral encephalitis.[33] In a study in the United Kingdom and Europe, 11% of the patients suspected of having encephalitis were positive for anti-NMDAR antibodies.[19] In a retrospective single-center cohort of 164 Australian children, 34% had an immune-mediated/autoantibody-associated encephalitis with anti-NMDAR encephalitis detected in 6% (second most frequent, ADEM most frequent), even with CSF testing performed on only a subset of patients.[34] These studies are consistent to find that anti-NMDAR encephalitis is not rare, and it should be considered prominently in the differential diagnosis.[33]

## Clinical Features

Nonspecific prodromal symptoms such as fever, headache, upper respiratory symptoms, vomiting, and diarrhea are observed in 48% to 86% of patients within less than 2 weeks before hospital admission.[3,5,25] The more specific symptoms leading to the diagnosis include agitation, memory loss, confusion, delirium, emotional disturbances, psychosis (delusions and hallucinations), seizures, dyskinesias, mutism, sleep disturbances, and autonomic instability.[3,5,21,35] These symptoms evolve to become more polysymptomatic over time.

Adolescents and young adults may present with a greater incidence of psychiatric symptoms including paranoia, severe anxiety, insomnia, auditory and visual hallucinations, agitation, disorganized behavior, memory disturbance, and mood lability.[1] Given the predominance of psychiatric symptoms, the initial presentation can often be confused with a manic or psychotic episode or with drug intoxication.[35]

In contrast, the early behavioral changes in young children can be subtle and nonspecific (and possibly ignored) such as temper tantrums, hyperactivity, or irritability. The diagnosis becomes more apparent with the onset of neurological symptoms, such as seizures, gait abnormalities, movement disorders, verbal reduction, or mutism.[1]

Seizures occur in approximately 75% of patients. Most of these are generalized tonic-clonic seizures, but focal seizures, refractory status epilepticus, and nonconvulsive status epilepticus have occurred.[3,5,36,37] Dyskinesias may include orofacial involuntary movements (eg, grimacing, chewing) and chorea, spastic rigidity (sometimes to the point of rhabdomyolysis), and dystonic posturing. Movement disorders are usually hyperkinetic, but parkinsonism has also been described.[31,38] The dyskinesias may seem similar to tardive dyskinesia and orofacial dyskinesias that can be a long-term adverse effect of some antipsychotic medications, which can be confusing if patients were treated with antipsychotic medications earlier in the course of the disease.

Later clinical findings, often days to weeks into the course of illness, may include sleep disturbances, aphasia/mutism, and unresponsiveness with catatonic features. The rapid disintegration of language, from reduction of verbal output and echolalia to frank mutism, may be more similar to that seen in schizophrenia rather than attributed to a cortical aphasia.[1] During this phase of illness, individuals may stop eating and drinking and will often need assistance in most, if not all, activities of daily living. During this phase, individuals may alternate between periods of agitation and catatonia.[1]

Autonomic instability may also be a later clinical finding, resulting in fluctuations of hyperthermia, tachycardia/bradycardia, hypertension/hypotension, hypersalivation, and/or hypoventilation. Supportive care may require vasopressors, pacemakers, and/or intubation for mechanical ventilation.[3,5]

Agitation may worsen in the hyperkinetic phase. Of note, this phase is just before the phase of gradual recovery, so agitation and autonomic instability may initially worsen before gradual improvement.[1]

## Differential Diagnosis

The clinical features that distinguish anti-NMDAR encephalitis from a primary psychiatric disorder are the acute onset of the mood and behavioral changes with no prior history, the waxing and waning of consciousness (delirium/encephalopathy), and primary neurological features such as seizures and abnormal involuntary movements, including dyskinesias and dystonias (Table 1).

In a toddler or child, the differential may include viral encephalitis, ADEM or other postinfectious or parainfectious autoimmune or inflammatory encephalitis, drug intoxication, or neuroleptic malignant syndrome. In an adolescent or young adult, the differential diagnosis may include a primary psychiatric disorder, drug abuse, neuroleptic malignant syndrome, adverse effects of antipsychotic medications (tardive dyskinesia, acute dystonic reaction), or infectious encephalitis. Other considerations may be manifestations of an epileptic condition, confusional migraine, postinfectious movement disorder, or psychogenic problems. Similarly, if any of these are in the differential, then anti-NMDAR encephalitis should be a serious consideration as well.

