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## ***Selected Topics: Psychiatric Emergencies***



### **PSYCHIATRIC EMERGENCIES FOR CLINICIANS: DETECTION AND MANAGEMENT OF ANTI–N-METHYL-D-ASPARATE RECEPTOR ENCEPHALITIS**

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#### **CLINICAL SCENARIO**

A 19-year-old female college freshman presented to the emergency department (ED) for exhibiting bizarre behavior. She presented with her roommate after complaining that her boyfriend was poisoning her food. Before this episode, she was a healthy woman with no medical or psychiatric history. She denied any history of drug use, alcohol use, and she had been on no medications in the past. Collateral history provided by her roommate revealed that she was normal when they started college, but had since become “really weird” over the past 2 weeks. On examination, her vital signs were a temperature of 37.3°C (99.1°F), heart rate of 87 beats/min, respiratory rate of 18 breaths/min, blood pressure of 125/85 mm Hg, and oxygen saturation of 100% on room air. She repeatedly stated that her food was poisoned and was making her sick. She was slightly disheveled, had pressured speech, and she appeared to be delusional with regard to being poisoned. The remainder of the physical and neurologic examination was normal. She had no nuchal rigidity, nystagmus, tremor, ataxia, rashes, or petechiae. Her gait was normal. Shortly after finishing the physical examination, she had a witnessed tonic-clonic seizure.

#### **WHAT DO YOU THINK IS GOING ON WITH THE PATIENT?**

The clinical presentation suggests a new-onset psychosis. However, there are some important “red flags” that indicate that the presentation is not consistent with a primary psychiatric disorder. First, the patient presented with a rapid progression of her symptoms before which she had been normal. Second, the convulsive episode does not fit with a psychiatric diagnosis. Despite having a seizure, her physical examination was not consistent with a sympathomimetic toxidrome. Cerebral venous thrombosis and other central nervous system infections can cause seizures, however, one would not expect delusions or other negative symptoms, such as poor hygiene and grooming to occur in these disease processes.

This is actually a case of anti–N-methyl-D-aspartate receptor (NMDAR) encephalitis, a lesser-known diagnosis in the emergency medicine community. Anti-NMDAR is a newer autoimmune condition described only in the past decade (1). In anti-NMDAR encephalitis, the patient’s own antibodies are directed against the NMDA receptor, producing a characteristic syndrome of psychiatric symptoms progressing to neurologic symptoms (2,3). The disease was initially described in

young healthy females with ovarian teratomas, but now the disease is known to exist in both males and females over a wide age range, and can be present without a tumor (1,3–5). Although a large number of emergency physicians are still unfamiliar with this diagnosis, this disease is likely more common than other serious forms of encephalitis, such as herpes simplex virus (HSV) (6).

### WHAT KEY FINDINGS LEAD TO DIAGNOSIS?

Although there are no findings on examination or in the history specific for the disease, there seems to be a recurring pattern for those affected. About 70% of patients have prodromal symptoms, such as fevers, nausea, vomiting, diarrhea, headache, or upper respiratory infection (7). The patients then typically progress to psychiatric symptoms, which can include hallucinations, psychosis, agitation, depression, and paranoia, so many patients are initially evaluated by a psychiatrist (1,3,5). There may also be a disruption of memory due to the effect of the disorder on the hippocampus (8). Patients then tend to move on to develop neurologic symptoms, including seizures, confusion, difficulty speaking, and movement disorders (3,5,6). Patients can also develop autonomic dysfunction, such as dysrhythmias, hyperthermia, hypothermia, or hypoventilation requiring intubation (2).

Computed tomography (CT) imaging is likely of no utility (9). Even imaging of the brain with magnetic resonance imaging (MRI) is reportedly normal in as many as 50%–70% of cases (1,10). When MRI abnormalities are present, there may be a T2 or fluid-attenuated inversion recovery hyperintensity in the hippocampi, cerebellar, or cerebral cortex, brainstem, basal ganglia, or spinal cord (7). These findings are usually subtle and transient when present (3). Patients who undergo electroencephalography (EEG) will have abnormal results in the majority of cases, with typically nonspecific findings, such as slow or disorganized activity (3). About half of the patients will show epileptiform activity (5). There may be some patterns that are even suggestive of anti-NMDAR encephalitis (11). Even patients without clinically obvious seizure may still be in status epilepticus (12). Lastly, a lumbar puncture is of great diagnostic utility. Patients may demonstrate signs of inflammation, such as a pleocytosis or elevated opening pressure. In studies, approximately 50%–90% of patients have a pleocytosis, and 25%–30% of patients have elevated protein (3,13,14). Patients suspected of having anti-NMDAR encephalitis may have an elevated antibody titer, even if all of other cerebrospinal fluid (CSF) studies are normal.

