ABSTRACT

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis may present with a wide variety of early neuropsychiatric symptoms such as psychosis, insomnia, catatonia, and agitation, and at times in the absence of fever. The literature highlights the vital role of psychiatrists in early recognition and timely treatment of this condition. Presence of immunoglobulin G antibodies in blood and cerebrospinal fluid (CSF) against the NR1a subunit of the NMDA receptor is considered the gold standard for confirming diagnosis. There may be other nonspecific findings in CSF and on electroencephalogram and brain magnetic resonance imaging. Management includes surgical removal of the tumor if identified, first- and second-line immunotherapy, supportive medical care, and management of psychiatric symptoms. The role of electroconvulsive therapy has been noted for treatment of catatonic symptoms in particular. [Psychiatr Ann. 2015;45(11):572-576.]

Glutamate is the primary excitatory neurotransmitter in the brain. The N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor on neuronal membranes that is highly permeable to Ca2+. The activation of these receptors requires the binding of two coagonists, glycine and L glutamate. Glycine acts as a modulator whereas glutamate is the active neurotransmitter. These receptors are found in many cortical and subcortical brain regions, with a higher concentration in the hippocampus. In the hippocampus, NMDA receptors are involved in spatial learning and long-term potentiation, thus explaining their role in learning and memory. Hyperactivity of NMDA receptors can lead to neurotoxicity and is possibly involved in the pathophysiology of acute brain injuries. On the other hand, sustained hypofunctioning of NMDA receptors can result in cognitive dysfunction and is thought to be involved in the pathophysiology of psychosis, Alzheimer’s disease, and autoimmune encephalitis. NMDA receptor antagonists such as phencyclidine...
and ketamine are known to have a dose-dependent psychomimetic effect similar to NMDA receptor encephalitis.¹

SIMULATED CASE

A 22-year-old woman with no personal or family psychiatric history who had previously been in good health until 4 days prior to presentation, when she started to have mild headaches, nausea, vomiting, and low-grade fever was evaluated at a local emergency department. She presented with insomnia, agitation, difficulty speaking, paranoia (ie, her parents were trying to poison her), and auditory hallucinations of intruders in her house. Basic blood investigations and urine drug screen were unremarkable, and head computed tomography (CT) scan was negative for a hemorrhage or infarct. An acute psychotic illness was suspected and psychiatric admission advised. Family members expressed reluctance for psychiatric hospitalization due to the patient’s upcoming wedding and decided on outpatient trial medications. The psychiatrist prescribed rapidly dissolving risperidone (for ease of compliance) at 2 mg twice daily along with lorazepam at a dose of 0.5 mg twice a day for agitation and insomnia.

The following day, she presented to the emergency department of a tertiary level teaching hospital with ataxia, generalized tonic-clonic seizures, and disorientation. Magnetic resonance imaging (MRI) results were unremarkable, and the results of lumbar puncture were within normal limits except for mild pleocytosis. An electroencephalogram (EEG) demonstrated diffuse slowing of background activity that was more prominent in the left temporal region. Infectious etiologies, including viral and tubercular, were ruled out and the patient was admitted to inpatient psychiatric services.

Over the next 2 days the patient received 3 mg of risperidone twice a day along with 1 mg of benztpine twice a day, but she continued to experience stiffness and was almost catatonic and disorganized until she had another seizure and needed to be intubated for hypoventilation. The medical and psychiatric treating teams were considering a diagnosis of neuroleptic malignant syndrome or catatonia until autoimmune encephalitis was suggested, at which point cerebrospinal fluid (CSF) was sent out for additional studies and found to be positive for NMDA receptor antibodies.

Upon confirmation of the diagnosis of anti-NMDA receptor encephalitis, extensive testing for an underlying malignancy was pursued but found to be negative. On the medical unit, treatment with methyl prednisolone and plasmapheresis was begun. Intravenous lorazepam was effective for the agitation, and electroconvulsive therapy (ECT) was considered for echolalia, auditory hallucinations, and fluctuating mental status. She continued to show improvement and ultimately ECT was not used.

