Anti-NMDA Receptor Encephalitis: A Cause of Acute Psychosis and Catatonia

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Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a newly described form of encephalitis associated with prominent psychiatric symptoms at onset. Recognition of the symptom complex is the key to diagnosis. Most patients with anti-NMDAR encephalitis develop a multistage illness that progresses from initial psychiatric symptoms to memory disturbance, seizures, dyskinesia, and catatonia. Psychiatric manifestations include anxiety, mania, social withdrawal, and psychosis (i.e., delusions, hallucinations, disorganized behavior). The disorder is more common in females (80%), in approximately half of whom it is associated with an underlying ovarian teratoma. Treatment involves immunosuppression, with steroids and intravenous immunoglobulin considered first line. The disorder is particularly relevant to psychiatrists, because most patients are initially seen by psychiatric services. Psychiatrists should consider anti-NMDAR encephalitis in patients presenting with psychosis as well as dyskinesia, seizures, and/or catatonia, especially if there is no history of a psychiatric disorder. We present the case of a 37-year-old woman who demonstrated many of the key clinical features of this potentially treatable disorder. (*Journal of Psychiatric Practice* **2013;19:157–161**)

KEY WORDS: a**nti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, psychiatric symptoms, psychosis, dyskinesia, seizures, catatonia, ovarian teratoma**

CASE PRESENTATION

A 37-year-old woman was involuntarily admitted to a psychiatric hospital after she became acutely agitated and exhibited bizarre behavior. She had had no prior medical or psychiatric illnesses. At the time of admission, she was not verbalizing and was catatonic. She had been in her usual state of health until the day before her admission. She had complained of feeling generally unwell and retired early to sleep. The following morning, she asked to be taken to her general practitioner (GP) and, while this was being organized, she became increasingly distressed and anxious. She removed her clothing and appeared confused to her partner. After assessing her, the GP felt that she was overtly psychotic and transferred her to the hospital. When her partner subsequently checked his telephone messages, he found that the patient had left him several rambling voice mails the night before, urging him to change his telephone network. He felt these messages were completely out of character for her. The patient was reported to be under increased stress because one of her children had recently been diagnosed with autism.

An acute psychotic episode was provisionally diagnosed, which was treated with a combination of olanzapine and haloperidol. The patient's condition deteriorated over the next 10 days despite trials of several different psychotropic agents, and electroconvulsive therapy (ECT) was being considered. The patient was transferred to a general medical ward on day 10 of her admission for intravenous fluids because she had become clinically dehydrated due to her catatonic state and failure to take an adequate amount of oral fluids.

On examination, she was catatonic with waxy flexibility; she was mute but responded to noxious stimuli. She had subtle orofacial dyskinesia and had bitten her tongue and lower lip. Initial extensive laboratory investigations, including liver function tests, autoimmune

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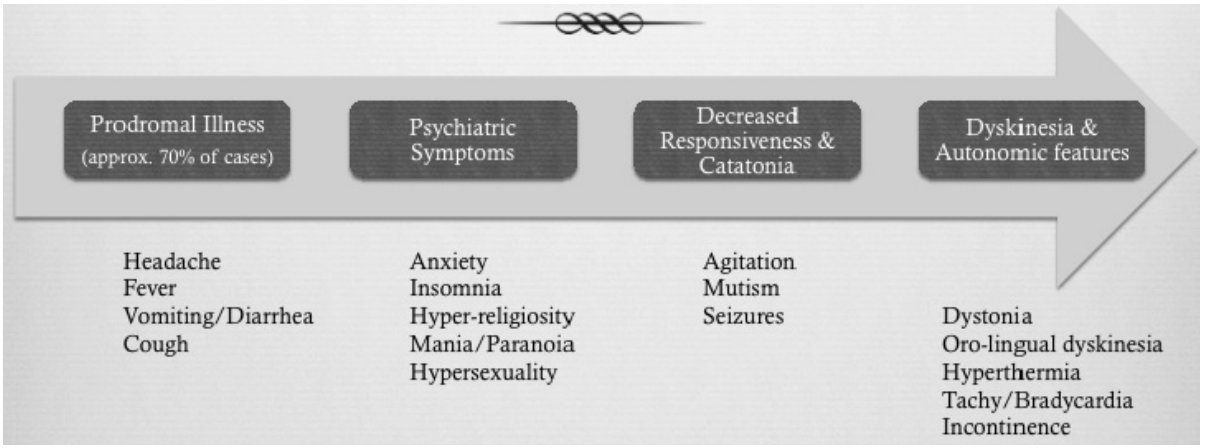
Figure 1. Progression of symptoms in anti-NMDA receptor encephalitis



