

Psychosis Associated with Anti-*N*-methyl-D-aspartate Receptor Antibodies

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ABSTRACT

We describe the eighth case study of a female diagnosed with anti-*N*-methyl-D-aspartate receptor encephalitis without an identified tumor who presented with floridly psychotic symptoms following a 2-week prodromal phase with new-onset headaches and presyncopal episodes. While hospitalized, the patient had seizures, autonomic dysfunction, involuntary movements, and a decline in mental status. A subsequent assay was positive for anti-*N*-methyl-D-aspartate receptor antibodies. In contrast to most reported cases, an initial trial with corticosteroids was therapeutically unsuccessful. Subsequent treatment with intravenous immunoglobulins, however, resulted in a prompt, robust clinical response and enabled the patient to be rapidly discharged from the hospital, with minimal neuropsychiatric sequelae.

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INTRODUCTION

Limbic encephalitis is a well-recognized, paraneoplastic syndrome characterized by neuronal inflammation and degeneration in the temporal regions of limbic gray matter, the development of seizures, and extensive neuropsychiatric and autonomic dysfunction.¹

Needs Assessment

Patients who present with the acute onset of psychosis and neurological symptoms are an enormous challenge for physicians. We present the case of a young female, who was admitted to the psychiatric ward for a presumptive primary psychotic disorder who later developed seizures, autonomic instability, and movement disorders. Subsequent medical workup revealed the presence of antibodies to heteromers of *N*-methyl-D-aspartate (NR₁/NR₂) subunits, which is highly specific for detecting *N*-methyl-D-aspartate receptor encephalitis. This is an increasingly reported paraneoplastic neurological syndrome, that untreated can be lethal. However, early diagnosis and treatment of this disorder portends a good prognosis.

Learning Objectives

- At the end of this activity, the participant should be able to:
- Know the classic presenting symptoms of limbic encephalitis.
 - Understand the pathophysiology of anti-*N*-methyl-D-aspartate receptor encephalitis and its relatedness to tumors, especially ovarian teratomas.
 - Recognize the diverse roles of different glutaminergic receptors and their respective roles in the central nervous system.
 - Be able to diagnose and treat anti-*N*-methyl-D-aspartate receptor encephalitis.

Target Audience: Neurologists and psychiatrists

CME Accreditation Statement

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This activity has been peer-reviewed and approved by Eric Hollander, MD, chair at the Mount Sinai School of Medicine. Review date: July 18, 2008. Dr. Hollander does not have an affiliation with or financial interest in any organization that might pose a conflict of interest.

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The term was first coined in 1968² in an article describing three patients with progressive memory impairment associated with bronchial carcinoma. "Classic" limbic encephalitis predominately affects older individuals with small cell lung carcinomas, but has also been associated with lymphomas, thymomas, and testicular carcinomas. Since then, advances in neuroimaging techniques and the discovery of several paraneoplastic antibodies (eg, small cell lung carcinomas, anti-Hu, and anti-Ma2) have led to increased recognition of this disorder.³ Discovery of these antibodies supported the hypothesis of an autoimmune etiology and implicated involvement of intrathecal onconeural antibodies. Vexing to clinicians, however, was the subsequent discovery of patients with similar behavioral and neurological syndromes but without evidence of paraneoplastic antibodies, tumors, or "atypical" tumors (ie, neoplasms that had not yet been associated with limbic encephalitis).⁴

Until recently, relatively few reports have associated the etiology of limbic encephalitis with the production of antibodies to the *N*-methyl-D-aspartate (NR)₁/NR₂ subunit heterodimers of the *N*-methyl-D-aspartate (NMDA) receptor. In fact, 13 out of the 23 total publications⁵⁻⁷ on the subject of anti-NMDA receptor encephalitis appeared in 2007, revealing a sharp increase in the incidence of this disorder, its recognition, or both. Estimates suggest that ~65% of these patients have an underlying tumor, usually a teratoma of the ovaries (J. Dalmau, MD, PhD, oral communication), and that the epitopes responsible for producing autoantibodies against the NMDA receptor originate from neural tissue ectopically expressed within the teratoma. Although anti-NMDA receptor encephalitis is potentially lethal, most individuals with this disorder experience near-complete resolution of symptoms with immunosuppressive therapy and fully recover with resection of the tumor.

In this article, we describe the eighth case study of a female diagnosed with anti-NMDA receptor encephalitis without an identified tumor⁵⁻⁷ who presented with floridly psychotic symptoms following a 2-week prodromal phase with new-onset headaches and presyncopal episodes.

CASE REPORT

Initial Presentation

The consultation-liaison psychiatry service at the Naval Medical Center Portsmouth was consulted regarding a 23-year-old female who was brought to the emergency room with acute onset of psychosis. Two weeks prior, she had presented to her primary care physician complaining of new-onset memory impairment, migraines, and presyncopal episodes. In the emergency room, the patient was initially combative, requiring intravenous (IV) administration of benztropine mesylate 1 mg, haloperidol 5 mg, and lorazepam 1 mg.