## Diagnostic Evaluation

The results of conventional investigations for encephalitis, including CSF examination, brain imaging, and EEG are fairly

**TABLE 1.** Differential Diagnosis for Acute Neurologic/ Psychiatric Symptoms With Encephalopathy

- Infectious encephalitis: herpes simplex virus, mycoplasma, enterovirus, human herpes virus 6, Epstein-Barr virus, influenza, etc
- Autoimmune/inflammatory encephalitis: ADEM, anti-NMDAR, anti-LGI1, anti-AMPA, anti-CASPR2 and other postinfectious or parainfectious autoimmune or inflammatory encephalitis, neuropsychiatric systemic lupus erythematosus, vasculitis
- Drug intoxication/drug abuse: phencyclidine, ketamine, MDMA (3,4-methylenedioxy-methamphetamine), cathinone (bath salts), cannabinoids, psilocybin mushrooms, serotonin syndrome
- Adverse effects of antipsychotic medication: neuroleptic malignant syndrome tardive dyskinesia, acute dystonic reaction
- Primary psychiatric disorder: brief reactive psychosis, major depressive disorder with psychotic episode, Kleine-Levin syndrome
- Epileptic condition: nonconvulsive status epilepticus, febrile infection related epilepsy syndrome (FIRES)
- Acute confusional migraine
- Postinfectious movement disorder
- Psychogenic problem

nonspecific for anti-NMDAR encephalitis and may be normal early in the disease course.

The prodromal symptoms may be signs of an early systemic immune activation, but the immune system abnormalities in the central nervous system eventually predominate. Cerebrospinal fluid is initially abnormal in approximately 80% (68%–91%) of patients and becomes abnormal later in the disease in most of the other patients.[3,19,25] Findings may include a mild-to-moderate lymphocytic pleocytosis and mildly increased protein concentration, and 60% of patients have CSF-specific oligoclonal bands[3,19,25] (suggesting an abnormal clone of cells producing an antibody).

*N*-methyl-D-aspartate receptor antibody testing is critical for the diagnosis of anti-NMDAR encephalitis because other clinical examination results are nonspecific. Anti-NMDA titers are higher in the CSF than in the serum. Cerebrospinal fluid titers can be positive when serum titers are negative.[3,21] Cerebrospinal fluid anti-NMDAR titers were reported to be 100% sensitive, compared with serum that was 86% sensitive.[20] Obtaining a reliable test result in a timely fashion can be a problem because this test is not routinely performed in most laboratories.

The "anti-NMDAR" assay is actually an immunofluorescence assay for anti-NR1 (the antibody to the NR1 subunit).[39] Thus, if there is a rare case of anti-NMDAR encephalitis in which the antibody is directed against the NR2 submit,[10] this anti-NMDAR assay would not necessarily be positive.

Electroencephalogram usually demonstrates a nonspecific encephalopathy with generalized or frontotemporal slowing or disorganized activity.[3,19,25] Initial EEG background may be normal in some patients but deteriorates with clinical progression. Epileptiform discharges are seen in only a minority of patients. A unique electroencephalographic pattern, "extreme delta brush," may be seen in approximately 30% of cases and is associated with EEG evolution of seizures and status epilepticus.[22,25,40] Other EEG abnormalities have been reported, which are beyond the scope of this report.[36,37,41,42]

Magnetic resonance brain images may initially appear normal. Up to half the patients eventually show hyperintensities on T2-weighted sequences or FLAIR [fluid-attenuated inversion recovery] images of the medial temporal lobes, corpus callosum, and/or cerebral cortex.[3,19,21,25] A minority of these patients may have faint or transient contrast enhancement of the cerebral cortex, the overlaying meninges, and/or basal ganglia.[3] Patients with follow-up MRI studies showed that many of those who recovered completely or those with only mild residual deficits had improved or normalized findings on subsequent MRI.[3]

The clinical suspicion of anti-NMDAR encephalitis should lead to the search for a neoplasm. Although younger children most often have nonparaneoplastic anti-NMDAR encephalitis, it is still worthwhile to search for neoplastic causes because tumor removal has proven to be the most expedient and effective means of treatment in cases that are tumor related. Tumors associated with anti-NMDAR encephalitis are most commonly ovarian teratomas in females and testicular germ-cell tumor in males.[1,3] Identification of microscopic tumors can lead to therapeutic resection, and some postmortem cases have identified microscopic teratomas.[43–45] Subsequent ongoing periodic screening for ovarian teratomas for at least 2 years after the diagnosis has been recommended,[1] even if patients have clinically recovered from the encephalitis.

## Management

The initial ED management often initially focuses on managing the patient's confusion and agitation thought to be secondary to delirium and psychosis. Atypical antipsychotic medications, such as olanzapine, quetiapine, and risperidone, have been shown to be effective in managing delirium symptoms in both adult and pediatric patients while the underlying etiology was being addressed.[46] Atypical antipsychotic medications are preferred given the lower incidence of extrapyramidal symptoms, dystonias, and dyskinesias, as compared with typical antipsychotics, such as haloperidol. Olanzapine is available intramuscular and as an orally disintegrating tablet formulation and can be very effective in the acute management of severe agitation/psychosis associated with anti-NMDAR encephalitis. Higher doses of antipsychotic medications may be required (compared with the usual management of delirium) to control the psychiatric symptoms present in anti-NMDAR encephalitis.

