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CASE REPORT

Anti-NMDA-Receptor Encephalitis: Case Report and Literature Review of a Frequently Misdiagnosed Condition

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Abstract

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a potentially fatal autoimmune syndrome in which IgG antibodies target the NR1 subunit of the NMDA receptor resulting in profound dysregulation and neurotransmission. Since its discovery in 2005, the illness is becoming more widely recognized. Despite this uptick in recognition, few cases are published in journals pertinent to primary care providers. Patients typically present with acute behavioral disturbances and psychosis, which then evolves into seizures, memory loss, dyskinesias, speech difficulties, and autonomic dysregulation. While the disease is lethal if left untreated, immunotherapy and surgical resection of any associated malignancy result in rapid symptom improvement. In this report, we detail a case of an 8-year-old with anti-NMDAR encephalitis not associated with malignancy.

Case

An 8-year-old female with a normal birth history and no significant past medical history presented to the ER with a chief complaint of left upper and lower extremity jerking and slurred speech that started on the day of arrival. On further questioning, her mom complained of a change in mood and affect over the last two weeks, stating that the patient had developed new onset anxiety, decreased verbal communication, and decreased activity level. The mother also reported that patient had been complaining of seeing "dark shadow people" throughout the house, with increasing frequency over the last three days.

The patient has no history of seizures. Her family history is significant for seizures in adulthood in her father and maternal grandfather and childhood seizures in her mother. Review of systems was positive for generalized headaches and diffuse, wandering myalgia and paresthesia. Physical exam was concerning for a blunted affect with minimal participation by the patient; she responded inappropriately to questions with, at most, two-word answers. The remainder of the physical exam was unremarkable. The patient was admitted for further evaluation and workup.

Labs, including CBC, CMP, vitamin levels and urinalysis, were unremarkable. Head CT was negative for intracranial hematoma, masses, or structural abnormalities. Electroencephalogram was significant for right focal seizure activity. The patient was diagnosed with complex partial seizure disorder and started on Keppra. She remained stable after initiation of Keppra and was discharged home after two days.

During her follow-up visit, parents reported that the patient had been having "rage attacks" lasting 30 minutes. They report worsening of her hallucinations and state that patient has been screaming "in a different language." Her parents are concerned that she is "possessed after touching an old family Bible" and are considering an exorcism. While in the clinic, the patient demonstrated seizure-like activity with brief shaking of her left arm and legs for less than 5 seconds. The patient then jumped off the exam table, punched the door, and grabbed at objects while screaming incomprehensible words, bucking, and fighting her parents. Her eyes

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were rolled back in her head during the two-minute event. This event resolved without intervention and the patient remembered what happened but could not elaborate. She was sent to the emergency department for further work-up.

On arrival to the emergency department, patient was tachycardic at 124 bpm, but her other vitals were normal. She had fluctuating levels of alertness. She had no speech output other than an occasional scream or moan. Her reflexes were 3+ throughout, and she had a slow gait with short steps. Otherwise, her physical exam was normal. During this admission, routine labs remained within normal limits. Cerebrospinal fluid studies, gram stain, culture, HSV and enterovirus PCR were negative. A 24-hour video monitored EEG was normal. Head MRI was normal. The patient's alertness fluctuated throughout her hospitalization. She would periodically chant speech in an unrecognizable language. She was otherwise reserved but able to answer questions appropriately. Psychiatry, neurology, and infectious disease were all consulted. Neurology recommended further CSF studies for auto-immune encephalitis. An abdominal CT and renal US were ordered to search for an adrenal or ovarian tumor; both were unremarkable.

The patient was started on clonidine for agitation. During hospitalization patient's mom remained convinced patient was possessed and needed to have an exorcism. She reported that she found an exorcist four states away and was planning on taking child there. Two days later, the patient's verbal outbursts decreased in quantity and she had no seizure-like activity. Her mom requested discharge with plans to take patient to exorcist against medical advice. The patient was discharged with mom with psychiatric follow-up. Two days post-discharge, anti-NMDA receptor antibody titers came back positive at 1:20 (normal < 1:1). Patients' mom was contacted, and patient was readmitted with a final diagnosis of anti-NMDAR encephalitis. She was started on IVIG and made a full recovery.

Etiology

First described in 2005 [1], anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a severe autoimmune disorder that is increasingly diagnosed as physicians are made aware of the illness. However, the majority of the literature on the subject is found in neurologic specialty journals with few references in journals targeting primary care physicians. Using data from the California Encephalitis Project, Gable, et al. found that Anti-NMDAR was the identified cause of encephalitis over 4 times more frequently than HSV-1, WNV, or VZV [2]. The disease has been documented in patients ranging from two months of age to 85-years-old [3,4], with a median age of 21 years [5]. In patients younger than 45, incidence is higher females (75%), however after the age of 45 this ratio nears 1:1 [5].

Pathophysiology

The NMDA Receptor is an ion channel receptor for glutamate, the primary excitatory neurotransmitter of the CNS. This transmembrane protein has two subunits, NR1 and NR2. The antibodies in this disease are specific to the NR1 subunit [6]. These receptors are most heavily expressed in the hippocampus, frontal lobe, and temporal lobe, and play an important role in neuroplasticity, synaptic transmission, memory, and learning [7].