It has been 2 months since she was discharged from the hospital; however, she continues to work in a neuropsychological rehabilitation program for impairments in multiple cognitive domains. She will also remain under annual surveillance for malignancy.

DISCUSSION

Encephalitis is typically defined as inflammation of the brain, with viral etiology being most common. However, up to 50% of encephalitis cases are of unknown etiology, and many of these cases have recently been reclassified as having an underlying autoimmune process since the development of NMDA receptor assays.²

Anti-NMDA receptor encephalitis may present with a wide variety of early neuropsychiatric symptoms such as psychosis, insomnia, catatonia, and agitation, at times in the absence of fever. Several cases similar to the illustrated case presented here could possibly have underlying anti-NMDA receptor encephalitis that might be going undetected in rural areas due to lack of awareness among clinicians and availability of sophisticated tests for autoantibodies against the NR1a subunit of the NMDA receptor in the CSF and serum. The literature highlights the vital role of psychiatrists in early recognition and timely treatment of this condition.

Presence of immunoglobulin G antibodies in blood and CSF against the NR1a subunit of the NMDA receptor is considered the gold standard for confirming diagnosis. Management includes surgical removal of the tumor (if identified), first- and second-line immunotherapy, supportive medical care, and management of psychiatric symptoms. The role of ECT has been noted for treating catatonic symptoms in particular. Neuropsychiatric rehabilitation may be tedious and prolonged.

This autoimmune encephalitis deserves particular consideration because it frequently targets children and young adults, it may often be a herald for an underlying teratoma, and is potentially treatable with full recovery in most cases, but it can be fatal if there is a delay in diagnosis and treatment.

CLINICAL PRESENTATION

Anti-NMDA receptor encephalitis is an autoimmune encephalitis that was first described as a paraneoplastic syndrome associated with ovarian teratomas. However, studies over time have
revealed that up to 50% of adults and 70% of children with these antibodies have no identifiable tumors. A female preponderance is noted, with some studies reporting up to 80% of patients being female. However, this condition is now being increasingly recognized in both genders across a wide age range (from 1-year-old children to patients in their 90s), although the median age of presentation is 21 years. The predominance of early psychiatric symptoms often results in psychiatrists being the first clinicians to evaluate these patients, possibly in as many as 77% of all cases. This may occur in various settings including the emergency department, inpatient psychiatric unit, consultation-liaison on a medical unit, or even in the outpatient clinic. The clinical manifestations are often divided into phases (Table 1).

In children, the behavioral symptoms may include temper tantrums, hyperactivity, and irritability. Initial presentation is more likely to be non-psychiatric than in adults, with seizures and motor abnormalities being more common. As the disease progresses in children, there is a decreased occurrence of catatonia but mutism may be as high as 70%. Autonomic instability and central hypoventilation tend to be less severe in children than in adults.

Differential diagnoses may include a wide variety of organic and psychiatric conditions, with the most common being infectious encephalitis that can be viral, bacterial, fungal, or parasitic in origin. Acute disseminated encephalomyelitis may be associated with post-infection or after systemic viral infection. Other immune-mediated cases of encephalitis, such as anti-voltage-gated potassium channel encephalitis and paraneoplastic etiologies, include antibodies to Hu; CRMP5 (collapsing response mediator protein) and AMPA (amino 3 hydroxy-5 methyl-4 isoxazolopropionic acid) would also need to be considered. Additionally, a wide variety of primary psychiatric diagnoses need to be ruled out, such as early stages of schizophrenia, brief psychotic disorder, bipolar mixed episodes, neuroleptic malignant syndrome, and some of the drug-induced psychotic disorders.

**INVESTIGATIONS**

Early diagnosis and treatment is of paramount importance due to the potential impact on prognosis. The gold standard diagnostic test for anti-NMDA receptor encephalitis is the presence of NMDA receptor antibodies in the patient’s serum or CSF. Because assays for NMDA receptor antibodies may not be routinely available at most laboratories, sending the specimens to outside laboratories at tertiary level academic centers may delay the diagnosis for several days. The detection of NMDA receptor antibodies in CSF is more sensitive than detection in the serum. Most cases may be extensively investigated prior to the definitive diagnosis. Results of EEG, MRI, and CSF examination are typically nonspecific. The most common abnormality on CSF examination is lymphocytic pleocytosis. Protein concentration may be mildly increased and observed as oligoclonal bands.