The patient was tachycardic (115–144 beats/minute), but vital signs were otherwise normal. Physical examination was unremarkable; there were no meningeal or focal neurological signs. Her mental status was notable for paranoid delusions, persistent agitation, disorientation (Mini Mental State Examination score of 15 out of 30), and loose associations. Routine laboratory studies, including electrolytes, were significant for an increased white blood cell count of 13.6 cells/mcL (normal: 4.8–10.8 cells/mcL) and a mildly increased serum protein of 8.6 g/dL (normal: 6.4–8.3 g/dL). Cerebral spinal fluid (CSF) analysis showed evidence of a traumatic lumbar puncture, but otherwise was unremarkable. A chest X-ray and a computed tomography scan of the head, without contrast, were normal. Electrocardiogram was remarkable only for sinus tachycardia. The patient's medical history was unremarkable with no history of mental illness, seizures, or significant head trauma.

Hospital Course

After a brief stay on the general medical ward, the patient was admitted to the psychiatric ward for a presumptive primary psychotic disorder (rule-out schizophrenia) and was noted to be disoriented and delusional. She had a Mini Mental State Examination score of 15/30. Shortly thereafter, the patient experienced two seizures, prompting her transfer to the intensive care unit where she suffered a third generalized tonic-clonic seizure. In the intensive care unit, the patient was intubated and treated with a loading dosage of lorazepam 3 mg IV and phenytoin 1.4 g IV. Following stabilization several days later, phenytoin was replaced with a regimen of intra-

venous valproate, lorazepam 2 mg, and quetiapine 25–50 mg every 6 hours as needed for agitation. Valproate 500 mg IV BID was replaced with levetiracetam 500 mg IV BID because the patient developed mild hyperammonemia.

The patient's mental status further declined, varying between periods of acute agitation that required restraints and periods when she appeared catatonic. The patient became progressively unresponsive and unable to follow commands, eventually limited to visually tracking her examiner. Autonomic instability complicated her course. She exhibited intermittent sinus tachycardia, hypertension, undulating fevers, and hyperhidrosis. Neurologically, she displayed hyperreflexia and myoclonus as well as several other movement disorders, including athetosis, hyperkinesia, and orolingual dyskinesias.

The consultation-liaison psychiatry service remained involved in this patient's care throughout her hospital course, offering treatment recommendations to address behavioral changes as well as aiding in diagnostic formulation. Although the working diagnosis was a primary psychotic disorder, the medical team continued diagnostic efforts to rule out other organic etiologies, including Hashimoto's encephalopathy, Cushing's disease, and other paraneoplastic limbic encephalopathies. During the third week of hospitalization, a resident (K.M.N.) on the consultation-liaison psychiatry service discovered a case report that described a patient with a remarkably similar clinical presentation,² which prompted a course of treatment with methylprednisolone and further CSF analysis to confirm the presumed diagnosis of anti-NMDA receptor encephalitis. The following day she demonstrated decreased psychomotor agitation, recognized family members, responded to simple commands, and began to form brief, rudimentary, but coherent sentences. However, her speech quickly became disjointed when her attention waned. Her modest improvement was brief. The following day, her mental status deteriorated, despite continued treatment with methylprednisolone. After the 5-day course of methylprednisolone was completed, a 5-day course of intravenous immunoglobulins was initiated. Several days into the immunoglobulin course, the patient recovered fully, except for mild amnesia.

Diagnostic Studies

Thyroid peroxidase antibodies were elevated to 507 IU/mL (normal: 0–34 IU/mL), although the remainder of her diagnostic laboratory studies were within normal limits, including erythrocyte sedimentation rate; C-reactive protein; thyroid-stimulating hormone; thyroxine; rapid plasma reagin; rheumatoid factor; heavy metals (lead, arsenic, mercury, cadmium); anti-nuclear antibody; CSF venereal disease research laboratory slide test; cryptococcal antigen; corticotropin; morning cortisol; carcinoembryonic antigen; and cancer antigen 125. A paraneoplastic antibody panel of the patient's CSF was also negative. Analysis of CSF revealed lymphocytic pleocytosis and an elevated immunoglobulin G (IgG) index, but cultures did not reveal an infection. Antibodies to NR₁/NR₂ heterodimers of the NMDA receptor were identified in a subsequent CSF analysis. Multiple electroencephalograms (EEGs) did not reveal epileptiform activity, including a 2-day continuous EEG. However, a diffuse slowing of the brain waves consistent with generalized encephalopathy was present. A transvaginal ultrasound did not reveal evidence of an adnexal mass. Magnetic resonance imaging (MRI) studies of the brain, with and without contrast, were also normal.

