

Case Report

Anti-NMDA Receptor Encephalitis in a Female with Previous Psychiatric Illness

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- Ovarian Teratoma
- Relapse

Abstract

In 2007, a rare form of autoimmune encephalitis was characterized by Dalmau et al. termed as anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis. Although it is more common in young females with ovarian teratomas who often present with psychiatric symptoms for the first time, this case reports a female diagnosed with anti-NMDA receptor encephalitis in the absence of a neoplasm and diagnosis of major depressive disorder and possibly bipolar disorder many years before the diagnosis of encephalitis. This case further presents multiple relapses of encephalitis, possibly due to absence of neoplasm and lack of treatment in first episode, since these factors have been reported to contribute to an increase in relapse risk rate. It is important to include anti-NMDAR encephalitis in the differential diagnosis of psychiatric illnesses such as schizophrenia and major depressive disorder as anti-NMDAR encephalitis is treated with immunotherapy and tumor removal (if applicable) and the role of psychotropic medications is not clear.

ABBREVIATIONS

NMDA: N-Methyl-D-Aspartate; NMDAR: N-Methyl-D-Aspartate Receptor; NR1: NMDA Receptor 1; MDD: Major Depressive Disorder; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; EEG: Electroencephalogram; CSF: Cerebrospinal Fluid

INTRODUCTION

Anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis, first discovered in 2007 by Dalmau et al., is a severe form of autoimmune encephalitis in which the body's immune system attacks its own NMDA receptors, particularly the NR1 subunit [1]. NMDA receptors are ligand-gated, voltage-dependent cation channels that play an important role in synaptic transmission and plasticity, which contributes to the mechanism of learning and memory [2,3]. Auto antibodies against these receptors attack membrane antigens in the neurophil of hippocampus and cerebellum [1]. Anti-NMDA receptor encephalitis was initially a disorder of young females and strongly associated with ovarian teratomas [1]. However, it has also been observed in older women, children, males and in the absence of a tumor. Clinically, anti-NMDAR encephalitis can present with pure psychiatric symptoms [4]. Kayser et al. reported up to 4% of patients eventually diagnosed with anti-NMDA receptor encephalitis to present with isolated psychiatric symptoms- 5 at first episode and 18 at relapse [4]. Psychotic symptoms with a

mood component were dominant [4]. These included auditory and visual hallucinations, delusional thinking, aggressive behavior, mania and depressed mood. It is not uncommon for patients to present to psychiatrists and be misdiagnosed with psychosis, schizophrenia or MDD [5]. Short-term memory loss, autonomic instability, dyskinesias, catatonia and seizures may also be part of the clinical presentation.

Diagnosis can be made by presence of CSF lymphocytic pleocytosis, Oligoclonal bands and increased protein concentration [1]. EEG and MRI may be abnormal. Imaging studies detect a tumor if present, which in most cases is an ovarian teratoma in females. Diagnosis requires a high degree of clinical suspicion as the most reliable test is presence of anti-NMDA receptor antibodies in the serum and CSF [1,5]. Treatment includes removal of the tumor (if present) along with immunotherapy with corticosteroids, intravenous immunoglobulins and plasmapheresis. In a recent study of 501 patients with anti-NMDAR encephalitis, 251/472 (53%) of the patients improved within four weeks with first-line immunotherapy or tumor removal [6]. 45/501 patients (12%) had one or more relapses within 2 years [6]. Patients without a tumor had a higher frequency of relapses than those with a tumor [6]. Patients who receive early tumor treatment (usually with immunotherapy) have better outcome and fewer neurological relapses [2], which may occur many years after the initial episode with less severe symptoms [7]. The earlier diagnosis and treatment of this condition can lead to a better prognosis and outcome [3]. Recovery time varies from 8-50 weeks [2].

CASE PRESENTATION

A 22-year old female presented to a transitional care clinic with depressed mood and anxiety, after being discharged from the university hospital with a diagnosis of mood disorder not otherwise specified. At the hospital, she presented with feelings of hopelessness and sadness, decrease in appetite and energy, and multiple awakenings during the night. She further endorsed frantic efforts to avoid abandonment, pattern of unstable and intense personal relationships, impulsivity, affective instability with irritability and chronic feelings of emptiness. The patient denied current substance abuse and medical causes of depression such as hypothyroidism, anemia, multiple sclerosis, syphilis, systemic lupus erythematosus, Cushing's syndrome and infectious mononucleosis were excluded with appropriate tests at the hospital. She was given Klonopin and discharged. She presented to the clinic after a few days with feelings of depressed mood, sleeping difficulties and decreased interest, energy, concentration and appetite. She was not suicidal. The patient reported experiencing episodes of dizziness, racing heart, chest pain and fear of dying, as frequently as 3-4 times per week since the past few months. She was given Zoloft 25 mg and Atarax 25 mg, despite which her symptoms did not improve and her dose of Zoloft was increased to 50 mg in the subsequent visit.