In up to 90% of patients with anti-NMDA receptor encephalitis, the EEG may be abnormal. Although not specific for anti-NMDA receptor encephalitis, EEG may be helpful in differentiating between the psychiatric and encephalitic etiologies of the psychiatric and behavioral disturbances. EEG may demonstrate a diffuse slowing of the background activity. Slowing may be more prominent in one or bilateral temporal regions. A unique EEG pattern seen with this condition has been called the “extreme delta brush pattern” because of its resemblance to waveforms seen in premature infants. This pattern has been found to be associated with prolonged hospitalization and worse prognosis.

MRI may be unremarkable in the majority of cases. Up to 33% of cases may have findings that are typically seen on T2 or fluid-attenuated inversion recovery sequences as hyperintensities in a variety of regions such as the hippocampus, amygdala and surrounding cortex, and the diencephalon. In view of the nonspecificity of the results, MRI by itself has not been found to be particularly helpful in making the diagnosis of anti-NMDA receptor encephalitis.

**TREATMENT CONSIDERATIONS**

Treatment may be broadly divided into four categories: surgical removal of the underlying teratoma, immunotherapy, general medical support, and management of neuropsychiatric symptoms.

**Surgical Removal of the Underlying Teratoma**

Once a diagnosis of NMDA receptor encephalitis is confirmed, a patient must be evaluated for ovarian teratoma (if female) and other occult malignancies. In the illustrative case of this patient, investigations for underlying malignancies were negative. If an ovarian malignancy is identified, a bilateral salpingo-oophorectomy should be performed.

**Primary and Secondary Immunotherapy**

First-line treatment includes intravenous glucocorticoids with plasmapheresis. In case there is lack of clinical response to these, treatment advancement to the second line may become imperative. Second-line treatment includes use of cyclophosphamide and rituximab. There is a fair degree of discrepancy in the reported literature with regard to the clinical response. Although some cases may respond to first-line treatment, a fair
number may not respond even to second-line treatment, as reported in 2014 by Kruse et al.9

**General Medical Support**

Along with ventilator support, nutrition, bladder/bowel care, back care, and prophylaxis for deep vein thrombosis are critical and should not be compromised in these critically ill patients.

**Management of Neuropsychiatric Symptoms**

Several psychotropic medications have been used to treat the common psychiatric symptoms associated with the early symptoms of anti-NMDA receptor encephalitis. Both typical and atypical classes of antipsychotics have been used. Caution needs to be exercised when using antipsychotic medications because these may worsen the abnormal involuntary movements and possibly the catatonic symptoms due to extrapyramidal side effects. These side effects may then be mistaken for neuroleptic malignant syndrome, so antipsychotic medications may need to be stopped.

Benztropine, trihexyphenidyl, and levodopa/carbidopa have been used for the dystonic symptoms. Trazodone and diphenhydramine have been reported to be beneficial for sleep disturbances. Effective dose range for the medications have been reported but not well established yet. ECT (8 to 10 sessions) and liberal use of intravenous lorazepam have been reported to be the most beneficial for catatonic symptoms. In addition, lorazepam may be effective in treating insomnia and agitation as well.

Because management of neuropsychiatric symptoms is an ongoing part of treatment along with immunotherapy and medical support, psychiatrists continue to play a role during this phase as well.

**COURSE AND PROGNOSIS**

Prompt initiation of immunotherapy and tumor removal seem to be one of the most important predictors of positive treatment response. Approximately 75% to 80% of cases have a favorable clinical outcome and substantial recovery, despite a severe course of the illness.6,7 Cognitive deficits of varying severity, mainly in the areas of executive functioning and memory, have been found in a significant number of individuals. Because the most severe deficits were found in cases where initial treatment was inefficient or delayed, it is proposed that long-term good cognitive outcome may depend on early and aggressive treatment.12 Risk of relapse is higher among those without a detectable tumor and is estimated to be about 12%. Relapse episodes tend to be less severe and occur frequently in patients who are not given immunosuppressive therapy during the first phase of the disorder. Risk of mortality is estimated to be up to 7% at 24-month follow-up.

