Case Report

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Nonparaneoplastic anti-NMDA receptor encephalitis in an adolescent girl: a case report

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Introduction: Anti-*N*-methyl D-aspartate (NMDA) receptor encephalitis is an autoimmune neurologic disorder that classically presents with psychiatric, neurologic, and autonomic symptoms, often with a viral prodrome.

Case presentation: A 17-year-old female presented to the hospital with an 11-day history of fever, altered behavior, abnormal body movements, and altered sensorium. Upon examination, she was found to be febrile, tachycardic, and tachypneic, with a Glasgow Coma Scale score of 8.

Discussion: The diagnosis of anti-NMDA receptor encephalitis is usually confirmed by the presence of anti-NMDA receptor antibodies in the cerebrospinal fluid. The first-line treatment options include steroids, intravenous immunoglobulin, and plasmapheresis, while second-line therapies such as rituximab and cyclophosphamide may be necessary for some patients. While most patients respond well to treatment, complications can arise, and as in this case, death can occur.

Conclusion: New onset symptoms like alteration in behavior, abnormal body movement, altered sensorium, and psychiatric symptoms in a young female should raise suspicion of this disease. Immunotherapy is promising; however, anticipation and management of complication are essential in reducing mortality.

Keywords: anti-NMDA receptor encephalitis, anti-NMDAR encephalitis, autoimmune encephalitis

Introduction

Anti-*N*-methyl D-aspartate (NMDA) receptor encephalitis is an autoimmune neurologic disorder in which antibodies are directed against the GluN1 subunit of the NMDA receptor. It is a rare disease with a prevalence of 1 in 1.5 million[1]. It classically involves a confluence of psychiatric, neurologic, and autonomic symptoms, often with a viral prodrome. It could also be associated with the presence of tumors (mostly ovarian teratoma)[1]. It can cause inflammation and damage to the brainstem, leading to respiratory failure requiring mechanical ventilation[2]. Recognizing anti-NMDA receptor encephalitis in order to initiate early treatment and avoid psychiatric misdiagnosis is crucial. Brain imaging is often normal or nondiagnostic. The presence of anti-NMDA receptor antibodies in cerebrospinal fluid (CSF) or serum confirms the diagnosis. Diffuse slowing being a common electroencephalogram (EEG) pattern; the majority of patients with this condition have abnormal EEGs[3]. The disease is highly treatable with immunotherapy and/or tumor removal and most patients demonstrate a full recovery. Despite the favorable outcome with treatment, mortality is still 5–11%[4,5]. The main causes leading to death are severe pneumonia, multiple organ dysfunction syndrome, and refractory status epilepticus[5]. We report a case of a 17-year-old female presenting with neuropsychiatric symptoms treated in the intensive care unit (ICU) with immunotherapy complicated with severe pneumonia. This is reported in line with CARE guidelines for case reports[6].

HIGHLIGHTS

- Anti-*N*-methyl D-aspartate (NMDA) receptor encephalitis is an autoimmune neurologic disorder with neuropsychiatric symptoms.
- The presence of anti-NMDA receptor antibodies in cerebrospinal fluid or serum confirms the diagnosis.
- First-line immunotherapy includes intravenous steroids and intravenous immunoglobulin, and/or plasmapheresis, and second-line includes rituximab and cyclophosphamide.
- The outcome is usually favorable; however, anticipation and management of complication are essential in reducing mortality.

Case presentation

A 17-year-old female presented to the Emergency Department (ED) in our center with an 11 days history of fever, altered behavior, abnormal body movement, and altered sensorium. Her acute onset of behavioral disturbance consisted of agitation,

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suspiciousness, and aggression. She was restless which became severe enough to disturb her sleep. She was suspicious that people were making fun of her and started being violent with her family members. Her symptoms then progressed to abnormal movement of the body, initially focal, then generalized, with five to seven episodes per day associated with up rolling of eyes, clenching of teeth, clenching of the fist, and tongue biting. She also had an altered level of consciousness. With all these complaints, her family consulted multiple health centers and was prescribed the antipsychotic olanzapine 5 mg and an injection of phenytoin 900 mg. However, these medications could not completely alleviate her symptoms, and she was referred here.

Upon physical examination, she was found to have a temperature of 101°F, blood pressure of 130/70 mmHg, and was tachycardic with a heart rate of 117 beats/min and a regular rhythm. She was also tachypneic with a respiratory rate of 20 breaths/min and had an oxygen saturation of 92% in room air. On the Glasgow Coma Scale (GCS) assessment, her total score was 8 out of 15 (E4, V2, M2), indicating a comatose state. Her Antibody Prevalence in Epilepsy and Encephalopathy (APE2) score was 7. Neurological examination revealed the absence of nuchal rigidity and bilaterally mute plantar reflex. The cognitive function could not be assessed. Her baseline investigations were conducted, and a lumbar puncture was performed. She was primarily managed in ED with oxygen, intravenous (i.v.) fluids, anticonvulsants, and antibiotics. Due to concerns about potential airway compromise, she was subsequently transferred to ICU for further management.