DISCUSSION

Unlike "classic" limbic encephalitis, anti-NMDA receptor encephalitis primarily affects young women between 20–50 years of age, presenting with prominent psychiatric symptoms following a brief prodrome of fever, headache, or malaise. The psychotic features are so severe, often including catatonic features, that patients are often misdiagnosed with schizophrenia, drug abuse, or malingering.¹² Investigation into neurological etiologies is often delayed until after the patient manifests seizures, autonomic instability, dyskinesias, and decreased consciousness. As the condition evolves, patients frequently become akinetic and unresponsive to verbal commands, often displaying bizarre, inappropriate smiling.⁵ Patients then typically begin to display hyperkinesia and lingual-facial-buccal dyskinesias, and hypoventilation.⁵

Analysis of CSF typically reveals pleocytosis, increased protein concentration, and a high IgG index. EEGs occasionally show epileptiform abnormalities but usually reveal only diffuse slowing of the brain waves.

As with the present case study, most cases of anti-NMDA receptor encephalitis have either normal or atypical brain MRI findings. Fluid-attenuated inversion recovery or T2-weighted magnetic resonance images reveal mild abnormalities surrounding the medial temporal lobes, often with cortical enhancement, in 75% of cases.⁸ Fluorodeoxyglucose F¹⁸-positron-emission tomography is particularly useful to screen for an underlying tumor in the absence of brain MRI findings.⁴ Tumors in patients with anti-NMDA receptor encephalitis often go undiscovered or are misdiagnosed as benign or physiological ovarian cysts.⁹ Therefore, combined use of fluorodeoxyglucose F¹⁸-positron-emission tomography and computed tomography has also been recommended due to a demonstrated high sensitivity for identifying tumors in patients with antineuronal antibodies associated with paraneoplastic syndromes.^{10,11} Our limited imaging studies did not reveal evidence of an ovarian tumor, but future management in this patient requires vigilant surveillance.¹² Though encephalitis associated with NMDA receptor antibodies is potentially fatal, symptoms typically abate rapidly with immunosuppressive therapy and resolve entirely with tumor removal.

Glutamate is the major excitatory neurotransmitter in the central nervous system, and glutamate receptors (GluRs) are vital in the mediation of excitatory synaptic transmission. Activation of these receptors is responsible for basal excitatory synaptic transmission and many forms of synaptic plasticity such as long-term potentiation and long-term depression, events that may underlie the process of learning and memory. Careful regulation of the glutamate system is important because hyperfunctioning of this system underlies glutamate excitotoxicity and can lead to neuronal injury or death, whereas glutamate hypofunction has been implicated in learning impairments and psychosis.

GluRs can be categorized as ionotropic or metabotropic receptors. The ionotropic GluRs can be further subdivided into three major receptor subtypes, named for the agonists that activate them: NMDA, α -amino-3-hydroxy-5-methyl-4-isoxazole propionate, or kainate. NMDA receptors are expressed on neurons throughout the brain; their highest densities are found in the amygdala, hypothalamus, prefrontal cortex, and

hippocampus. Functioning of these receptors is complex because NMDA receptor activation occurs only if binding of both glutamate and a co-transmitter, either glycine or D-serine, occurs in concert with membrane depolarization. Cells with a high density of NMDA receptors are usually located in immunoprivileged sites, protected by the blood-brain barrier.

NMDA receptors are heteromeric receptors comprised of NR₁ subunits (which bind glycine or D-serine) and NR₂ subunits (which bind glutamate); most functional receptors require two of each. These receptors are largely heterogeneous, mostly because there are four forms of the NR₂ subunit (NR_{2A-D}). However, the NR₁/NR_{2A}/NR_{2B} combination is likely the major receptor found in mature neurons of the forebrain¹³⁻¹⁵; the prefrontal cortex and the hippocampus are especially rich in NR_{2B} receptor subunits. Ectopic expression of extracellular epitopes of the NR₁/NR₂ heterodimers is hypothesized to underlie the formation of pathogenic IgG autoantibodies that attack the patient's own NMDA receptors in anti-NMDA receptor encephalitis.

Hypofunctioning of the NMDA receptors is likely to underlie the psychosis of patients with anti-NMDA receptor encephalitis, which are often similar to schizophrenia. The NMDA receptor hypofunction hypothesis of schizophrenia was derived from observations that NMDA receptor antagonists have an inhibitory effect in cellular and animal studies,¹⁴ where they have been associated with psychosis and memory impairments. In contrast, NMDA receptor agonists ameliorate psychotic symptoms.^{5,14} Phencyclidine (PCP), a noncompetitive NMDA receptor antagonist, was first implicated in psychosis in 1962 by Luby and colleagues¹⁶ when they noted PCP "produced a predictable series of changes mimicking the primary symptoms of schizophrenia." Since then, PCP and derivatives, such as ketamine, have been repeatedly shown to produce a psychosis that is nearly impossible to distinguish from schizophrenia.¹⁷

CONCLUSION

The diagnosis of a primary psychiatric disorder requires that a general medical condition be first excluded. This case notes the importance of conceptualizing psychosis as a non-specific neurobiological syndrome before attributing

psychotic symptoms to a primary psychiatric disorder. Encephalitis associated with anti-NMDA receptor antibodies has been frequently underdiagnosed. However, we hope the sharp increase in case reports over the past several years will lead to greater recognition and earlier diagnosis of this potentially fatal disease. **CNS**

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