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A YOUNG WOMAN PRESENTING WITH PSYCHOTIC AND MOOD SYMPTOMS FROM ANTI-N-METHYL-D-ASPARTATE RECEPTOR (NMDA-R) ENCEPHALITIS: AN EMERGING DIAGNOSIS

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ABSTRACT

Anti-N-methyl-D-aspartate receptor (NMDA-R) encephalitis, first characterized in 2005, is a neurological disease with prominent psychiatric features that frequently involves the consultation of psychiatrists. Since its discovery, the rate of diagnosis of new cases has increased rapidly and several epidemiological studies now confirm that NMDA-R encephalitis may be as common as many other prominent infectious etiologies of encephalitis. We describe a case of a young woman presenting initially with psychotic and mood symptoms who was found to have anti-NMDA-R encephalitis. We further provide details of her treatment and prolonged recovery process after hospital discharge with a review of the literature and discussion of the epidemiology, symptomology, diagnosis, and management of both the neurologic and psychiatric manifestations of this condition. Last, we contextualize the importance of anti-NMDA-R encephalitis for psychiatrists, highlighting the role for psychiatrists in establishing the initial diagnosis as well as in providing ongoing psychiatric care.

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INTRODUCTION

Anti-N-methyl-D-aspartate receptor (NMDA-R) encephalitis is a rare but increasingly diagnosed neurological disease with prominent psychiatric features frequently requiring the consultation of psychiatrists. Since the first case descriptions of this condition in 2005 of four women with ovarian teratomas, neurological deficits, and psychosis, significantly better understanding of the symptoms, pathogenesis, and treatment of this disease has emerged [1]. A recently published cohort study of 501 anti-NMDA-R encephalitis patients, the largest to date, has further helped characterize this disease, articulating a patient population that is predominantly female, in the late teens to early twenties, with greater than half of patients older than 18 years having ovarian teratomas [2]. These patients exhibit a characteristic symptom profile that begins with anxiety, mood dysregulation, sleep disturbance, and psychosis, followed by rapid neurological decline that may include movement abnormalities, autonomic instability, central hypoventilation, and ultimately coma.

Epidemiological studies reveal that anti-NMDA-R encephalitis is quite common with an increasing number of cases now being diagnosed. In England, one study demonstrated that this condition was nearly as prevalent as encephalitis due to Varicella Zoster Virus (VZV) or Mycobacterium Tuberculosis (M. TB) [3]. The California Encephalitis Project's findings from 2007 to 2011 similarly showed that NMDA-R encephalitis, which represented 4.2% of cases in the California Encephalitis Project cohort, was the leading diagnosed cause of encephalitis in individuals under 30 years old. The condition was more than four times as frequent as encephalitis due to Herpes Simplex Virus 1 (HSV1), West Nile Virus (WNV), or VZV in this age group [4].

As one of the few encephalitides that presents with prominent psychiatric symptoms, anti-NMDA-R encephalitis is a condition that results in frequent psychiatric hospitalization and consultation and is often misdiagnosed as a primary psychotic disorder, malingering, or substance abuse. During the years after this disease was first articulated, nearly 75% of patients with this condition were initially seen by a psychiatrist and/or admitted to a psychiatric unit [5]. Here we describe a case of a young woman who presented with many classic neurological and psychiatric features of anti-NMDA-R encephalitis, including the acute development of prominent psychotic symptoms.

CASE PRESENTATION

Ms. L was a 22-year-old, previously healthy woman who presented to the emergency room of an outside hospital with a three-week history of left arm numbness followed by the development of hypersomnolence, disinhibited behavior, and left arm weakness with neglect. She was brought in after her mother observed her driving erratically and distractedly with prominent left-sided

neglect, at one point reaching across the steering wheel to use the turn signal with her right hand. During the weeks prior to this event, Ms. L had exhibited extreme affective lability as well as several episodes of inappropriate laughter and name-calling. Such behavior was uncharacteristic, as she was known to be very sensitive and caring at baseline. Her friends had also noticed that she had been having difficulty paying attention in class and completing homework assignments. Given the patient's prominent motor symptoms, the physicians at the outside facility suspected a stroke but were unable to confirm any abnormalities on brain MRI. The decision was then made to transfer the patient to the neurology service at our academic center for further workup.