In patients with anti-NMDA receptor encephalitis, approximately 70% will experience some prodromal symptoms, which are then followed by a multi-stage illness encompassing psychiatric, neurologic, and autonomic features.

screen, thyroid antibodies, copper studies, and HIV serology, were all negative. Based on her clinical presentation, anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis was suspected and the patient underwent brain magnetic resonance imaging (MRI), lumbar puncture, and electroencephalography (EEG). Her cerebrospinal fluid (CSF) tested positive for NMDAR antibodies. MRI with gadolinium was normal and the EEG demonstrated diffuse theta-range background slowing without epileptiform discharges.

The patient was treated with intravenous steroids, intravenous immunoglobulin, and a combination of cyclophosphamide and rituximab. Her condition was complicated by the development of seizures and autonomic disturbance, first noted clinically on day 20 of her admission. In this case, the autonomic disturbance manifested as labile blood pressure in the absence of any infection or other discernible cause. After 4 months of treatment, the patient made an almost complete recovery, which was primarily attributed to rituximab, and returned to independent living with her family. Gradual recovery occurring slowly over months, as in this case, is not unusual in this condition, with average inpatient stays of over 90 days reported in many case series.[1,2] Due to the strong association between NMDAR antibodies and underlying ovarian teratomas, the patient was referred for a formal gynecological consultation and underwent transvaginal ultrasound as well as computed tomography of her thorax, abdomen, and pelvis. These investigations proved negative for a teratoma or any other neoplasm/tumor.

Discussion

Initially discovered in 2007, anti-NMDAR encephalitis and its clinical manifestations have changed our approach to patients presenting with acute psychosis, altered behavior, and catatonia. Most patients with anti-NMDAR encephalitis are initially evaluated by psychiatry services before neurology or medical teams become involved.[1] It is usually the development of seizures or dyskinesia that alerts treating physicians to the possibility of general medical pathology.

The condition is associated with a characteristic syndrome that evolves over several stages,[2,3] recognition of which can lead to early diagnosis (Figure 1). Most patients are female (80%) and experience a prodromal period of non-specific symptoms that can include headache, nausea, fever, or viral-like upper respiratory symptoms. Within a few days, psychiatric symptoms typically become prominent.

The psychiatric manifestations associated with this condition are wide-ranging. In one series of 100 patients, 77 were initially assessed by a psychiatrist with symptoms including insomnia, mania, agitation, and delusional or paranoid thoughts.[1] Some patients exhibited echolalia or mumbled unintelligible words. Memory impairment is common but can be difficult to assess due to prominent psychiatric disturbance. In the pediatric population, behavioral changes ranging from irritability and hyperactivity to overt psychosis are possible.[4]

Patients then progress to a state of decreased consciousness and catatonia. Waxy flexibility may be pres-

ent on examination. This clinical state is typically refractory to standard antipsychotic therapies. Most patients then develop some form of dyskinesia—usually orofacial but chorea, dystonia, and rigidity have been described.[5] As the condition progresses, seizures and autonomic disturbance manifesting as temperature alteration, bradycardia, and hypoventilation can occur.

To make the diagnosis, the treating physician must recognize the clinical constellation of symptoms and then test peripheral blood and/or CSF for NMDAR antibodies.[1,6] If the diagnosis is confirmed, female patients should be screened for an underlying ovarian teratoma, which can be present in up to 50% of cases.[1] Brain MRI can be normal in up to half of affected patients, although non-specific T2 or fluid attenuated inversion recovery (FLAIR) signal hyperintensity has been described in various areas of the brain, including the hippocampus, cerebellar or cerebral cortex, basal ganglia, brainstem, and spinal cord.[7] The EEG is abnormal in most patients but this is not diagnostic. Treatment involves immunosuppression and removal of the underlying tumor if identified. Prolonged treatment is usually required and relapse can occur.[8]

Since its initial description, reported cases of anti-NMDAR encephalitis have increased exponentially worldwide. The majority of patients present first with neuropsychiatric symptoms, so that recognition by mental health professionals is key to early diagnosis. It is possible that certain patients with anti-NMDAR antibodies may have isolated psychiatric symptoms, at least for a certain period of time. Psychiatrists should consider anti-NMDAR encephalitis in the differential diagnosis of acute psychosis and catatonia, particularly in patients with no prior mental health issues.

