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Clinical Observations

Anti–N-Methyl-D-Aspartate Receptor Encephalitis: A Potential Mimic of Neuroleptic Malignant Syndrome

Margaret Rozier MD [a], **Denise Morita MD** [b], **Marta King MD, MEd** [a,*]

[a] *Department of Pediatrics, Saint Louis University School of Medicine, St. Louis, Missouri*
[b] *Department of Pediatric Neurology, Granger Medical Clinic, Riverton, Utah*

ABSTRACT

BACKGROUND: Anti–N-methyl-D-aspartate receptor encephalitis is an autoimmune disorder characterized by behavioral changes, dyskinesia, and autonomic instability. **PATIENT DESCRIPTION:** We describe a 14-year-old girl who initially presented with acute behavioral changes and seizures and who over a 2-week period developed high fever, tachycardia, and elevated blood pressures. **RESULTS:** Because she received multiple medications including anticonvulsants and a neuroleptic, our patient was initially diagnosed with neuroleptic malignant syndrome, a disorder characterized by autonomic dysfunction, hyperthermia, muscle rigidity, and mental status changes usually caused by the use of a neuroleptic agent. Further investigation, however, revealed the presence of N-methyl-D-aspartate receptor antibodies and an ovarian teratoma. Symptoms resolved after teratoma resection and intravenous immunoglobulin therapy. **CONCLUSION:** We propose that anti–N-methyl-D-aspartate receptor encephalitis can cause a paraneoplastic syndrome mimicking neuroleptic malignant syndrome.

Keywords: anti-NMDA receptor encephalitis, neuroleptic malignant syndrome, ovarian teratoma, paraneoplastic syndrome

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Introduction

Anti–N-methyl-D-aspartate (NMDA) receptor encephalitis is a multistage autoimmune disorder with variable presenting symptoms, first described as a paraneoplastic syndrome in young women with ovarian teratomas.[1] Initial symptoms often include anxiety, mania, fear, paranoia, or hyperreligiosity.[1] Over a period of weeks to months, the disease progresses to a stage of abnormal movements (commonly oro-lingual-facial dyskinesias) and autonomic instability (hyperthermia, hypertension, tachycardia, hypotension, bradycardia, and urinary incontinence).[1]

Many of the later anti-NMDA receptor encephalitis symptoms overlap with the clinical features of neuroleptic malignant syndrome (NMS). NMS is characterized by mental status changes, bradykinesia with rigidity, autonomic dysfunction, and hyperthermia usually caused by the use of a neuroleptic and/or antipsychotic agent.[2] Many patients with early, undiagnosed anti-NMDA receptor encephalitis are prescribed antipsychotic medications to help alleviate the acute symptoms of agitation or delirium. This fact raises the question of whether NMS is caused by these medications *or* the possibility that NMS is a feature of the anti-NMDA receptor encephalitis itself, at least in some patients.

Patient Description

This previously healthy 14-year-old girl was transferred from the pediatric intensive care unit (PICU) to the pediatric hospitalist service for further management of NMS. One week before admission, the patient had had a seizure-like episode at home. Electrolytes, urine drug screen, and head computed tomography (CT) scan were normal. Electroencephalography showed left temporal epileptiform discharges, and levetiracetam was started. The patient continued to complain of headache, lightheadedness, and insomnia. The family observed periods of unprovoked crying and arm jerking. Lethargy and dystonic arm movements were noted during a follow-up primary care visit. The patient was referred back to the emergency department and re-evaluated by neurology. The symptoms were attributed to levetiracetam, and the patient was discharged on a lower dose. At home, she developed hallucinations and

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* Communications should be addressed to: Dr. King; Division of General Academic Pediatrics (GAP); Department of Pediatrics; St. Louis University; 1465 S Grand, Room 3711 North Tower; St. Louis, Missouri 63104.
E-mail address: Making@slu.edu

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paranoia, and levetiracetam was discontinued and oxcarbazepine was started.

