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Anti-NMDA receptor encephalitis: An emerging differential diagnosis in the psychiatric community

Taylor A. Nichols, PharmD, BCPP[1]

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Abstract

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is a new diagnosis, as recent as 2007, that develops as a result of autoantibodies to the NMDA receptor. The clinical manifestations of the disorder include complex psychiatric symptoms, seizures, movement disorders, cognitive dysfunction, and autonomic instability. Tumor resection, if present, and immunotherapy are the mainstays of therapy. Treatment should be initiated early and aggressively as it has been associated with better patient outcomes. A significant proportion of patients with anti-NMDA receptor encephalitis initially seek the help of a psychiatrist, highlighting the importance of its recognition within the mental health community. In an effort to promote disease awareness, this article will review a patient case and the pathophysiology, clinical presentation, diagnosis, and management of anti-NMDA receptor encephalitis.

Keywords: N-methyl-D-aspartate (NMDA), anti-NMDA, autoimmune, encephalitis, teratoma

[1] (Corresponding author) Mental Health Clinical Pharmacy Specialist, Phoenix VA Health Care System, Phoenix, Arizona, taylornichols26@yahoo.com

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Background

In 2007, Dalmau and colleagues[1] described a new form of autoimmune encephalitis in 12 females with ovarian teratomas. The observed subjects developed significant psychiatric symptoms, memory and cognitive deficits, dyskinesias, seizures, and autonomic dysfunction. Serum and cerebrospinal fluid (CSF) samples revealed antibodies to the N-methyl-D-aspartate (NMDA) receptor. The authors identified the newly discovered disorder as anti-NMDA receptor encephalitis.

The exact prevalence of anti-NMDA receptor encephalitis is unknown. Since discovery, more than 600 cases have been reported.[1-4] Furthermore, the disorder has been identified as the second most common autoimmune cause of encephalitis and more frequent than any other paraneoplastic encephalitis.[3,5] In the California Encephalitis Project, anti-NMDA receptor encephalitis frequency exceeded any viral etiology of encephalitis.[6] The rapid influx of diagnoses, more than 400 cases in a 3-year period, is suggestive of a relatively common disease.[5]

Approximately 80% of diagnosed patients are female, and 40% to 65% of patients are 18 years old or younger.[5-7] Patients at highest risk of developing anti-NMDA receptor encephalitis include young females with co-occurring tumors.[5] Tumors, primarily ovarian teratomas, are found in approximately half of all patients.[2] Although higher rates are found in pediatric patients, this finding could be confounded by the fact that this population is more likely to receive a thorough medical evaluation to rule out organic causes of psychiatric symptoms.

Psychiatric symptoms are the most frequent initial symptoms to present with 77% of patients soliciting the help of a psychiatrist first.[2,8] The probability of a full recovery decreases as the disease progresses, thus highlighting the importance of early detection and treatment. The recent discovery of the disorder and prominent psychiatric symptoms warrants a heightened awareness of anti-NMDA receptor encephalitis among the psychiatric community.

Patient Case

A 19-year-old black female with no significant past medical or psychiatric history presents with altered mental status and episodes of staring and shaking with concern for possible seizures. Per the patient's mother, she had her eyebrow pierced a month prior and subsequently developed cellulitis at the site. Shortly after, the patient appeared confused and less responsive. Upon hospitalization, an electroencephalogram confirmed generalized seizure events. Psychiatry was also consulted for depressed affect. The patient was discharged home on valproic acid and paroxetine. At home, she began to exhibit bizarre behavior (humming, dancing, laughing to self) and appeared to be responding to internal stimuli. The patient was rehospitalized. Serum/CSF laboratory results, diagnostic imaging, and urine drug screen were unremarkable. Serum/CSF samples were sent for antibody testing approximately 3 weeks later. The CSF sample returned positive for NMDA receptor antibodies while the serum sample was negative. The patient received intravenous immune globulin and rituximab with marked improvement in behavioral and cognitive status.