COMMENTARY by Sander Markx, MD

Limbic encephalitis comprises a group of autoimmune disorders, including anti-NMDAR encephalitis, in which a patient's immune system becomes dysregulated and starts to target neuronal antigens in the brain. Neuronal autoimmunity was first described in patients with paraneoplastic neuropathy, cerebellar degeneration, or encephalitis.[9] In these disorders, the target epitopes are typically intracellular (i.e., antigens located in the nucleus or cytoplasm, such as Hu, Yo and Ma2), and therefore the antibodies have only limited accessibility. As such, it has been suggested that many of these antibodies are not pathogenic, but rather reflect a T-cell mediated immune response.[9] Other brain disorders involve antibodies that target intracellular synaptic proteins (e.g., GAD65, ampiphysin) so that both antibody- and cell-mediated mechanisms could play a role in the pathogenesis of the disease. More recently, a third group of disorders involving neuronal autoimmunity was described in patients with encephalitis, in which antibodies target cell-surface antigens or synaptic proteins. Examples of neuronal antigens identified so far include the NMDA receptor,[7] the α amino 3-hydroxy 5-methyl 4-isoxazolepropionic acid (AMPA) receptor,[10] the γ-aminobutyric acid receptor-B (GABAB),[11] the glycine receptor (GlyR),[12] and the metabotropic glutamate receptor 5 (mGluR5).[13]

Antibodies to cell-surface and synaptic antigens are associated with a broad spectrum of neuropsychiatric symptoms, including seizures, psychosis, catatonia, cognitive abnormalities (e.g., memory problems, attention deficits), and movement disorders (e.g., dyskinesias). Interestingly, in contrast to intracellular antigens, cases of limbic encephalitis that involve cell-surface or synaptic antigens are often not paraneoplastic in nature and patients frequently show a dramatic response to treatment, often returning to premorbid levels of functioning.

NMDAR antibodies were first identified in 2007 in 12 women with teratomas who presented with prominent psychiatric symptoms, memory loss, seizures, a decrease in level of consciousness, frequent dyskinesias, and autonomic dysfunction.[7] The spectrum of psychiatric symptoms included delusions, hallucinations, bizarre behavior, disorganized thinking, anxiety, and "acute personality change." Since then, over 500 cases have been described in the literature involving pediatric and adult populations, male and female patients, and patients with and without teratomas.[4,9,14] Recently, the California Encephalitis Project determined that the incidence of anti-NMDAR encephalitis surpassed that of encephalitis with any specific viral etiology in young patients.[15]

The characteristic presentation of anti-NMDAR encephalitis involves a prodrome resembling a viral illness, typically followed by an acute stage, which can involve prominent neuropsychiatric symptoms—catatonia, agitation, psychosis, seizures, decreased level of consciousness, dyskinesias, and autonomic instability—which can all evolve over the course of days to weeks following the initial presentation.[1] This is often followed by a protracted phase of recovery, during which there can be deficits in executive functions and psychiatric symptoms often resurface. A unique EEG pattern described as "extreme delta brush," recently identified in

30% of adult patients with anti-NDMAR encephalitis, has been described as possibly characteristic of the disorder and associated with more prolonged hospitalization.[16] This EEG pattern was also recently found in pediatric patients.[17] It is estimated that approximately 75% of patients ultimately recover form the illness over a period of months.[14] As Ryan and colleagues noted, ovarian teratomas have been associated with anti-NMDAR encephalitis,[18] and surgical removal of the tumor, together with immunotherapy, is often associated with a more rapid treatment response of the encephalitis.[14] Interestingly, it was recently suggested that intrathecal anti-NMDAR antibody synthesis can persist for years after clinical recovery, indicating that the presence of these antibodies does not necessarily reflect disease activity.[19]