**NEUROBIOLOGIC UNDERPINNINGS**

Glutamate is the major excitatory neurotransmitter in the brain. NMDA is an ionotropic receptor that is a ligand-gated cation channel. NMDA receptors are composed of two subunits: the NR1 that binds to glycine, and the NR2 that binds to glutamate. NMDA receptors have been extensively studied as they are thought to play a vital role in learning, memory, and overall development of the central nervous system. Anti-NMDA receptor antibody encephalitis is characterized by the presence of immunoglobulin G antibodies in blood and CSF against the NR1a subunit of NMDA receptor.

Similarities between anti-NMDA receptor encephalitis and schizophrenia spectrum disorders have been noted, raising concerns about an underlying common link between the two.

### TABLE 1. Clinical Manifestations of Anti–NMDA Receptor Encephalitis

<table>
<thead>
<tr>
<th>Phase</th>
<th>Prominent Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodromal</td>
<td>Nonspecific symptoms such as fever, headache, and nausea</td>
</tr>
<tr>
<td>Psychotic</td>
<td>Prominent emotional disturbances such as anxiety, agitation, cognitive fluctuations, paranoia, delusions, amnesia, and auditory or visual hallucinations</td>
</tr>
<tr>
<td>Unresponsive/ hyperkinetic</td>
<td>Catatonic symptoms such as cataplexy, mutism, rigidity Abnormal involuntary movements such as orolingual dyskinesia may be prominent Seizures develop in most cases, decreased level of consciousness may alternate with periods of agitation and catatonia Autonomic instability, including tachycardia, bradycardia, central hypoventilation, hypotension, and hyperthermia, may be seen in up to 69% of the cases.6 Sleep disturbances, such as inversion, insomnia, or hypersomnia, are frequent</td>
</tr>
<tr>
<td>Recovery</td>
<td>In most cases there is gradual but complete recovery; however, this typically depends on the timeliness of initiation of treatment</td>
</tr>
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</table>

Abbreviation: NMDA, N-methyl-D-aspartate.
Moreover, several studies have reported the presence of anti-NMDA receptor antibodies in the serum of people with primary psychiatric disorders, including schizophrenia, schizoaffective disorder, bipolar disorder, and major depressive disorder, from several independent cohorts. However, the NMDA hypofunction in anti-NMDA receptor encephalitis is primarily due to a reversible loss of surface NMDA receptor. Drugs that block the NMDA receptors, such as phencyclidine, are known to produce similar symptoms of psychosis in previously normal and healthy people.

FUTURE DIRECTIONS

The information discussed here does suggest some common underlying links and pathways between this autoimmune condition and several psychiatric illnesses in the psychotic spectrum; however, much more needs to be learned before these ideas can be applied in clinical practice.

CONCLUSIONS

Given that anti-NMDA receptor encephalitis may first present with neuropsychiatric symptoms, it is critical for psychiatrists to have increased awareness and keep a high degree of suspicion for this disease, especially when symptoms are unresponsive or only partially responsive to antipsychotic medications. This may be most crucial when dealing with younger women presenting with acute onset neurobehavioral symptoms in the background of a stressor, as the diagnosis may be delayed and potentially fatal in this otherwise-treatable encephalitis. Timely referral to a tertiary level facility may be pivotal because early institution of treatment has prognostic implications. An interdisciplinary team approach involving clinicians from various disciplines, including psychiatrists (who may be the first to encounter the patient), neurologists, pediatricians, gynecologists, oncologists, and immunologists, is needed to collaborate and bring their expertise together for the timely identification and treatment of this challenging but treatable encephalitis. Psychiatrists may play a crucial role on an ongoing basis, initially at the time of presentation, then for appropriate management of behavioral symptoms, and eventually during neurocognitive rehabilitation.

REFERENCES