

# Anti-NMDA Receptor Encephalitis: Diagnosis Delayed Is Almost Treatment Denied

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**D**M. is a 17-year-old Asian-Indian young woman with no prior psychiatric or medical history. She was in her usual state of health until she began experiencing difficulties with memory, attention, concentration, and erratic sleep patterns. D.M. described herself to her parents as “Not myself...everything is bad...I am going down.” Alarmed, D.M.’s parents brought her to an emergency department (ED) to be evaluated. She was assessed and medically cleared the same day and returned home with a plan to follow up with her primary physician.

Two days later, D.M. had her first witnessed seizure. In the ED, D.M.’s neurological exam, comprehensive metabolic profile, serum magnesium and phosphorous levels, urine analysis, and urine drug screen were all clinically unremarkable. The white blood cell count was slightly elevated at 14.3 (4.5-13.0 thousand microliter [mcL]). Given the largely unremarkable medical work-up, she again was discharged home that day. Three days later, D.M. had yet another witnessed seizure at home and returned to the ED. An electroencephalogram revealed mild diffuse slowing, which is suggestive of cerebral dysfunction. D.M. was prescribed levetiracetam for seizure prophylaxis and was discharged home. Later that same day, while speaking with her parents, D.M. demonstrated frank thought disorganization and reported that she was experiencing thoughts to cut herself. Her parents brought her back to the ED, and D.M. was medically cleared and transferred to an inpatient psychiatric facility for stabilization and treatment, given concerns for suicidal ideation.

At the psychiatric facility, D.M. was reportedly mute, isolative, unfocused, refused to eat, exhibited sleep disturbance with frequent waking, and demonstrated ongoing thought disorganization in addition to emerging behavioral disorganization. During this

psychiatric hospitalization, D.M.’s parents refused any standing medications.

Due to concern for an underlying medical condition as the potential cause of D.M.’s psychiatric symptomatology and clinical presentation, D.M. was transferred back to the ED and admitted to the neurology inpatient service, where she underwent further diagnostic medical work-up. Her differential included nonspecific functional neurologic symptom disorder or questionable infectious etiology or adjustment disorder, and D.M. was discharged home.

Four days after D.M.’s discharge, the results of both her serum anti-N-methyl-D-aspartate (NMDA) receptor antibody titers and cerebrospinal fluid (CSF) anti-NMDA receptor antibody titers returned elevated (1:40 and 1:1, respectively). D.M.’s parents were called to have D.M. medically readmitted due to concerns of anti-NMDA receptor encephalitis. After readmission, an MRI of the pelvis with and without contrast showed a right adnexal teratoma. Meanwhile, she was treated with intravenous immunoglobulin (IVIg) for 2 days, intravenous steroids for 5 days, and this was followed by a 6-week oral steroid taper. This regimen improved her confused mental status and rigidity. She was continued on 500mg of levetiracetam orally in the morning and 1000mg orally at night for seizure prophylaxes, with no further seizure activity. Finally, she received gynecologic oncology treatment for a tumor resection.

## Anti-NMDA Receptor Encephalitis

### Introduction, Presentation, and Differential Diagnosis

Anti-NMDA receptor (anti-NMDAR) encephalitis is an acute form of encephalitis that is potentially lethal, but has a high probability for recovery.<sup>1</sup> Most patients with anti-NMDAR encephalitis develop a progressive,

multistage illness that can involve an initial prodrome, the emergence of neuropsychiatric symptoms, and the development of critical medical instability. Potential symptoms include anxiety, social withdrawal, mania, psychosis, impaired cognition, memory deficits, seizures, dyskinesia, catatonia, loss of consciousness, hemiparesis, cerebellar ataxia, and autonomic dysfunction. Distinguishable from primary psychiatric illnesses, a characteristic of anti-NMDAR encephalitis is that a majority of patients experience at least four symptoms over the course of the disease, with many patients experiencing six or seven.<sup>2</sup> Behavior changes are less likely to be the first symptoms in children as compared to adults. While there is a broad range of severity of these symptoms, new and increasingly severe symptoms typically emerge and rapidly progress over a five-to-fifteen-day period.

When considering a diagnosis of anti-NMDAR encephalitis, other infectious, metabolic, and toxic causes should be considered. Serotonin syndrome and neuroleptic malignant syndrome can also have similar presentations, and should be high in the differential. Though less likely than the above mentioned disorders, one should still include in the differential, degenerative diseases, autoimmune causes of primary vasculitis, systemic autoimmune diseases, and steroid-responsive encephalopathy associated with autoimmune thyroiditis.

### Incidence

The overall incidence of anti-NMDAR encephalitis is unknown,<sup>3</sup> but we do know that 81% of reported cases have occurred in female patients and that there seems to be a higher frequency of the illness in Asian and African populations.<sup>2</sup> Furthermore, anti-NMDAR encephalitis is increasingly recognized in adolescents and young adults.<sup>4</sup> Over a third of reported cases have occurred in children, and only 5% of reported cases are over the age of 45. Disease onset is skewed towards adolescents and young adults, with a median age of diagnosis of 21 years.

