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A Case of Severe Anti-N-Methyl D-Aspartate (Anti-NMDA) Receptor Encephalitis with Refractory Autonomic Instability and Elevated Intracranial Pressure

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, 21
Final Diagnosis: Anti-NMDA receptor encephalitis
Symptoms: Altered mental status • headache
Medication: Intravenous immunoglobulin • methylprednisolone • cyclophosphamide • rituximab
Clinical Procedure: Cardiac pacemaker • bilateral salpingo-oophorectomy
Specialty: Neurology • Critical Care

Objective: Unusual clinical course

Background: Anti-N-methyl D-Aspartate (anti-NMDA) receptor encephalitis is a rare autoimmune panencephalitis that typically presents with acute psychiatric disturbances and neurological deficits. Anti-NMDA receptor encephalitis is associated with certain tumors, most commonly ovarian teratomas. First-line therapy typically involves immunotherapy and tumor resection, if present, with up to 53% of patients experiencing improvement within 4 weeks. Cardiac arrhythmias and increased intracranial pressure have been reported in anti-NMDA receptor encephalitis, but these complications have usually been self-limited.

Case Report: We report the case of a previously healthy, obese 21-year-old female who presented with acute encephalopathy. Her psychiatric and neurological function rapidly deteriorated, warranting intubation and mechanical ventilation. Lumbar puncture was performed. Cerebrospinal fluid (CSF) opening pressure was elevated and a lumbar drain was placed. Infectious disease work-up was negative and anti-NMDA receptor antibodies were present in the CSF and serum. Initial treatment included intravenous immunoglobulin (IVIG) therapy, plasmapheresis, methylprednisolone, and bilateral salpingoophorectomy, without clinical improvement. Second-line immunotherapy with cyclophosphamide and rituximab was then administered. The patient also developed intermittent episodes of severe bradycardia and asystole that remained refractory to treatment and required placement of a permanent cardiac pacemaker.

Conclusions: Anti-NMDA receptor encephalitis presents with rapidly progressive psychiatric and neurologic dysfunction and can develop a severe and prolonged course with limited response to treatment. Patients can develop severe autonomic dysfunction with bradycardia and asystole that may require placement of permanent cardiac pacemakers. Elevated intracranial pressure may also be associated with anti-NMDA receptor encephalitis, and might contribute to the autonomic instability.

MeSH Keywords: Anti-N-Methyl-D-Aspartate Receptor Encephalitis • Arrhythmias, Cardiac • Intracranial Hypertension

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Background

Anti-N-methyl D-aspartate (anti-NMDA) receptor encephalitis was first described by Dalmau et al. in 2007 [1]. They reported the disease in 12 young women (ages 14–44 years) who predominantly had ovarian teratoma [1]. However, more recent case series have shown that a wider range of patients can be affected [2] and anti-NMDA encephalitis can occur without any underlying neoplasm [3].

Anti-NMDA receptor encephalitis is an autoimmune encephalitis syndrome characterized by a viral prodrome followed by progression of clinical symptoms, including psychiatric disturbances (e.g., agitation, delusions, disorganized thinking, and behavioral changes), insomnia, memory deficits, language deficits, loss of consciousness, catatonia, seizures, dyskinesia, and autonomic instability (e.g., tachycardia, bradycardia, hyperthermia, and hypoventilation requiring mechanical ventilation) [4].

NMDA receptors are ligand-gated cation channels with crucial roles in synaptic transmission and plasticity [5]. Anti-NMDA receptor encephalitis is associated with presence of IgG antibodies against GluN1 subunit of the NMDA receptor in the serum and cerebrospinal fluid (CSF) of the patients [5,6]. The sensitivity of NMDA receptor antibody testing is higher in CSF than in serum [6].

Anti-NMDAR encephalitis has been associated with certain tumors, most notably ovarian teratomas [7]. It is also associated with preceding herpes simplex virus encephalitis [8].

While no randomized or prospective data exist, recommendations for first-line therapy in adult patients includes intravenous methylprednisolone, immunoglobulin G or plasma exchange, and removal of the tumor if present [4]. According to an observational study on anti-NMDA receptor encephalitis patients [3], 53% of the patients who received the first-line therapy experienced improvement within 4 weeks [3]. Second-line therapy includes rituximab and/or cyclophosphamide [4].