Pathophysiology

N-methyl-D-aspartate receptors are heteromers composed of glycine-binding NR1 and glutamate-binding NR2 subunits.[2,9] In anti-NMDA receptor encephalitis, immunoglobulin G (IgG) autoantibodies bind to the NMDA receptor via the NR1 subunit, resulting in a reversible internalization of NMDA receptors from cell surfaces. Ultimately, this internalization leads to decreased gamma-aminobutyric acid (GABA) neuronal function in addition to glutamate and dopamine dysregulation.[5] GABAergic neurons express NMDA receptors in greater numbers than other neurons. It is hypothesized that NMDA receptor antibody binding decreases glutamate activation of GABAergic neurons, resulting in diminished GABA release.[5] Reduced GABA activity is thought to produce significant glutamatergic hyperactivity and lead to many of the characteristic symptoms of anti-NMDA receptor encephalitis.[5]

How or why humans develop NMDA receptor antibodies remains unclear. High rates of co-occurring tumors have directed attention toward teratomas as a potential source. Teratomas possess neural tissue containing NMDA receptors.[2] It is postulated that they might elicit an immune response creating antibodies; however, this does not account for why patients without tumors still develop the disease.[10] Another proposed theory identifies infection as a source of immune system activation.[10] The frequent occurrence of a prodromal phase may support this theory, but a link has yet to be elucidated.

Clinical Presentation

Anti-NMDA receptor encephalitis commonly begins with a prodromal phase characterized by headache, malaise, and flu-like symptoms.[2,5] In a case series[2] of 100 patients, 86% experienced this prodrome in the 2 weeks prior to psychiatric symptom development. It is unclear whether this phase is a manifestation of early immune system activation or an actual infection. Subsequent to the prodromal phase, patients experience a fairly rapid deterioration. Several features characterize the ensuing presentation of anti-NMDA receptor encephalitis.[2,5,11] These features are often considered hallmarks of the disease and are described in the Table. The clinical presentation often follows a staged progression with psychiatric symptoms and seizures appearing first followed by motor, cognitive, and autonomic dysfunction.[2,12] Although symptoms frequently overlap and compound, making diagnosis challenging. Additional objective findings can include elevated creatine kinase, CSF pleocystosis, diffuse slowing on electroencephalogram, and nonspecific abnormalities on magnetic resonance imaging.[2,5]

Diagnosis

Diagnosis relies on clinical presentation and confirmed presence of NMDA receptor antibodies. Based on symptom presentation, a differential diagnosis should include a primary psychiatric disorder, serotonin syndrome, neuroleptic malignant syndrome, toxic ingestion, viral encephalitis, other limbic encephalitis forms, systemic lupus erythematosus cerebritis, antiphospholipid antibody syndrome, encephalopathy due to Hashimoto thyroiditis, etc.[5,13] To confirm diagnosis, antibody testing should be performed. Antibody testing should be specific to IgG as they have been identified as pathogenic in this disease.[1,2,14] Current debate exists regarding the appropriate sampling and method of antibody testing. One controversy surrounds whether serum, CSF, or both should be utilized for testing. Serum antibody testing reportedly exhibits 85% sensitivity, and CSF antibody testing exhibits 100% sensitivity and 100% specificity.[3,15] Several other studies[5,16] replicated these results. Contradictory studies[4,17] have found serum antibody titers to be higher than in CSF. Conflicting results are likely due to differences in the method of antibody testing, which spurs additional controversy. This debate surrounds the use of 1 versus multiple confirmatory methods, primarily cell-based assay and brain immunohistochemistry techniques.[15] It has been suggested that the use of only cell-based assay testing might potentially lead to overdiagnosis of anti-NMDA receptor encephalitis and that a confirmatory immunohistochemistry test should be performed.[15] Although a study has yet to confirm that multiple methods testing is superior to cell-based assay

