The Journal of Emergency Medicine, Vol. 51, No. 2, pp. 136–139, 2016

0736-4679/$ - see front matter

http://dx.doi.org/10.1016/j.jemermed.2016.05.003

Selected Topics: Neurological Emergencies

ANTI-*N*-METHYL-D-ASPARTATE RECEPTOR ENCEPHALITIS AS AN UNUSUAL CAUSE OF ALTERED MENTAL STATUS IN THE EMERGENCY DEPARTMENT

Michael Weaver, MD and Richard T. Griffey, MD, MPH

Barnes-Jewish Hospital, Washington University School of Medicine, Saint Louis, Missouri
Reprint Address: Michael Weaver, MD, Barnes-Jewish Hospital, Washington University School of Medicine, 1 Barnes-Jewish Hospital Plaza, Saint Louis, MO 63110

☐ **Abstract—Background: Anti-*N*-methyl-D-aspartate (NMDA) receptor autoimmune encephalitis is a newly identified form of encephalitis whose incidence is on the rise. Awareness of this condition and symptom recognition are key to early diagnosis and prompt treatment, which may alter the course of the disease. Case Report: A 35-year-old woman presented to our Emergency Department (ED) with lethargy, bizarre behavior, agitation, confusion, memory deficits, and word-finding difficulties. Her symptoms and evaluation were potentially consistent with a primary psychiatric disorder, but the absence of frank psychosis and presence of neurologic features related to memory and cognition prompted other considerations. In the ED we performed a lumbar puncture, and in addition to routine studies, ordered anti-NMDAR antibody screening. The screening studies returned positive, leading to treatment with glucocorticoids and intravenous immune globulin and resulting in improvement to near baseline function. Why Should an Emergency Physician Be Aware of This? Although anti-NMDAR encephalitis is relatively uncommon, reports of this previously unrecognized condition are increasing, with an unclear true incidence of disease. Emergency providers should consider this diagnosis in their differential for patients presenting with new neuropsychiatric symptoms, particularly in young women. Prompt treatment leads to near complete neurologic recovery in 75% of patients, whereas delays in diagnosis and treatment may be associated with worse outcomes including death.** © **2016 Elsevier Inc. All rights reserved.**

☐ **Keywords—NMDA encephalitis; encephalitis; NMDA; psychosis; autoimmune**

INTRODUCTION

First discovered in 2007, *N*-methyl-D-aspartate receptor (NMDAR) autoimmune encephalitis is a multistage illness whose symptoms progress from a prodromal illness to bizarre behavior, memory deficits, and psychosis to autonomic instability, respiratory failure, and coma (1,2). The prevalence of this disease is unknown; however, the rapid increase in the number of cases suggests that the incidence may be on the rise and the prevalence may be higher than previously appreciated. The degree to which this condition was previously undiagnosed or misdiagnosed is not clear. A study from the United Kingdom suggests that NMDAR autoimmune encephalitis may account for up to 4% of encephalitis cases (3). Patients often present with a constellation of psychiatric symptoms that can lead to attribution of the symptoms to a primary psychiatric disorder and unsuccessful treatment for an acute psychotic episode (2).

Awareness of this disease and recognition of its symptoms are key to early diagnosis and prompt initiation of treatment, which may lead to improved outcomes. With treatment, 75% of patients will completely recover or have mild sequelae, whereas the remaining 25% will be severely disabled or may die (1,4). We report a case of a patient with anti-NMDAR encephalitis in which early consideration of this condition and initiation of testing

RECEIVED: 21 January 2016; FINAL SUBMISSION RECEIVED: 31 March 2016;
ACCEPTED: 5 May 2016

from the emergency department (ED) led to timely diagnosis of anti-NMDAR encephalitis, introduction of treatment, and a successful clinical outcome.

CASE REPORT

A 35-year-old previously healthy woman was seen at an outside ED after a 6-week history of headaches, lethargy, and sinus congestion. Initially, she was evaluated by her primary care physician, who treated her for sinusitis with levofloxacin. The family was concerned she may have had an allergic reaction to this medication, as she seemed to develop anxiety, for which she was subsequently prescribed alprazolam. Her condition continued to decline and she now started to display signs of lethargy, bizarre behavior, agitation, confusion, memory deficits, and word-finding difficulties. Her husband stated, "she would walk around the house like a zombie," and for a period of time forgot the name of their young son. The family thought her worsening symptoms might be related to the alprazolam, but when this persisted while off the medication they decided to seek further medical care. Her medical history was negative for any previous psychiatric or neurologic illnesses.