About 75% of patients with anti-NMDA receptor antibodies recover or have mild sequelae [7]. In a report of 100 anti-NMDA receptor encephalitis cases [5], patients that had a tumor identified and removed within the first 4 months of the onset of the neurological disease had better outcomes and lower rates of neurological relapse [5].

Cardiac arrhythmias occur frequently in anti-NMDA receptor encephalitis [2] but there are only a few reports of severe bradycardia/asystole requiring placement of cardiac pacemakers [5,9–12]. Increased intracranial pressure (ICP) is an atypical finding in anti-NMDA receptor encephalitis, and to the best of our knowledge has only been reported in 4 articles [7,12–14].

We report a severe and refractory case of anti-NMDA receptor encephalitis with elevated ICP and recurrent episodes of bradycardia and asystole requiring a permanent cardiac pacemaker.

Case Report

A 21-year-old African American woman with no significant past medical history was brought to the Emergency Department (ED) for altered mental status. Over the course of a few hours, her father stated she displayed inappropriate crying and laughing, an inability to answer questions, and unintelligible speech. Other reviews of systems were only positive for headache that started 2 days prior to admission. She had no recent emotional stressors, trauma, recent illness, or sick contacts and did not have any other symptoms. The patient had no history of previous medical or psychiatric disorders or any surgeries. She had never been pregnant. The patient did not use tobacco or alcohol, but did use marijuana. She was not on any medications.

In the ED, the patient was very agitated, pulling at her IV line. During the first few hours in the emergency room, her blood pressure ranged within 114–200 mmHg systolic and 65–144 mmHg diastolic. Her heart rate was 51–105 beats per minute and respiratory rate was 24 per minute. Body temperature was 36.7°C. Her oxygen saturation was 98% on room air. The patient's weight was 117.4 Kg with a body mass index of 36.1 kg/m^2. The patient was awake, but disoriented and confused. She was unable to follow commands. Her speech was incomprehensible, with rare, intermittently coherent words. Her Glasgow Coma Scale (GCS) was 11 (Motor: 5, Verbal: 2, Eye: 4). She moved all extremities spontaneously. Deep-tendon reflexes were 2+ throughout and plantar reflexes were downward. Pupils were normal in size and reacted to light normally. Nuchal rigidity was present. Other parts of the physical exam were unremarkable.

Initial lab findings, including lactate, procalcitonin, and C-reactive protein, were within normal limits. A urine drug test was positive for tetrahydrocannabinol. Head computed tomography (CT) was negative for acute intracranial process. The patient's mental status continued to deteriorate. She was intubated and transferred to the Intensive Care Unit on mechanical ventilation. Lumbar puncture was performed, which demonstrated an opening pressure of 30 cm H_2O. Cerebrospinal fluid (CSF) analysis showed a white blood cell (WBC) count of 133 cell/µL with 99% mononuclear cells, normal glucose and protein concentrations, and positive oligoclonal bands. CSF opening pressure was 30, 43, and 45 cm H_2O on the third, fourth, and fifth days of admission, respectively, and necessitated placement of a lumbar drain. Empiric antibiotic therapy with vancomycin, ceftriaxone, ampicillin, and fluconazole was administered. Intravenous acyclovir was given for 12 days.

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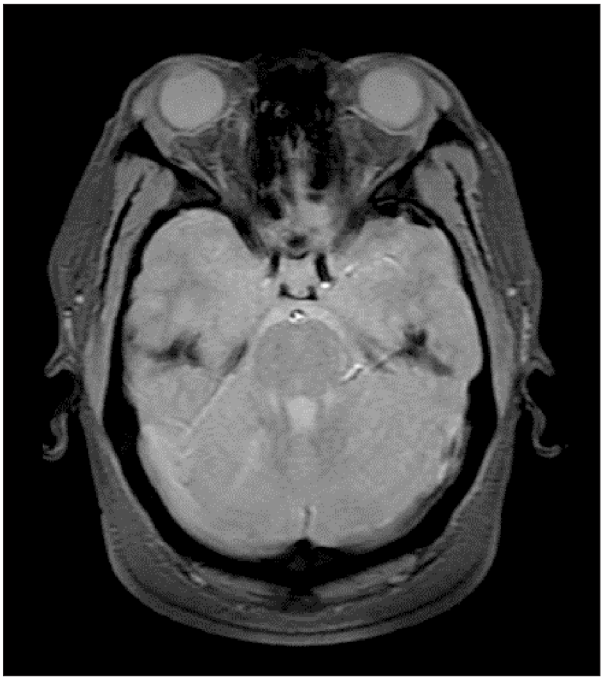

Figure 1. Axial T2-weighted brain MRI shows mild signal hyperintensity in right mediotemporal lobe.