The patient described here by Ryan et al. was treated with intravenous steroids, intravenous immunoglobulin, and a combination of cyclophosphamide and rituximab and made an almost complete recovery over the course of 4 months. An observational cohort study by Titulaer et al. recently demonstrated that the majority of patients with anti-NMDAR encephalitis respond to treatment.[20] First-line treatment, defined as corticosteroids, intravenous immunoglobulins, or plasma exchange, either alone or combined with tumor removal, proved effective in at least half of all patients. When not successful, second-line treatments such as rituximab or cyclophosphamide, either alone or combined, often lead to good clinical response. However, recovery in some patients can be prolonged and take up to 1–1.5 years, if not longer in rare cases. Predictors of good outcome include 1) early treatment, and 2) no admission to an intensive care unit.[20]

The NMDA receptor is critical for learning and memory formation and also plays a direct role in excitatory neurotransmission.[21] The original hypothesis that the NMDA receptor might also be involved in the pathogenesis of schizophrenia was based on the notion that NMDA receptor antagonists (e.g., phencyclidine, ketamine) cause a variety of symptoms seen in patients who suffer from schizophrenia, including psychosis, working memory deficits, and social withdrawal.[22] Moreover, mice with partial genetic disruption of the NR1 subunit of the NMDAR—the subunit that is also the primary target of the antibodies—show impaired learning and stereotyped behavioral abnormalities suggestive of schizophrenia.[23] Together, the clinical and mouse model data have led to the hypothesis that glutamate hypofunction is involved in the pathophysiology of schizophrenia.[21] NMDAR antibodies, and possibly also the pharmacological antagonism of the NMDA receptor, can disrupt glutamate signaling in a fashion similar to genetic disruption.[9] It has therefore been suggested that anti-NMDAR encephalitis could be a good model for studying schizophrenia. It has also been hypothesized that a subset of patients diagnosed with schizophrenia may in fact have anti-NMDAR encephalitis. If indeed the case, the etiology of these patients' psychiatric illness could potentially be targeted with treatment to achieve a full remission.

In support of this, a growing number of case reports have described patients who developed psychotic symptoms and were subsequently diagnosed with schizophrenia, but who were later found to have IgG NMDAR antibodies.[24] In these reports, first- or second-line treatment for limbic encephalitis typically led to a complete remission or significant improvement in the psychiatric symptoms. To evaluate this hypothesis more systematically, Steiner et al. examined 121 patients who met DSM-IV-TR criteria for schizophrenia and had been off medication for at least 6 weeks and found different NMDAR antibodies in 9.9% of these patients.[25] Of the patients with NMDAR antibodies, 2 patients had specific serum and CSF fluid IgG NR1a antibodies, whereas all other seropositive cases involved antibodies of classes IgA and/or IgM which were directed against both NR1a and NR2b. It has been questioned whether IgA and IgM antibodies directed at the NMDAR have any direct relationship with the clinical disease observed in patients (J. Dalmau, personal communication). In contrast, Masdeu et al. reported that they did not detect serum IgG antibodies directed against the NR1 subunit of the NMDA receptor in a group of 80 patients who, 1 year after their first psychotic episode, met DSM-IV-TR diagnostic criteria for what were referred to as schizophrenia spectrum disorders.[26] However, the sample size of this study may not have been sufficiently large; there is also a possibility that patients who meet diagnostic criteria for a primary psychotic disorder (e.g., schizophrenia, schizoaffective disorder) have neuronal auto-antibodies present only in CSF but not in serum. It is also possible that neuronal antibodies are present in patients with acute psychosis, but not in patients who meet DSM-IV-TR criteria at 1 year for schizophrenia spectrum disorders.[26] Thus, it remains to be seen if a fraction of patients who are diagnosed with schizophrenia are actually suffering from anti-NMDAR encephalitis. Larger studies that include control subjects and assess CSF are needed; findings

from such studies will ultimately determine how we screen patients for neuronal antibodies.* Since early intervention leads to better outcomes in patients with limbic encephalitis, this is an important question to address. For now, however, as Ryan et al. suggest, when a patient presents with new-onset psychosis, especially in combination with dyskinesias, seizures, memory problems, decreased level of consciousness, and/or catatonia, anti-NMDAR encephalitis should be an important differential diagnostic consideration.