TABLE: Clinical features of anti-N-methyl-D-aspartate receptor encephalitis

Hallmark Features	Detailed Symptoms	Comments
Psychiatric symptoms[2,6,7]	Auditory/visual hallucinations Delusions Agitation Catatonia Paranoia Mania Dissociation Anxiety Depression	Psychiatric symptoms are most likely to appear first Present in more than 70% of patients
Neurologic/Motor dysfunction[2,5-7,35,36]	Seizures Dyskinesias Orofacial (grimacing, masticatory movements) most common Limb/trunk choreoathetosis Dystonia Rigidity	Seizures 69% to 76% experience seizures Seizures present earlier in the disease course Wane in frequency and intensity throughout disease progression Males suffer from seizures at a higher rate than females Dyskinesias 63% to 86% experience movement disorders
Cognitive dysfunction[2,6]	Language deficits Persistent memory impairment Sleep disturbances Decreased levels of consciousness	Language deficits Approximately 72% experience language difficulties Memory impairment Nearly all patients experience memory deficits Decreased levels of consciousness Approximately 88% experience decreased levels of consciousness
Autonomic instability[2,5,6]	Autonomic instability Cardiac arrhythmias Hypotension/hypertension Dysthermia Hypersalivation Urinary dysfunction Central respiratory dysfunction	Autonomic instability Approximately 69% experience autonomic instability Autonomic instability commonly presents in later stages and leads to intensive care unit admission Central respiratory dysfunction Significant proportion require mechanical ventilation
Tumor presence[2,5]	Ovarian teratomas Nonovarian teratomas Nonteratomas	More than 50% of patients possess co-occurring tumors Tumors more common in females Affect black women at higher rates compared with other ethnicities Teratomas Approximately 98% of tumors present as teratomas More than 90% are ovarian in nature

alone, leading experts in the field appear to prefer cell-based assay and brain immunohistochemistry testing on both serum and CSF samples for means of diagnosis.[5,8,15]

Misdiagnosis of Psychiatric Disorder

Given the prominent psychiatric symptoms, questions have arisen as to whether patients with anti-NMDA receptor encephalitis are being misdiagnosed with psychiatric disorders. Multiple small studies[18-23] have examined this relationship with conflicting results. Steiner et al[18] prospectively evaluated 459 serum samples for NMDA receptor antibodies. The analysis compared samples from patients diagnosed with schizophrenia, major depressive disorder, and borderline personality disorder with non-psychiatric controls. The authors found 9.9%, 2.8%, and 0% of patients with schizophrenia, major depressive disorder, and borderline personality disorder, respectively, were antibody positive. In comparison, 0.4% of controls were antibody positive. A limitation of the study is the inclusion of immunoglobulin A (IgA) and immunoglobulin M (IgM) antibodies rather than testing specifically for IgG antibodies. Immunoglobulin A and IgM antibodies have not been linked to pathogenicity in anti-NMDA receptor encephalitis. Of the 12 (9.9%) patients with schizophrenia who tested positive, 2 (1.7%) possessed IgG antibodies. Alternatively, lack of CSF sampling may have potentially led to false negatives. The majority of patients diagnosed with schizophrenia in this study had a long-standing history of schizophrenia (average duration of illness: 9 years), which may have biased the results toward a smaller likelihood that another diagnosis may have existed. As many patients with anti-NMDA receptor encephalitis present with psychiatric symptoms first,

efforts were directed to examine the presence of antibodies in patients with first episode psychosis. Zandi and colleagues[19] performed an observational, cohort study in 46 adults with first episode psychosis. The authors found 7% to be serum NMDA receptor antibody positive, confirming the results of the Steiner et al[18] study. Similarly, this study did not examine IgG antibodies specifically, potentially overestimating the presence of pathogenic NMDA receptor antibodies. A contradictory study,[20] published in 2012, found no antibodies in either patients with schizophrenia or healthy controls. This study performed a more rigorous antibody testing technique, requiring 3 separate tests for IgG antibodies, indicating a more sound methodological design. A major limitation was that CSF samples were not tested, potentially leading to false negatives.