### WHAT OTHER DIAGNOSES SHOULD YOU CONSIDER?

As the patient in the vignette presented with new-onset psychosis and manic-type features, the differential diagnoses are numerous. Initial considerations include a primary psychiatric illness, hyperthyroidism, or sympathomimetic intoxication or abuse. Given seizure, the differential diagnosis must also include potential CSF infections like meningitis, HSV encephalitis, and autoimmune conditions. If patients with anti-NMDAR encephalitis present with autonomic instability, dyskinesias, and rigidity, this may also mimic neuroleptic malignant syndrome (NMS). Several patients with anti-NMDAR encephalitis who had presented to a psychiatrist initially were started on neuroleptics for their psychiatric symptoms, which further suggested NMS (15).

### AS AN EMERGENCY PHYSICIAN, WHAT DO YOU NEED TO KNOW ABOUT THE MANAGEMENT OF ANTI-NMDAR ENCEPHALITIS?

First-line treatment consists of intravenous immunoglobulin (IVIG), steroids, and plasma exchange, as well as tumor resection, if present (3,7,10,16,17). While this treatment will likely not be initiated in the ED, knowing what studies to order can help expedite diagnosis that could be of significant benefit as patients treated earlier seem to have better outcomes (10). In the ED, if the diagnosis is suspected, anti-NMDAR antibodies can be sent from both the CSF and the serum, although the CSF seems to be a more sensitive study (13).

### How Should You Stabilize This Patient?

- The mainstay of treatment in the ED will be focused on treating psychosis, seizures, or hypoventilation if present.
- Patients with fevers or seizures should also be treated for possible meningitis. Antibiotics and antivirals should not be omitted if meningitis or HSV encephalitis remains viable on the differential diagnosis.
- Patients with catatonia caused by anti-NMDAR encephalitis do not seem to respond to benzodiazepines, but benzodiazepine administration can help differentiate the patient from other causes of catatonia.
- Patients who develop status epilepticus or hypoventilation may require mechanical ventilation.
- EEG should be used to evaluate intubated patients for ongoing status epilepticus and assess for the need of additional anti-convulsant therapy.

## CONTROVERSIES IN TREATMENT: WHAT ARE THE MOST IMPORTANT STEPS IN THE MANAGEMENT OF THIS PATIENT?

Although the mainstay of treatment consists of steroids, IVIG, and plasma exchange, along with tumor resection if present, typically, definitive therapy is not initiated in the ED. Therapy is usually delayed until the disease can be confirmed with antibody titers and, unfortunately, antibody titers are currently available only as a send-out laboratory test. Patients who do not improve with the initial regimen are often trialed on immunomodulators like rituximab or cyclophosphamide. At this time, no prospective studies have yet been done comparing the various treatment modalities head to head (7,10).

From the standpoint of the emergency physician, the most important role in treatment is making or at least entertaining the correct diagnosis. Schizophrenia should be a diagnosis of exclusion in new-onset psychosis. Likely, the diagnosis of anti-NMDAR encephalitis has been missed for several years in the ED due to lack of recognition. One retrospective study showed that 1% of all intensive care unit admissions had NMDAR autoantibodies and a large number of unexplained encephalitis cases were likely due to NMDAR autoantibodies that were found much later (18).

## CLINICAL BOTTOM LINES

- Anti-NMDAR encephalitis can have a varied presentation with nonspecific psychiatric symptoms, neurologic symptoms, or autonomic instability.
- Consider sending anti-NMDAR antibodies from either the serum or CSF if it is obtained in a previously healthy new-onset psychiatric patient who has new neurologic symptoms or dysfunction of memory.

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