A randomized controlled trial of the treatment for anti-NMDAR encephalitis has not been reported, but based on case series and retrospective reviews in the literature, the most effective treatment for anti-NMDAR encephalitis includes immunotherapy (to reduce the amount and production of circulating anti-NMDAR antibodies) and tumor removal when possible because it expedites improvement and reduces the risk of relapse.[1]

First-line therapy usually includes high-dose intravenous corticosteroids, intravenous immunoglobulins, and/or plasma exchange. In patients who fail to respond (often without a tumor or with a delayed diagnosis), second-line therapies such as cyclophosphamide, monoclonal antibodies (eg, rituximab), as well as azathioprine, mycophenolate mofetil, tacrolimus, and/or methotrexate may be used in sequence or sometimes in combination.[1,3,5,21] Although a few patients retrospectively identified with anti-NMDAR encephalitis had recovered to their normal state with only supportive care alone (ie, the untreated natural course is occasionally good), there may be a greater tendency for relapse, and most of the patients eventually required further treatments such as tumor resection and immunotherapy.[1,3,21]

A multidisciplinary approach in the rehabilitation and recovery phases of anti-NMDAR encephalitis is essential and often consists of physical therapy, occupational therapy, speech therapy, and behavioral health (psychology/psychiatry). Cognitive therapy for pediatric patients is often best done through school, although certain accommodations may be necessary, depending on the stage of recovery.[47,48]

Because relapses occur in approximately 25% of patients,[3,5,19,21,49] more commonly in those without teratoma, prolonged immunosuppression might be recommended for patients. The ED might encounter these patients on prolonged immunosuppression, or patients might present to the ED with relapsing symptoms that would require the reinitiation of immunotherapy. The mean time to relapse was 2 years, ranging from 1 month to 13 years.[3,49]

## Prognosis

Approximately 75% to 81% of patients with anti-NMDAR encephalitis recover fully or have mild sequelae.[3,20] Studies report mortality rates from 4% to 10% with identified causes including sepsis, sudden cardiac arrest, acute respiratory failure, refractory status epilepticus, withdrawal of support, or tumor progression.[1,3,20,21]

Identification of a teratoma is a good prognostic sign because tumor resection and immunotherapy have a faster clinical response and a reduced need for second-line immunotherapy compared with patients without a teratoma.[1,3,20]

The typical duration from initial symptom presentation to initial signs of clinical improvement with treatment ranges from weeks to months.[3] The median duration of hospitalization is in the range of 2 to 2.5 months (range, 1–14 months).[3,21,25] Recovery may take 2 years or longer, and the patient may not always return to their premorbid levels of motor function and cognition.[3,5,21,50,51] Cognitive deficits can be pronounced both during the acute phase of illness and in the long-term recovery because of the role of the NMDAR in executive functioning, learning, and memory.

Titers of anti-NMDAR antibodies have some correlation with prognosis and clinical recovery. In multivariable analysis, CSF and serum titers were significantly higher in patients with poor outcomes than in those with good outcomes.[20] Anti-NMDAR antibody titers in CSF and serum usually decline when patients show substantial clinical recovery.[3,19,45,52] However, absolute values of titers of anti-NMDAR antibodies do not necessarily correlate with the degree of clinical recovery. Serum anti-NMDAR titers may become negative, whereas CSF titers are positive. Anti-NMDAR titers often remain elevated even when patients are clinically recovered. In one study, 24 of 28 CSF and 17 of 23 serum titers from patients remained antibody positive despite clinical recovery.[20]

Neuropsychological assessments performed in the earlier phase of recovery can show deficits in attention, problem-solving tasks, verbal fluency, and overall executive functioning.[47] Although many individuals recover completely, others continue to display persistent cognitive deficits such as difficulties with attention, working memory, episodic memory, and executive functioning.[47,53] A characteristic feature of patients who recover from anti-NMDAR encephalitis is a persisting amnesia of most of the illness (without more retrograde amnesia before the illness), which is compatible with the disruption of the mechanisms of synaptic plasticity involved in learning and memory, which would usually require functioning NMDARs.[3]

## Summary and Conclusions for Anti-NMDAR Encephalitis

- This presents with acute to subacute psychiatric and/or neurological complaints including new onset behavioral changes, which may evolve to psychosis and catatonia, cognitive decline, new onset seizures, progressive encephalopathy, and/or movement disorders.
- Avoid delays in diagnosis and treatment by not mistaking anti-NMDAR encephalitis for psychosis or viral encephalitis.
- The clinical features that distinguish anti-NMDAR encephalitis from a primary psychiatric disorder are the acute onset of the mood and behavioral changes with no prior history, the waxing and waning of consciousness (delirium/encephalopathy), and primary neurological features such as seizures, and abnormal involuntary movements, including dyskinesias and dystonias.
- Prognosis is improved with earlier recognition and prompt immunotherapy treatment, making this an important diagnosis for emergency physicians.
- The diagnosis requires confirmatory serum and/or CSF findings of anti-NMDAR antibody titers, but these results will not be available for the emergency physician in most instances.

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