While almost half of patients with anti-NMDAR encephalitis have unknown triggers, tumors and viral infections have been identified as known immunologic triggers [6]. Anywhere between 7.8% to 59% of patients with the disease have been reported to have tumors [6,8-13]. The most frequently reported among these tumors is ovarian teratomas, which may contribute to the disease's overall prevalence for females [2]. Other tumors linked to the disease include ectopic teratomas and lung, testicular, breast, and colon carcinomas. These tumors are mostly seen in males and/or older patients [3,4,14].

Diagnosis

After reviewing case studies published between 2007 and 2015, Hau, et al. have identified three separate periods of illness. The first period presents as a non-specific viral prodrome. The second period occurs 1-2 weeks later predominantly featuring psychiatric symptoms, including aggression, sleep disturbances, hallucinations, and behavioral disturbances [15,16]. Shortly after the psychiatric symptoms begin, the patient develops an array of neurologic symptoms, often multiple simultaneously, including chorea, dyskinesias, athetosis, dystonia, ballismus, dysautonomia, speech deficits, central hypoventilation, and coma [15-17].

Criteria for probable diagnosis of anti-NMDAR encephalitis were laid out in a 2016 position paper by Graus, et al. First, onset over less than three months of at least four of the following six groups of symptoms must have occurred: Abnormal behavior or cognitive dysfunction, speech dysfunction, seizures, movement disorders, decreased levels of consciousness, and autonomic dysfunction or central hypoventilation. Next, either an abnormal EEG or abnormal findings of pleocytosis or oligoclonal bands on CSF studies must have been found. Finally, other diseases must have been appropriately assessed for [16]. A diagnosis may also be made if three of the six groups of symptoms occur in the presence of a systemic teratoma. Certain diagnosis can only be made if at least one of the six major groups of symptoms is present and IgG anti-NR1 antibodies have been found [16,18].

These criteria were found to have a sensitivity of 81.2%, specificity of 76.9%, positive predictive value of

31.7%, and negative predictive value of 96.9% in a study of 137 Japanese patients [19,20]. Application of these criteria to another group of 220 patients demonstrated a sensitivity of 87.2% and specificity of 96.7% [17]. Considering her prior abnormal EEG, the patient in our case presented above would have fit all three criteria for a probable diagnosis of anti-NMDAR encephalitis at her follow-up appointment. Earlier recognition of the disorder would enable initiation of immunotherapy before antibody titers resulted [16,18,21,22].

In about 20% of patients, CSF studies are normal. Other patients demonstrate lymphocytic pleocytosis, increased protein levels, or oligoclonal bands [6]. At least 50% of patients have been reported to have normal brain MRIs [6,8]. Our patient had both normal CSF studies and brain MRI.

Treatment and Prognosis

The first step in determining a treatment plan for a patient with anti-NMDA receptor encephalitis is to determine if the patient has underlying cancer. If the patient has a resectable tumor, excision can improve treatment outcomes [6,15,23].

The mainstay of treatment of this autoimmune disorder is immunotherapy. First, patients should be started on a high-dose steroid, IVIG, and plasma exchange. Studies have shown a rate of improvement of 53-80% after this immunotherapy [3,4,6]. In non-responders, rituximab or cyclophosphamide are often used to increase rates of remission [6,13]. Those patients who still show no signs of improvement may yet respond to bortezomib or a combination of tocilizumab and methotrexate [6,24,25].

Patients who are younger, have lower antibody titers, milder symptoms, and have treatment initiated within 40 days of symptom onset have better response to treatment [10]. About 66-80% of patients recover almost all neurologic function and 12-25% relapse [3,4,6-8,10,13]. Relapse occurred more often in two groups of patients: Those with delayed or insufficient therapy, and those without an underlying tumor [3,4,26]. Overall, mortality rates have been reported between 5-7%, but some studies report rates as high as 11.46% [22].

Discussion and Conclusion

Anti-NMDAR encephalitis is a potentially lethal autoimmune syndrome presenting with psychiatric and neuromotor dysfunction. The disease is increasingly recognized since it's discovery in 2005. Diagnosis is challenging given shared similarities with other infectious, neuroanatomic, and psychiatric diseases. Early diagnosis, administration of immunotherapy, and treatment of any underlying malignancy are the mainstays of management. In our case, a previously healthy 8-year-old female presented with acute behavioral changes and seizure-like activity. Through CSF studies, the patient was diagnosed with anti-NMDAR encephalitis and made a full recovery following IVIG therapy. Though she recovered, the delay in diagnosing this patient during her first admission could have proved costly, as approximately 25% of patients with delayed treatment develop debilitating neuropsychiatric dysfunction or death. Primary care physicians are a trusted source for most patients, and as such are often the first to see patients when new symptoms present. When presented with an assortment of new-onset psychiatric and neuroanatomic disturbances, anti-NMDAR should be in the differential and a further workup should not be delayed.

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