The day after starting oxcarbazepine, the patient was seen by her primary care physician with a new complaint of fever up to 40°C. Rapid influenza test was negative, and she was sent home with a diagnosis of a viral illness. Emergency medical services and police were called that night when the patient became agitated, disoriented, and violent toward herself and others. A single dose of haloperidol was administered en route to the emergency department, and there she was agitated, confused, febrile (39.5°C), hypertensive (155/70 mm Hg), tachycardic (132/minute), and had abnormal movements and muscle rigidity. She was admitted to the PICU.

While in the PICU, her diagnostic evaluation included five negative urine drug screens, two normal head CT scans, a normal cranial magnetic resonance imaging and angiogram, negative blood and urine cultures, normal cerebrospinal fluid studies, bacterial cultures, and herpes simplex virus polymerase chain reaction. A creatinine kinase level was measured at 9200 U/L. She was diagnosed with NMS and treated with bromocriptine and dantrolene. The diagnosis was based on the presence of high fevers, hypertension, muscle rigidity, and rhabdomyolysis in the setting of recent exposure to haloperidol, levetiracetam, and oxcarbazepine.

History was reviewed and diagnosis reassessed at the time of transfer from the PICU to the hospitalist service. She met all the Diagnostic and Statistical Manual of Mental Disorders V criteria for NMS with one exception: it was not yet proven that the symptoms of NMS were not due to another substance or neurological or general medical condition.[3] Furthermore, although the patient's presentation did fit some of the features of NMS, this diagnosis did not explain all her symptoms nor their persistent nature. For example, many of her symptoms began several days before receiving haloperidol. We were unable to find any reported cases of NMS secondary to levetiracetam and found only one reported case of NMS involving the addition of oxcarbazepine to long-term amisulpride therapy.[4] Although haloperidol and other typical antipsychotics are well known to cause NMS, our patient's high fevers and tachycardia began several days before this drug was first administered.

Other etiologies of encephalopathy were explored including paraneoplastic syndrome. Diagnosis of anti-NMDA receptor encephalitis was confirmed when serum and cerebrospinal fluid antibody titers came back positive with 1:40 and 1:5, respectively, consistent with the diagnosis of anti-NMDA receptor encephalitis.[5] A mature ovarian teratoma was found on a screening ultrasound, confirmed on pelvic CT, and resected. She was treated with intravenous immunoglobulin and steroids and subsequently transferred to an inpatient rehabilitation center. She experienced full recovery and was back to her baseline less than eight weeks after surgery.

Discussion

Although the pathophysiology of NMS is not well understood, the dopamine hypoactivity hypothesis is the most widely accepted theory.[6] This theory proposes that the clinical features of NMS are precipitated by the blockade of dopamine receptors in the hypothalamus, which leads to temperature dysregulation.[6] The decrease in dopamine through the basal ganglia leads to Parkinsonian symptoms such as muscle rigidity and tremor.

Given this theory, it is understandable that typical antipsychotic medications, which are dopamine antagonists, can give rise to NMS in some patients. However, it may be that NMDA receptor antibodies themselves have some role in dopamine blockade as well, especially because patients whose CSF is positive for NMDA receptor antibodies and who have not received antipsychotic drugs can also develop the clinical picture of NMS.[1] Yet our patient's symptoms were not relieved by bromocriptine, which is a dopamine receptor agonist.

It is possible that some patients develop manifestations similar to NMS on the basis of a paraneoplastic syndrome of anti-NMDA receptor encephalitis and that NMDA receptor antibodies affect the hypothalamus and basal ganglia by a completely different mechanism. If further cases of NMS due to anti-NMDA receptor encephalitis are identified, it may be possible to differentiate these clinically from cases of NMS due to neuroleptics. For instance, the typical age range or distribution between sexes may be different in each disease. Observations such as this could lead to improved understanding of both diseases. Further studies investigating the link between anti-NMDA receptor antibodies and dopamine activity are needed for a better understanding of the pathophysiology of the disease.

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