Her physical examination demonstrated normal vital signs as well as normal cardiovascular and pulmonary findings. She responded to questions slowly and was unable to provide crisp answers to questions. She was otherwise silent, with her husband providing the history. The neurologic examination revealed an alert and oriented female with delayed cognition. Examinations of the cranial nerves, motor strength, sensory, and gait were unremarkable. She was unable to recite the months of the year backwards. Initially, during her examination, she did not appear to respond to internal stimuli or exhibit frank psychosis. However, at one point, she was noted to rock back and forth, striking her head with her fist and repeating the phrase "I'm a good boy."

Initial work-up in the ED included a normal complete blood count, complete metabolic panel, thyroid-stimulating hormone, alcohol level, urine drug screen, and ammonia. Magnetic resonance imaging (MRI) of the brain was unremarkable. A lumbar puncture was performed in the ED, which revealed a mildly elevated protein level (52 mg/dL), nine nucleated cells, and normal glucose. Routine infectious panels for bacteria and viral screens in the cerebrospinal fluid (CSF) were ordered, as well as paraneoplastic and multiple sclerosis panels. Given our concern for an encephalitic process and aware of case reports of anti-NMDAR encephalitis presenting with similar features, we also ordered a CSF NMDAR antibody screen.

The patient was admitted to the neurological service. Bacterial, viral, and extended CSF studies returned negative. However, the NMDAR antibody screen returned positive with a titer of 1:64. On hospital day 4 she began treatment with 5 g intravenous methylprednisolone and intravenous immunoglobulin that continued over the course of 4 weeks. Her hospital course was complicated by autonomic instability with tachycardia, tachypnea, and respiratory failure, requiring a brief stay in the intensive care unit. At 3-month follow-up post-hospital discharge, the patient had returned to near-baseline cognitive function.

DISCUSSION

Diagnosis of anti-NMDAR continues to rise, with an unknown true incidence and prevalence. Eighty percent of cases occur in females. Roughly 20% of cases in women between the ages of 30 and 35 years present as a paraneoplastic syndrome associated with an ovarian teratoma (1,5,6). The pathogenesis of anti-NMDAR encephalitis is initiated when autoantibodies against the NMDA receptor result in a profound, but reversible, decrease of NMDARs, resulting in modulation of synaptic plasticity (7). Decreased NMDARs leads to effects on dopaminergic, noradrenergic, and cholinergic systems, resulting in autonomic instability (1).

Consequently, patients begin to develop predominantly psychiatric symptoms, as described above, and are often initially seen primarily or in consultation by psychiatrists, which may result in delays in treatment (1). Viral encephalitis, acute psychosis, and drug-induced psychosis can have features, including psychiatric symptoms, which are often indistinguishable from anti-NMDAR encephalitis. These conditions are thus generally part of the differential diagnosis for presentations typical of anti-NMDAR encephalitis (1). Depending on the clinical context, paraneoplastic encephalitis, neuroleptic malignant syndrome, serotonin syndrome, and lupus cerebritis might also be considered (8). Features that might raise suspicion for anti-NMDAR encephalitis include insomnia, mania, paranoia, catatonia, and orofacial dyskinesias (2). In addition, memory impairment, echolalia, slowed speech, and the lack of frank psychosis may also be suggestive of anti-NMDAR encephalitis rather than an acute primary psychiatric disorder (2).

Patients progress through predictable, discrete, well-described phases of illness (1). This begins with a prodromal phase of up to 2 weeks with what may appear to be a viral illness that may include lethargy, nausea, headache, upper respiratory infection symptoms, myalgias, fever, and diarrhea. This is followed by a primarily neuropsychiatric phase lasting 1–3 weeks with agitation, behavioral changes, anxiety, fear, manic symptoms, paranoia, and disorganization, delusions, hallucinations,