It is unclear, based on current evidence, whether patients with primary psychotic disorders possess higher rates of pathogenic NMDA receptor antibodies. Future studies with strong methodological design are needed to elucidate this relationship. Identification and request for further medical testing in patients with psychiatric symptoms exhibiting key characteristics of anti-NMDA receptor encephalitis may be the appropriate practice recommendation in consideration of conflicting evidence.

Management

The backbone of anti-NMDA receptor encephalitis treatment includes tumor removal and immunotherapy.[3,5] Benefits of early tumor removal, defined as less than 4 months after neurological symptom development, were described in a case series of 100 patients.[2] Patients with early tumor removal were more likely to fully recover or recover with mild deficits (returned to most activities of daily living) than those with late tumor removal or no treatment ($P = .03$) and those without tumors ($P = .006$). Additionally, early tumor removal resulted in fewer relapses.

First-line pharmacologic therapy includes corticosteroids in combination with intravenous immune globulin or plasmapheresis.[3,5,24] Immunotherapy has been associated with optimal patient outcomes, including improved modified Rankin scale scores and fewer relapses.[3-5,7] Patients with co-occurring tumors respond more favorably to first-line immunotherapy compared with those without tumors.[5] Plasma exchange may prove difficult to conduct in patients with notable agitation or autonomic dysfunction. If no response is noted after 10 days, Dalmau and colleagues[5] recommend initiation of second-line therapy based on their clinical experience. In patients who do not respond to first-line therapies, use of second-line therapy is associated with better outcomes than continuation of first-line therapy or no further treatment.[3] Roughly 30% of those diagnosed with anti-NMDA receptor encephalitis receive second-line pharmacologic therapy, which includes rituximab, cyclophosphamide, or both.[3,5] Patients with a delayed diagnosis or without co-occurring tumors appear to require second-line therapy more often.[5,7,25] Administration of third-line therapy can include azathioprine, mycophenolate, or methotrexate.[2,3,25,26] According to Dalmau et al,[5] immunotherapy may be discontinued once a "substantial clinical recovery" [5(p72)] is observed, which is usually accompanied by a decrease in CSF or serum antibody titers.

Psychiatric Symptoms

Simultaneous administration of psychotropics with immunotherapy is often necessary to provide psychiatric symptom control. Case reports[11,13,27,28] have described antipsychotic use to manage the psychotic symptoms and agitation associated with anti-NMDA receptor encephalitis although results have been mixed. Antipsychotics reported include a variety of first-generation and second-generation agents. Chapman et al[13] described a case report in which trials of aripiprazole (2.5 mg/d) and haloperidol (2 mg twice daily) were ineffective in relieving psychotic symptoms and produced marked extrapyramidal symptoms (EPS). Low-dose risperidone (0.5 mg twice daily) produced symptom improvement and was well tolerated. Kuppuswamy et al[28] described 2 cases in which olanzapine produced EPS in 1 patient and none in the other. The patient who experienced EPS was successfully transitioned to quetiapine with no mention of further side effects. Despite their reported use, antipsychotics should be used with caution in this population. Patients with anti-NMDA receptor encephalitis appear to be more sensitive to development of EPS.[12,13,27,28] Antipsychotic dosing should be conservative, and agents with a lower propensity to cause EPS are preferred. Additionally, the later stages of the disease can mimic neuroleptic malignant syndrome, which may complicate the clinical picture if the patient is simultaneously on antipsychotics. Reserving antipsychotic use for psychotic symptoms only may help to decrease confusion regarding symptom presentation.

Very little evidence has been published on the use of mood stabilizers in mood dysregulation and agitation.[13,28] Valproic acid and lithium use did not produce any improvement in target symptoms in case reports. Valproic acid may theoretically provide the added benefit of anticonvulsant effects and sedation for individual cases. The majority of reports[13,27,28] suggest the successful use of benzodiazepines to manage agitation. In addition, benzodiazepines may offer added benefits of sedation and parenteral availability. Antidepressant use for anxiety or depression has not been reported. The recommended

duration of psychotropic treatment remains unclear. Individualized treatment is necessary considering the variable degree of recovery.