MRI brain showed no intracranial mass or mass effect. However, mild signal hyperintensity was noted in the right medio-temporal lobe (Figure 1), consistent with underlying focal encephalitis. Magnetic resonance angiography (MRA) and magnetic resonance venography (MRV) of the brain were unremarkable. Pelvic MRI showed polycystic ovaries with a 2-cm septated cyst in the right ovary. No solid mass was identified. Additional work-up for malignancy was negative.

Blood, urine, and CSF cultures were negative. Infectious disease work-ups, including CSF herpes simplex virus (HSV) type 1 and 2 DNA polymerase chain reaction (PCR), CSF West Nile Virus DNA PCR, serum IgM West Nile Virus titer, CSF human immunodeficiency virus (HIV) PCR, and serum IgM Enterovirus titer, were negative. CSF Coccidioides antibody, Cryptococcal antigen, and TB CSF PCR were all negative. Anti-NMDA receptor antibodies were present in serum and CSF, which confirmed the diagnosis of anti-NMDA receptor encephalitis. Five cycles of intravenous immunoglobulin (IVIG) was administered, and plasmapheresis was started 20 days later.

The patient had several episodes of suspicious rhythmic movements of the extremities, which was concerning for seizure activity. Multiple electroencephalography (EEG) exams were performed, which showed diffuse background slowing with no evidence of an ongoing seizure or interictal epileptiform discharges.

The patient demonstrated autonomic instability with wide fluctuations in blood pressure, heart rate, and temperature. Standard treatments with hydralazine, atropine/dopamine, and acetaminophen were administered. She had several episodes of symptomatic bradycardia and sinus pauses, which necessitated placement of a temporary transvenous pacemaker on hospital day 18.

Intravenous immunoglobulin (IVIG), plasmapheresis, and methylprednisolone were given, without clinical improvement. Although abdominopelvic imaging findings were non-specific for ovarian teratoma, the bilateral ovarian cysts were concerning for possible ovarian teratomas, and a bilateral salpingoophorectomy was performed on hospital day 51, as the patient had shown no clinical improvement with medical therapy. During the operation, the complex cyst on the right ovary was examined using frozen sections, and a histological diagnosis of teratoma was obtained. Pathology confirmed presence of a 2-cm mature cystic teratoma in the right ovary that contained neural tissue (Figure 2).

The patient received repeated courses of IVIG and plasmapheresis, without improvement. She underwent tracheostomy and percutaneous endoscopic gastrostomy (PEG) tube placement. Subsequently, second-line immunotherapy with rituximab and cyclophosphamide was started.

Due to recurrent episodes of severe bradycardia and sinus pauses up to 15 seconds, a temporary transvenous cardiac pacemaker was placed for a second time on hospital day 106. Three weeks later, the temporary pacemaker was removed and a dual-chamber permanent pacemaker was placed. After receiving treatment for more than 10 months, the patient's neurologic status is modestly improved. She now follows simple commands, but is non-verbal and exhibits paresis of both lower extremities. She remains dependent on tracheostomy and gastrostomy tubes, but has been weaned off mechanical ventilation.

Discussion

This case demonstrates an unusual presentation of anti-NMDA receptor encephalitis. The patient developed severe autonomic instability, which was refractory to treatment and eventually necessitated placement of a permanent cardiac pacemaker. She also had an elevated ICP, which is not a common finding in anti-NMDA receptor encephalitis. Moreover, CT and MRI imaging are usually diagnostic for ovarian teratomas [15], but in this case imaging identified cysts but no specific features of ovarian teratoma.