On review of symptoms, the patient had no history of headaches, dizziness, or seizures. She had experienced no dysphagia, slurred speech, or gait difficulties, with her only motor and sensory symptoms confined to her left arm. Furthermore, she had no incontinence, back pain, or symptoms consistent with a recent illness or infection. Ms. L was a university student and had been previously high functioning with plans to apply to graduate school. She did not use drugs, alcohol, or medications and there was no known family history of neurological or psychiatric disease.

Physical exam revealed normal bulk but decreased tone and strength in her left upper extremity with slowed finger taps and posting of her right hand around her left when told to imitate the examiner in rotating her hands around one another. There were no discernable sensory, cerebellar, gait, or reflex abnormalities. The patient was found to be alert and oriented but displayed little spontaneous speech and employed only short phrases. Her affect was blunted and restricted but also punctuated at times with inappropriate laughter. Ms. L denied having hallucinations or delusions but maintained poor insight and judgment, stating that she came to the hospital because "[her] mom had brought [her] here." She exhibited dysfunction in working and short-term memory as well as very concrete thinking. The patient also had prominent visuospatial deficits, best demonstrated by an abnormal clock draw with poor planning that neglected the left side.

Upon further workup, the patient was found to have a normal brain MRI with cerebrospinal fluid (CSF) significant for moderate lymphocytic pleocytosis (white blood cell count = 44 x 10E6/L) and protein elevation (67 mg/dl) with oligoclonal bands. Her infectious workup revealed negative bacterial and fungal blood cultures and negative tests for HSV1, VZV, syphilis, HIV, Lyme disease, and Human Herpes Virus-6 (HHV6). She had no detectable abnormalities by autoimmune and endocrine assays. A video electroencephalogram (EEG) demonstrated diffuse excess slowing with delta brush pattern, a finding seen in up to half of patients with anti-NMDA-R encephalitis [6]. A transvaginal ultrasound and pelvic MRI showed no evidence of teratoma. A paraneoplastic antibody panel was negative.

Given the patient's age, normal MRI imaging, negative infectious workup, and EEG findings, the leading initial diagnosis favored an autoimmune etiology such

as anti-NMDA-R encephalitis, systemic lupus erythematosus, or Hashimoto's encephalitis. The patient was subsequently begun on intravenous solumedrol one gram daily for three days and intravenous immunoglobulin (IVIG) therapy for five days.

On day nine of hospitalization, Ms. L acutely developed agitation and psychosis. She expressed a sudden desire to leave, proffering grandiose thoughts of owning a luxury sports vehicle to which she needed to attend as well as paranoid delusions that her parents and the hospital staff were plotting to kill her. Her agitation was accentuated with several violent outbursts during which she punched staff, subsequently requiring restraints and sedation. She endorsed auditory hallucinations of threatening voices as well as visual hallucinations. At one point the patient proclaimed that she wanted to commit suicide and attempted to jump out of her room's window. After consulting the psychiatry service for management recommendations, the primary team treated Ms. L with one milligram (mg) of haloperidol every six hours with an additional one mg of lorazepam every four hours as needed, and her psychosis and agitation gradually resolved over several days.

On day sixteen, the patient's anti-NMDAR antibody assay returned positive and she was treated with a five-day course of plasmapheresis. Upon completion, the patient was started on rituximab therapy, which was subsequently discontinued after she developed an adverse reaction consisting of facial flushing, fine reticular rash, pruritus, and oropharyngeal edema.

By this time, Ms. L's left upper extremity weakness and neglect had nearly resolved, and it was felt that her remaining symptoms could be best addressed in an outpatient setting. Upon discharge, the patient's mental status was significantly improved. However, she continued to have reduced spontaneous speech and blunted but reactive affect. Her insight was very limited, only understanding that she had a brain illness despite several attempts by her care team to explain additional details. She also exhibited deficits in short-term and working memory as well as concrete thinking, unable to interpret proverbs such as "the early bird gets the worm" or "the squeaky wheel gets the grease."

At a follow-up appointment two months after initial presentation, Ms. L complained of frequent daily headaches as well as continued visual and auditory hallucinations. On exam she was noted to still have affective lability, impulsivity, as well as impaired short-term and working memory, verbal skills, and executive function. She scored a 23 out of 30 on the Folstein Mini-Mental State Exam (MMSE). The patient was dependent for several of her Activities of Daily Living (ADLs), requiring help from her family with bathing, dressing, and cooking. Although the patient had no confirmed seizures, given the patient's almost daily episodes of cognitive slowing and mood alteration, her medical regimen consisted of 300 mg of phenytoin every evening for seizure prophylaxis and 1 mg of lorazepam as needed for agitation or anxiety, averaging 1 mg of lorazepam every three days. She was subsequently prescribed 12.5 mg quetiapine each day before bedtime to help control her psychotic symptoms.