References

1. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: Case series and analysis of the effects of antibodies. Lancet Neurol 2008;7:1091–8.
2. Iizuka T, Sakai F, Ide T, et al. Anti-NMDA receptor encephalitis in Japan: Long-term outcome without tumor removal. Neurology 2008;70:504–11.
3. Iizuka T, Sakai F. Anti-NMDA receptor encephalitis: Clinical manifestations and pathophysiology. Brain Nerve 2008;60:1047–60.
4. Florance NR, Davis RL, Lam C, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 2009;66:11–8.
5. Dalmau J, Panzer J. Movement disorders in paraneoplastic and autoimmune disease. Curr Opin Neurol 2011;24: 346–53.
6. Irani SR, Bera K, Waters P, et al. N-methyl-D-aspartate antibody encephalitis: Temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain 2010;133(Pt 6): 1655–67.
7. Dalmau J, Tuzun E, Wu HY, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007;61:25–36.
8. Gabilondo I, Saiz A, Galán L, et al. Analysis of relapses in anti-NMDAR encephalitis. Neurology 2011;77:996–9.
9. Lancaster E, Dalmau J. Neuronal autoantigens—Pathogenesis, associated disorders and antibody testing. Nat Rev Neurol 2012;8:380–90.
10. Lai M. Hughes EG, Peng X, et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. Ann Neurol 2009;65:424–34.
11. Lancaster E, Lai M, Peng X, et al. Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: Case series and characterisation of the antigen. Lancet Neurol 2010;9:67–76.
12. Hutchinson M, Waters P, McHugh J, et al. Progressive encephalomyelitis, rigidity, and myoclonus: A novel glycine receptor antibody. Neurology 2008;71:1291–2.
13. Lancaster E. Martinez-Hernandez E, Titulaer MJ, et al. Antibodies to metabotropic glutamate receptor 5 in the Ophelia syndrome. Neurology 2011;77:1698–1701.
14. Dalmau J., Lancaster E., Martinez-Hernandez E, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 2011;10:63–74.
15. Gable MS, Sheriff H, Dalmau J, et al. 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. Clin Infect Dis 2012;54:899–904.
16. Schmitt SE, Pargeon K, Frechette ES, et al. Extreme delta brush: A unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology 2012:79:1094–100.
17. Armangue T, Titulaer MJ, Málaga I, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis—Clinical analysis and novel findings in a series of 20 patients. J Pediatr 2012 Nov 16 [Epub ahead of print].
18. Tuzun E. Zhou L, Baehring JM, et al. Evidence for antibody-mediated pathogenesis in anti-NMDAR encephalitis associated with ovarian teratoma. Acta Neuropathol 2009;118:737–43.
19. Hansen HC, Klingbeil C, Dalmau J, et al. Persistent intrathecal antibody synthesis 15 years after recovering from anti-N-methyl-D-aspartate receptor encephalitis. Arch Neurol 2012 Oct 15:1-3. [Epub ahead of print].
20, Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: An observational cohort study. Lancet Neurol 2013;12:157–65
21. Gordon JA. Testing the glutamate hypothesis of schizophrenia. Nat Neurosci 2010;13:2–4.
22. Krystal JH, Anand A, Moghaddam B. Effects of NMDA receptor antagonism: Implications for the pathophysiology of schizophrenia. Arch Gen Psychiatry 2002;59:663–4.
23. Belforte JE, Zsiros V, Sklar ER, et al. Postnatal NMDA receptor ablation in corticolimbic interneurons confers schizophrenia-like phenotypes. Nat Neurosci 2010;13: 76–83.
24. Barry H, Hardiman O, Healy DG, et al. Anti-NMDA receptor encephalitis: An important differential diagnosis in psychosis. Br J Psychiatry 2011;199:508–9.
25. Steiner J, Walter M, Glanz W, et al. Increased prevalence of diverse N-methyl-D-aspartate glutamate receptor antibodies in patients with an initial diagnosis of schizophrenia: Specific relevance of IgG NR1a antibodies for distinction from N-methyl-D-aspartate glutamate receptor encephalitis. JAMA Psychiatry 2013 Jan 23:1–8 [Epub ahead of print].
26. Masdeu JC, González-Pinto A, Matute C, et al. Serum IgG antibodies against the NR1 subunit of the NMDA receptor not detected in schizophrenia. Am J Psychiatry 2012;169: 1120–1.

*An increasing number of specialized laboratories now test both serum and CSF for neuronal auto-antibodies directed at the NMDA receptor and a few other recently identified cell surface antigens. Kits to assess for NMDAR antibodies are now also commercially available. However, these laboratories currently only screen for a limited number of neuronal auto-antibodies and a patient with symptoms consistent with limbic encephalitis in whom NMDAR antibodies were ruled out may still in fact have auto-antibodies directed at another neuronal antigen.