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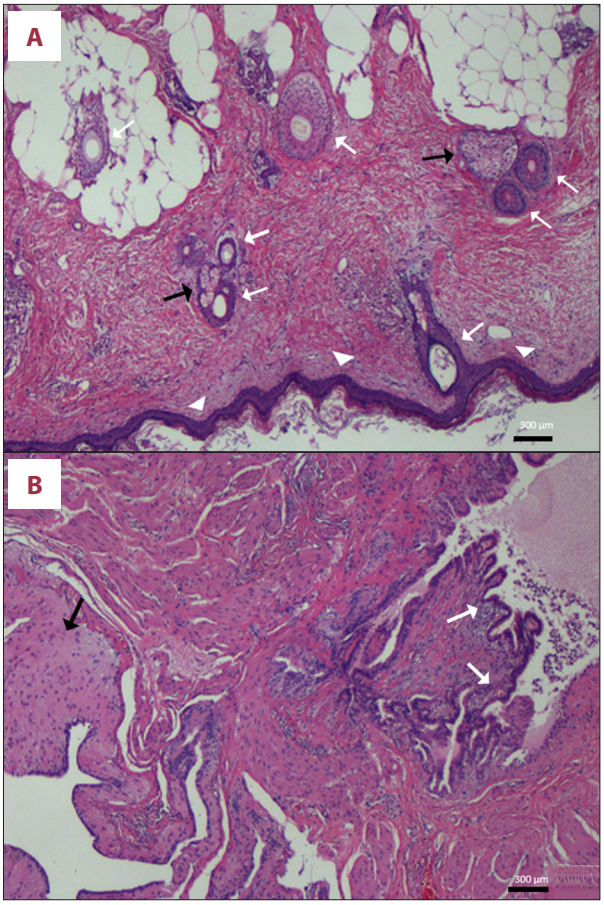

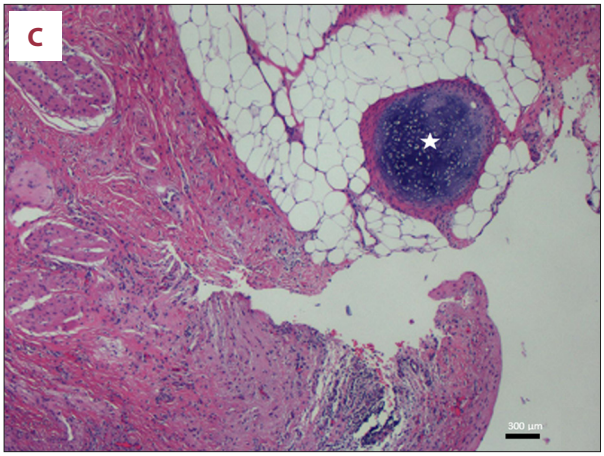

Figure 2. Photomicrograph of the cyst wall showing components of a mature cystic teratoma. (**A**) (H&E, 40×) squamous cell epithelium (white arrowheads), hair follicles (white arrows), and sebaceous glands (black arrows); (**B**) (H&E, 40×) glandular epithelium (white arrows), and neural tissue (black arrow); (**C**) (H&E, 40×) cartilage (white star).

Autonomic instability, such as intermittent episodes of tachycardia and bradycardia has previously been described in anti-NMDA receptor encephalitis [2,5,9–11,13,16,17], but severe bradycardia or asystole necessitating cardiopulmonary resuscitation [9] or pacemaker placement [5,9–12] is rare. In a series of 100 patients with anti-NMDA receptor encephalitis [5], 37 patients had cardiac arrhythmias, 7 patients had prolonged pauses, and 4 patients required pacemakers [5]. Tonomura et al. [11] reported 4 patients with ovarian teratoma-associated encephalitis who developed cardiac dysrhythmias, but all 4 patients fully recovered from the cardiac symptoms, including the one who needed a temporary cardiac pacemaker [11]. In a case of anti-NMDA receptor encephalitis reported by Mehr et al. [9], the episodes of autonomic instability were initially induced by vasovagal maneuvers and were controlled by reduction of the vagal stimuli, but the episodes later escalated in severity and frequency, necessitating pharmacologic interventions, temporary pacemaker, and eventually a permanent pacemaker [9]. To the best of our knowledge, the present case is the second [9] reported case of anti-NMDA receptor encephalitis patient who required placement of a permanent cardiac pacemaker.

It has been hypothesized that cardiac arrhythmias in patients with anti-NMDA receptor encephalitis might be associated with seizure activity [2] or induced by vasovagal stimuli [9]. However, most of the references have attributed cardiac arrhythmias to involvement of the areas of the brain that regulate the heart rate [2,3,12].