At a second follow-up appointment three months after initial presentation, Ms. L's hallucinations and delusions had been well controlled with quetiapine, and she had discontinued the medication the week before without symptom recurrence. She reported feeling extremely frustrated on occasion by how her condition had strained her friendships, telling the examiner "I felt like I had no one to talk to except my parents and sister and that gets hard sometimes." Nevertheless, the patient was significantly improved on exam with markedly better performance in memory, verbal skills, and executive function. She scored 28 out of 30 on the MMSE and had no more detectable motor or sensory deficits except for a mild intention tremor in her left hand. At this point, the patient's only psychoactive medication was 300 mg of phenytoin every day.

By the patient's 6-month follow-up visit, Ms. L had begun to take two classes at her college. Her memory, executive functions, and language skills had improved to the point where she was able to schedule and attend class independently as well as read and complete homework assignments on time. She continued to have periods of mood lability and anxiety for which she now sees a psychologist once a week, but claimed that, otherwise "everything has been getting better" and she has begun to reconnect with her friends. She and her parents were discussing plans for having the patient live independently once again. A repeat NMDA-R antibody assay returned negative.

DISCUSSION

Anti-NMDA-R encephalitis is caused by antibodies that bind the NR1 subunit of the NMDA receptor and induce NMDA receptor internalization [5, 7]. The trigger for such antibody production is still unknown, although it is presumed to be secondary to sensitization from ectopic cells expressing neural elements such as in ovarian teratomas. The antibodies themselves are assumed to be pathologic since antibody titers correlate with clinical symptoms and removal of ovarian teratomas is associated with improved prognosis [2].

NMDA receptors are ligand-gated cation channels that are most highly expressed in the forebrain, limbic system, and hypothalamus. Receptor overactivity has been linked to the pathologic symptoms associated with ischemic stroke and traumatic brain injury [8]. Receptor underactivity can be seen in schizophrenia as well as the use of NMDA-R blocking drugs such as ketamine and phencyclidine (PCP) [9]. Not surprisingly, the symptom profile of anti-NMDA-R encephalitis has features that include both neurological and psychotic symptoms seen in these conditions.

Ms. L, as a female in her early twenties, fit the typical demographic for anti-NMDA-R encephalitis in a patient without a detectable ovarian teratoma. To our knowledge, she did not experience the prodrome seen in 70% of patients consisting of headache, fever, nausea, vomiting, and diarrhea [10]. However, as with most cases, she developed early-on psychiatric manifestations, including

anxiety, sleep disturbance, and mood dysregulation, later followed by delusions and paranoia. Patients also frequently experience rapid disintegration of language with reduction of verbal output, echolalia, and in severe cases, mutism. Fortunately for our patient, she did not sustain neurological decline beyond her upper extremity weakness and cognitive deficits. The natural history of this disease can involve developing alternating periods of agitation and catatonia, progressive loss of consciousness resulting in coma, and movement disorders such as oro-lingual-facial dyskinesia, choreoathetosis, and dystonia. Patients will often also exhibit autonomic instability with dysregulation of temperature, heart rate, blood pressure, saliva production, and urinary continence, as well as central hypoventilation requiring intubation and mechanical ventilation.

The diagnosis of anti-NMDA-R encephalitis is established with detection of the pathologic antibodies in serum or CSF. Patients typically will have CSF demonstrating moderate lymphocytic pleocytosis and normal or mildly increased protein levels [10]. Over 60% of patients will have oligoclonal bands. Two-thirds of patients will have a normal brain MRI and the other third may display diffuse hyperintensities on T2/FLAIR MRI [2]. As in Ms. L's case, the EEG will often show non-specific, slow, disorganized activity.

The mainstay of treatment for anti-NMDA-R encephalitis is immunosuppression. First line therapy is corticosteroids, IVIG, plasmapheresis, and teratoma removal. Using this treatment strategy, 53% of patients have been shown to improve significantly at 4 weeks with 97% having a good outcome (defined as a modified Rankin Scale score of 0-2) at 24 months [2]. Second line therapy includes rituximab or cyclophosphamide and results in 74% of patients who failed first-line therapy demonstrating a good outcome at 24 months [2]. Overall mortality for this condition is 4%, with a median time of 2.5 months from symptom onset to death [10].

