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Selected Topics: Neurological Emergencies

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

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☐ **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

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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,

and psychosis. Changes in speech are also commonly observed in this phase (1,4,9). In the neurologic phase that can last from weeks to months, patients experience short-term memory loss, speech difficulties, and various motor symptoms including facial dyskinesias, choreoathetosis, and rigidity (1,2). Seizures, dystonia, and mutism may follow, and in children these may be a part of the initial presentation (1). As the disease progresses, patients may experience dysautonomia, hypoventilation, coma, and death (1,2,4). The last phase of acute illness, increasingly in the course of treatment, consists of an improvement of symptoms roughly in reverse order of onset, and often includes recurrence of psychotic features and agitation (1). The last phase of illness is the chronic phase in which cognitive and behavioral deficits may persist, including deficits in executive function, disinhibition, impulsivity, and sleep abnormalities. Amnesia of the entire acute phase of illness is common.

Brain MRI may be useful in diagnosis and should be performed to rule out metastatic disease, a cerebrovascular event, or other disease processes (10). Although this imaging may be unremarkable in 50% of patients, the remaining 50% may have FLAIR (fluid-attenuated inversion recovery) abnormalities or T2 hyperintensity in the cortex, basal ganglia, brainstem, and hippocampus (1,4). Lumbar puncture should be performed and is critical for diagnosis. Cerebrospinal fluid is abnormal in 80% of patients, often revealing mildly increased protein concentration, lymphocytic pleocytosis, and cerebrospinal fluid-specific oligoclonal bands (1). This can have a similar appearance to viral encephalitis, and so CSF testing should also be directed at typical viral pathogens (eg, herpes simplex virus polymerase chain reaction). In all reported cases, anti-NMDAR antibodies have been detected in cerebrospinal fluid and in some cases can be detected in serum (1). Because many cases are associated with a paraneoplastic syndrome, all patients should be evaluated for an underlying tumor such as an ovarian teratoma or germ-cell tumor during their hospital admission (1,5,6).

In cases not associated with an underlying tumor, treatment consists of high-dose corticosteroids, intravenous immunoglobulin, and plasma exchange to manage the immune response, with cyclophosphamide and rituximab as second-line agents for refractory disease (1). Limited experience suggests that early initiation of treatment has been associated with better outcomes (1,11). The hospital course is generally prolonged, with mean length of stay equal to 7 months, whereas total neurologic recovery may take up to 3 years. Mortality has been estimated to be 4% of cases (1).

When faced with a patient, particularly a young female, with new neuropsychiatric features, the most important intervention in the ED setting is to consider anti-NMDAR encephalitis and to look for signs and symptoms in the history and physical examination. History of a viral prodrome in the week or two leading up to onset of agitation, changes in behavior and personality, altered memory and speech, the presence of motor symptoms including orofacial dyskinesia or rigidity, or autonomic dysregulation should raise suspicion of anti-NMDAR encephalitis. A lumbar puncture should be performed if an encephalitic process is considered, including titers for NMDAR antibodies if suspected. Imaging with MRI is recommended. Early neurologic consultation and communication of concern is important, and depending on the level of suspicion, might prompt empiric treatment, which may be associated with improved outcomes.

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

We present the case of a previously healthy 35-year-old woman with no prior psychiatric or neurologic history who presented to the ED with bizarre behavior, memory deficits, agitation, and confusion. Awareness of anti-NMDAR encephalitis and its early manifestations can be the key to arriving at an early, accurate diagnosis and initiating prompt treatment. This can avoid attribution of symptoms to a primary psychiatric disorder, which could result in delayed diagnosis or failure to diagnose this disease. In light of the overall mortality as well as the severe neurological sequelae with delayed diagnosis and treatment, it is important that emergency physicians be aware of anti-NMDAR encephalitis and its features and to consider this in the differential diagnosis in patients, particularly young women, presenting with new onset of acute neuropsychiatric symptoms.

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