Central autonomic control of the heart rate is surprisingly complex [9]. Simplistically, the resting heart rate is a function of the innate cardiogenic pacemaker and a balance between the parasympathetic system and chronotropic sympathetic system [9]. Mapping studies in animals have shown that several regions of the telencephalon, including the insula, anterior cingulate cortices, and amygdala, are involved in modulation of the cardiac sympathetic and parasympathetic outflow [9]. These connections eventually influence the preganglionic sympathetic and parasympathetic neurons of the heart [9]. Also, hypertension and autonomic instability may enhance antibody entrance to the CNS [1], and further aggravate the symptoms.

Seizure activity can also induce bradycardia. In a patient with anti-NMDA receptor encephalitis, a 15-second episode of asystole was observed during an electrocardiographic ictal discharge of temporal origin [2]. Ictal asystole is thought to be related to a direct effect of the seizure discharge on central nervous system (CNS) control of cardiac rhythm [2]. Seizure activity in the insula, anterior cingulate cortices, and amygdala can lead to autonomic cardiac responses, including bradycardia and asystole [2]. Seizure-induced activation can result in a synchronization of cardiac autonomic discharges with epileptogenic activity called the “lockstep” phenomenon and can induce a lethal bradyarrhythmia or even asystole [18].

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Our case of anti-NMDA receptor encephalitis demonstrated spasticity and vague rhythmic movements of the extremities that were concerning for seizure. EEG showed no evidence of seizure activity; however, medical prophylaxis for seizure was instituted based on clinical symptoms. Although it is unlikely, there is a possibility that seizure activity contributed to the autonomic instability and bradycardia in this case.

The patient also had increased intracranial pressure (ICP). To the best of our knowledge, there are only 4 articles, including 2 case reports [12,13], that have reported elevated ICPs in patients with anti-NMDA receptor encephalitis [7,12–14]. However, one of these articles, which is a retrospective study on 35 cases of severe anti-NMDA receptor encephalitis, indicates that up to 42.86% of the patients had elevated intracranial pressures [14]. This suggests that the incidence and clinical significance of elevated ICP in patients with anti-NMDA receptor encephalitis is not well understood. Further studies are required to identify the incidence of elevated ICP in these patients and to investigate its association with disease severity and complications.

The combination of severe bradycardia with sinus pauses requiring permanent pacemaker and elevated ICP is a rare feature of anti-NMDA receptor encephalitis. To the best of our knowledge, only one previous case has been described, by Chawla et al. [12]. Increased ICP may result in hemodynamic instability, as seen in the Cushing's reflex. Cushing's reflex is characterized by the occurrence of hypertension, bradycardia, and apnea secondary to raised ICP [19]. We hypothesize that among patients with anti-NMDA receptor encephalitis, those who have elevated ICPs might be more susceptible to developing severe autonomic instability. If future research proves this hypothesis correct, measuring the ICP during the lumbar puncture, which is usually done early in the course of the disease, may help to identify patients who are more prone to develop severe or refractory autonomic instability.

Anti-NMDA receptor encephalitis is a newly described disease and its incidence is likely underestimated [7]. Some of its rare clinical manifestations or associated pathologies may not be readily identified or widely reported. Presenting some of the more unusual complications of anti-NMDA receptor encephalitis may increase awareness of its clinical features and identify challenges in its diagnosis and treatment. This will hopefully improve outcomes for patients with anti-NMDA receptor encephalitis, especially those with refractory disease.

Conclusions

Anti-NMDA receptor encephalitis can rapidly progress and remain refractory to treatment, despite early diagnosis and treatment. CT and MRI may fail to identify the specific features of ovarian teratomas if they are small. The course of anti-NMDA receptor encephalitis can be complicated by recurrent episodes of severe bradycardia and sinus pauses, which may persist for months and warrant placement of a permanent cardiac pacemaker to correct autonomic instability. Increased ICP may be associated with anti-NMDA receptor encephalitis and might potentially exacerbate the autonomic instability of these patients. More studies are required to determine the incidence of increased ICP in patients with anti-NMDA receptor encephalitis and its association with cardiac arrhythmia.

Department and Institution where work was done

Department of Medicine, Riverside University Health System, Moreno Valley, CA.

Conflict of interest

None.

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