Catatonic symptoms of anti-NMDA receptor encephalitis are primarily treated with benzodiazepines.[27,28] Several case reports[29-31] found electroconvulsive therapy helpful in refractory cases. Interestingly, electroconvulsive therapy was shown to upregulate NMDA receptors in animal models, potentially warranting future evaluation as a promising treatment of anti-NMDA receptor encephalitis symptoms.[32]

Sleep Disturbances

Case reports[13,27,28] describe the use of trazodone, clonidine, diphenhydramine, melatonin, gabapentin, and benzodiazepines for insomnia. Of these agents, trazodone, clonidine, and benzodiazepines were most helpful; however, details regarding dosing, duration, and efficacy were minimal.

Extrapyramidal Symptoms

Anticholinergic agents, including benztropine, diphenhydramine, and trihexyphenidyl, may be used to alleviate EPS.[13,27] Improvements in dystonia, rigidity, and pseudoparkinsonism have been noted throughout the literature.[13,27]

Seizures

Although no published guidelines exist for treating seizures associated with anti-NMDA receptor encephalitis, case reports indicate that management mirrors current standards of practice for seizure management. Case reports[33,34] describe the use of phenytoin, carbamazepine, and levetiracetam although presumably other anticonvulsants would be reasonable alternatives. Of note, patients may not require long-term therapy with anticonvulsants post–symptom resolution.[5]

Prognosis

Approximately 75% of patients experience recovery to near-baseline function with a median time to initial signs of improvement of 8 to 10 weeks.[2] The definition of recovery was based on modified Rankin scale and mini mental status examination scores. The remaining 25% of patients exhibit severe sequelae or death. Symptoms typically improve in reverse chronological order based upon first presentation[5] although psychiatric symptoms and cognitive function may take months or years to fully improve.

The mortality rate associated with anti-NMDA receptor encephalitis is estimated to be between 4% and 7%.[3,5] Early initiation of treatment, including tumor removal and immunotherapy, has been associated with a good disease prognosis.[2,3] Additional good prognostic factors include presence of tumor, decreased symptom severity, and lack of intensive care unit admission.

Symptom recurrence, or relapse, occurs in approximately 10% to 20% of patients and is more likely to be less severe symptomatically.[3,5] Those without co-occurring tumors are at highest risk of relapse.[3] To help prevent recurrence, experts recommend chronic, oral immunosuppression for 1 year.[5] Currently, there are no studies to support this recommendation. Additionally, numerous patients relapse greater than 1 year post–initial episode, so the proposed immunosuppression may not actually target many patients.[2,7] Accordingly, chronic immunosuppression may be considered for patients at highest risk.

Conclusion

Anti-NMDA receptor encephalitis is a newly discovered disorder characterized by prominent psychiatric symptoms, seizures, movement disorders, cognitive dysfunction, and autonomic instability. Treatment should be initiated early with a low threshold to progress to second-line therapies. Close monitoring for symptom recurrence is recommended.

Anti-NMDA receptor encephalitis creates an interesting situation for those in the psychiatric community. The majority of patients with the autoimmune disorder present to a health care setting with psychiatric symptoms first. Considering the importance of early diagnosis and initiation of treatment, this provides an opportunity for mental health professionals to make a significant impact.

Providers should suspect anti-NMDA receptor encephalitis in patients less than 50 years of age, especially females, presenting with new onset psychiatric symptoms in conjunction with seizures or pronounced movement disorders.[5] A recent history of viral or respiratory illness should also be investigated. Poor response to typical psychopharmacologic management may be an additional trigger for further medical evaluation. Awareness of these key characteristics of the disorder may lead to early detection and improved patient outcomes.

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