The patient in question was diagnosed with anti-NMDA receptor encephalitis in September 2013. She initially presented with headache, malaise and fatigue followed by changes in behavior, sleep pattern and cognition in February 2013. She felt angry, aggressive, depressed, anxious and paranoid, and complained of confusion and difficulty remembering simple tasks. She recalled having episodes of slurred speech, locked jaw, catatonia and autonomic instability. She also experienced restless sleep with multiple awakenings. However, workup at the hospital was unremarkable. In September 2013, the patient presented with similar symptoms at which time multiple tests were carried out, including transvaginal ultrasound, MRI of the brain, CT scan of the head, chest, abdomen and pelvis, all of which showed no abnormality. CSF studies excluded viral causes, including Cytomegalovirus, Epstein-Barr virus and Herpes Simplex virus. Lyme antibody was negative. India ink stain revealed no fungal cause. Urine screening for drugs was negative. Lumbar puncture revealed colorless CSF with lymphocytic pleocytosis. Oligoclonal bands were not present. IgG antibodies against NMDA receptors in serum and CSF were elevated, confirming the diagnosis of anti-NMDA receptor encephalitis. She underwent plasmapheresis after which her antibody levels came down to normal and her symptoms improved. She returned with similar episodes in February 2014 and May 2014. Since plasmapheresis had helped improve her symptoms in the past, she underwent plasmapheresis at these points that resulted in decline in IgG antibody levels and improvement of symptoms. She is scheduled to receive additional immunotherapy with corticosteroids and intravenous immunoglobulins to possibly prevent further relapses.

This patient had a past psychiatric history of depression and possibly bipolar disorder diagnosed at 15 years of age. She was given Abilify and Lexapro, which she took for 2 months, without improvement in symptoms. She also reported injuring herself

multiple times in the past. She had abused marijuana. The patient explained that even prior to her diagnosis of anti-NMDA receptor encephalitis; she had always felt depressed, angry and aggressive. She felt this disorder had further aggravated these symptoms. Her family history is remarkable for a sister with a diagnosis of bipolar disorder. She also reported anger and aggression being present among all family members.

DISCUSSION

This patient's presentation of depression, anxiety and possibly borderline personality disorder, could be a part of anti-NMDA receptor encephalitis or separate entities. To the best of our knowledge, there is no literature showing correlation between past psychiatric symptoms with development of anti-NMDA receptor encephalitis in the future. Most cases of anti-NMDA receptor encephalitis have been reported in individuals with no significant past psychiatric history. It is also not known if anti-NMDA receptor encephalitis could possibly aggravate psychiatric symptoms already present or the role of a positive family psychiatric history in the development of this disorder. There have been studies in the past focusing on whether patients diagnosed with primary psychiatric disorders, such as schizophrenia and MDD, have IgG antibodies against NR1 subunit. Steiner et al examined the prevalence of NMDAR antibodies in serum from 121 patients with initial diagnosis of schizophrenia, 70 with major depressive disorder, 38 with borderline personality disorder, and 230 healthy individuals [8]. The NR1 IgG antibodies were identified in only 2 patients, who in retrospect had a classic picture of anti-NMDA Rencephalitis [8]. IgA, IgM, or IgG antibodies reacting with NR2 subunit were identified in 10 of 119 patients (8%) with schizophrenia and 2 of 70 patients (3%) with major depressive disorder [8]. However, the causative antibodies in anti-NMDAR encephalitis are IgG antibodies against NR1 subunit, not IgA or IgM antibodies against NR2 subunit. It is important to include anti-NMDA receptor encephalitis as a differential diagnosis in patients, particularly females, with diagnosis of schizophrenia or MDD, as anti-NMDA Rencephalitis is treated differently and responds well to immunotherapy. Atypical antipsychotics have been tried for psychotic symptoms in the treatment of anti-NMDA Rencephalitis, with their success being marginal [9]. Since these medications are usually tried after immunotherapy, their efficacy remains uncertain [9].

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