While the vast majority of literature to date has focused on treating the neurological symptoms of anti-NMDA-R encephalitis, little has been published on the management of the psychiatric symptoms associated with this condition. This is perhaps attributable to the difficulty in assessing the efficacy of psychiatric treatments, since patients often present with multiple psychiatric symptoms and are treated simultaneously with several interventions, some of which, such as corticosteroids, can themselves precipitate psychiatric symptoms. Furthermore, the newness of this condition and its relative rarity as a diagnosis have made large studies difficult. A review of the case literature demonstrates that standard treatment to date has been symptomatic psychiatric management [11]. Agitation and psychotic symptoms have been treated using typical and atypical antipsychotics with limited success and sometimes additionally complicated by the worsening of motor deficits. Insomnia is addressed with benzodiazepines, clonidine, or trazodone. Mood dysregulation has been managed with valproate and lithium with mixed results. Movement abnormalities are usually treated with anticonvulsants. Electroconvulsive therapy (ECT), which may upregulate

NMDA receptors in animal models, has been successfully used in a few case reports [12-14]. However, its effect in humans has yet to be firmly established. In the case of our patient, we successfully managed her agitation and psychosis with a standard combination of haloperidol and lorazepam. This treatment regimen was selected because it could be administered parenterally and was known to be safe and effective for managing acute psychotic agitation. Her continued auditory and visual hallucinations after discharge were adequately treated with a standard dosing of quetiapine.

The recovery process from anti-NMDA-R encephalitis is multistage and lengthy [5]. Patients typically recover in reverse order of symptom presentation: first regaining consciousness, respiratory drive, autonomic functions, and motor control, and only then restoring higher level neurological and cognitive functions. As part of this process, patients will occasionally re-present with agitation and psychotic symptoms. Executive function is most often the last to improve and patients may display prolonged periods of impulsivity, disinhibition, hyperphagia, hypersexuality, and hypersomnia among other behavioral disorders. Such symptoms often require ongoing management with psychoactive medications. At two months after treatment, Ms. L continued to have anxiety, mood lability, as well as significant deficits in memory, executive function, abstract thinking, and verbal abilities. Even after significant recovery of her cognitive abilities after six months, the patient continued to struggle with mood disorder related to both the direct effects of her encephalitis as well as the condition's debilitating secondary effects on her social functioning and relationships.

CONCLUSION

Given its widespread prevalence and the growing awareness and diagnosis of this condition, anti-NMDA-R encephalitis is becoming an especially important disease for psychiatrists to recognize. Our patient was fortunate to have been referred quickly to a neurology service at a specialty center experienced with anti-NMDA-R encephalitis cases because of her prominent motor deficits. However, not all patients display such significant neurologic symptoms early on. Instead, patients with this disease are frequently first seen at a psychiatry clinic or admitted from the emergency room to a psychiatric service since cognitive and behavioral symptoms are the most prevalent primary presentation of this disorder. This condition is furthermore easy to misdiagnose as its features overlap with primary psychiatric disorders. Recognizing the constellation of psychiatric symptoms in the setting of neurological dysfunction can help distinguish anti-NMDA-receptor encephalitis from other types of encephalitides. Indeed, it is the only autoimmune encephalitis syndrome that involves prominent psychotic features with other syndromes preferentially affecting memory and orientation [15]. Infectious encephalitides are similarly associated with much lower rates of psychosis. In our patient's case, early recognition of this condition

and prompt treatment may have prevented further neurological and psychiatric decline, speaking to the importance of coordinating care among emergency medicine, internal medicine, psychiatry, and neurology services and considering anti-NMDA-R encephalitis early in the diagnostic workup of these patients. Although the anti-NMDA-receptor antibody assay is still only performed at a select number of specialty centers, given the prevalence of this condition, this test may become more widely available in the near future and would be worthy of consideration as a screening test for specific symptomatic patient populations. Lastly, anti-NMDA-R encephalitis patients, although often treated acutely for their neurological dysfunction, can require long-term psychiatric care given that psychiatric symptoms are the first to present and the last to resolve. As in Ms. L's case, one study showed that 85% of anti-NMDA-R encephalitis patients at discharge continued to have poor attention and planning, impulsivity, and behavioral disinhibition [5]. Current treatment of the psychotic symptoms of this disease has remained relatively unstandardized and unstudied, derived almost exclusively from anecdotal reports. With the number of diagnosed anti-NMDA-R encephalitis cases on the rise, more research into the management of the psychiatric symptoms of this condition, both in the acute as well as chronic settings, will be needed.

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