### Possible Pathophysiology

The exact pathophysiology of anti-NMDAR encephalitis is still unknown, but several theories exist. The reasons

why NMDA receptor antibodies are produced in humans are unclear. The association between anti-NMDAR encephalitis and ovarian teratomas may exist as a result of the NMDA receptor-containing neural tissue frequently present in ovarian teratomas (which often contain many different cell types), suggesting that anti-NMDAR encephalitis may be a paraneoplastic syndrome.<sup>1</sup> It is presumed that teratomas might elicit an immune response, resulting in the production of antibodies. In general, patients with an underlying tumor develop more robust immune responses than those without a tumor. The antibodies produced to target NMDA receptors in the teratoma then are thought to develop cross-reactivity for the NMDA receptors in the brain, perhaps reflecting a breakdown in immunological tolerance.<sup>5</sup> This potential mechanism, however, does not account for the presence of anti-NMDAR encephalitis in individuals without any identified neoplasms.<sup>5</sup> Another theory regarding the etiology of anti-NMDAR encephalitis suggests that infection may trigger immune system activation that then shifts to an autoimmune response, resulting in the production of anti-NMDA receptor antibodies. The fact that anti-NMDAR antibodies consistently are found at greater concentrations in the serum than in the CSF (on average, 10-fold higher) strongly suggests that the antibody production is systemic rather than localized to either the brain or CSF.<sup>4</sup>

A pathogenic role of the anti-NMDAR antibodies is suggested by the correlation between antibody titers and neurological outcome, and by the decrease in the number of postsynaptic clusters of NMDA receptors caused by the antibodies. Several NMDA-receptor antagonists, such as dizocilpine (MK801), ketamine, and phencyclidine, cause psychosis and autonomic dysfunction similar to those observed in anti-NMDAR encephalitis, suggesting that a reduction in NMDA receptor function due to the antibody-mediated reduction in number of NMDA receptors may be a contributor to the pathophysiology of anti-NMDAR encephalitis. Of note, a characteristic feature of patients who recover from anti-NMDAR encephalitis is a persisting amnesia, which would be consistent with a reduction in NMDA receptor function, given the NMDA receptors' key role in learning and memory and associated mechanisms of synaptic plasticity.<sup>6</sup>

## Treatment

Anti-NMDAR encephalitis is a potentially treatable disorder and has a better prognosis with early identification. About 77% of patients with anti-NMDAR encephalitis initially seek the help of a psychiatrist,<sup>3</sup> so this diagnosis needs to be included in the differential diagnosis of patients presenting with acute onset of psychiatric symptoms, perhaps accompanied by seizures or movement disorders.

Aggressive treatment and a multi-disciplinary approach is vital for this complex syndrome. Initial therapy includes high-dose steroids, IVIg, plasma exchange, and removal of any causative neoplasm, if present. During the acute phase, most patients require care in an intensive care unit to stabilize breathing, heart rate, and blood pressure. In approximately 75% of patients, manifestations resolve with treatment. Long-term outcomes show that 79% have a recovery to near-baseline functioning in 24-month, 6% die, and the rest are left with mild to severe deficits.<sup>2</sup> Recovery is slow and may take 3 or more years, or those affected may not regain their premorbid level of health.<sup>7</sup> A possible explanation for the slow recovery could be the inability of most commonly used treatments to lead to rapid and sustained control of the immune response. Once improvement is noted, most patients continue to improve over weeks or months until fully recovered. As a result of general deconditioning and occasional spinal cord involvement, patients often need prolonged physical therapy. Relapses in children may be multiple and occur in 20-25% of cases, so ongoing monitoring and screening for at least 2 years is recommended.<sup>8</sup>

## Conclusion

Anti-NMDAR encephalitis is a relatively new diagnostic entity which represents a new category of immune-mediated disorder that is potentially lethal, but usually reversible if promptly recognized. Since most patients with neuropsychiatric symptoms present for psychiatric care in the initial period, it is important for psychiatrists to be familiar with this condition, diagnose it, and

collaborate treatment with multi-specialty teams for a better overall prognosis. It will be of future interest to research and assess further the potential role of various psychotropic medications as well as electroconvulsive therapy in lessening the psychiatric symptom burden associated with anti-NMDAR encephalitis.

## Take Home Summary

D.M.'s initial presentations without neurologic symptoms or past history of encephalitis suggests that some cases of anti-NMDAR encephalitis can be mistaken for a primary psychiatric disorder. Since no specific treatment guidelines exist, psychiatric treatment is based on clinical experience and anecdotal evidence.

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### About the Author

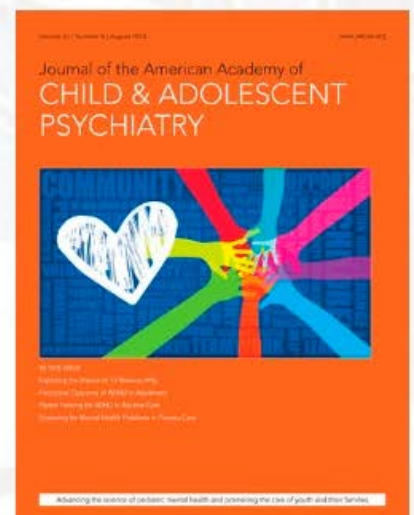
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