The computed tomography (CT) scan of the head and MRI of the brain both revealed no abnormal findings. Similarly, the CT scan of the abdomen and pelvis did not show any abnormalities. CSF analysis revealed lymphocytic pleocytosis with protein and glucose within normal range. However, reverse transcription polymerase chain reaction (RT-PCR) assay for qualitative detection of herpes simplex virus (HSV-1 and HSV-2) and *Mycobacterium tuberculosis* of CSF specimen were negative. At this point, the possibility of an autoimmune phenomenon was suspected as all investigations were unrevealing. The autoimmune encephalitis panel of the CSF sample was then sent, which includes AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), CASPR2 (contactin-associated protein-like 2), GABA (gamma-aminobutyric acid), LGI1 (leucine-rich glioma inactivated protein 1), and NMDA (*N*-methyl-D-aspartate). The test was strongly positive for anti-glutamate receptor (type NMDA) and the diagnosis of anti-NMDA receptor encephalitis was confirmed. She received 5 days of courses in i.v. methylprednisolone 1 g per day and 5 days intravenous immunoglobulins (IVIGs) 16 g per day. However, her condition did not improve. Immunotherapy with rituximab could not be administered because she developed ventilator-associated pneumonia. Despite aggressive treatment efforts, her condition worsened and she developed septic shock, which was unresponsive to vasopressor therapy (norepinephrine). She passed away due to intractable cardiac failure.

Discussion

Anti-NMDA receptor encephalitis was initially thought to be exclusively associated with paraneoplastic syndrome in young females with ovarian teratomas[7]. However, it is now recognized to affect individuals of all age groups, although it is less prevalent in those over 50 years old, and it occurs more frequently in females than males with a ratio of 8 : 2[8]. Affected females over 18 years of age frequently present ovarian teratomas (> 50%), whereas prepubertal girls and male patients show a low rate of associated neoplasm (0–9%)[4]. The clinical picture shown by most of the patients are usually considered to be multiphasic; a prodromal phase (viral infection-like symptoms), psychotic and/or seizure phase (schizophrenia-like psychiatric symptoms and seizures), unresponsive and/or catatonic phase (patients become mute and unresponsive but awake in an akinetic state), hyperkinetic phase (orofacial-limb dyskinesia and autonomic instability), and gradual recovery phase. However, as in the typical course, the sequence may not always appear. Furthermore, the appearance of symptoms together makes the treatment more complicated[9–14]. Although the initial presentation of anti-NMDA receptor encephalitis is generally nonspecific, the combination of neurological and psychiatric symptoms should raise suspicion of the disease[13]. Distinguishing it from the primary psychiatric disorder may be challenging at the time of the onset of symptoms. The approach should involve multispecialty such as neurology psychiatry, pediatrics, and child neurology, for timely diagnosis and treatment with earlier recovery[15]. The neuropsychiatric manifestation like a seizure, autonomic instability, and catatonia following the prodromal stage can be life-threatening and may require ICU-level care[16]. Tachycardia, bradycardia, central respiratory depression, hypotension, hypertension, hypersalivation, sweating, constipation, urinary retention, and hyperthermia are some of the clinical signs of autonomic dysfunction in anti-NMDA receptor (anti-NMDAR) encephalitis[17]. In a study by Yan *et al.*[18], 61.63% of patients with anti-NMDAR encephalitis had autonomic dysfunction. They found that seizure, abnormal movement, and decreased consciousness is more prevalent with patient manifesting autonomic dysfunction. The requirement for ICU admission and mechanical ventilation is also higher in these patients. The proposed mechanism for epilepsy, dementia, and stroke is the overactivity of NMDA receptors causing excitotoxicity, whereas schizophrenia-like symptoms occur on its low activity[11].

Because of the multiple symptomatologies of the patients, many neurological, psychiatric, infectious, and other possible causes need to be ruled out by undergoing extensive investigation, for which diagnosis of autoimmune origin tends to be delayed[11]. Brain imaging is often normal or nondiagnostic[7,11]. In 79–100% of cases, CSF will come abnormal, with elevated leukocytes showing a lymphocytic predominance, normal glucose, and normal or elevated protein, with or without oligoclonal bands[4,9,12,19]. The presence of anti-NMDA receptor antibodies in CSF or serum confirms the diagnosis. CSF anti-NMDA receptor antibodies are more sensitive than serum studies[20]. The appearance of 'extreme delta brush' in the EEG's diffuse slow-wave, which predominates, aids in the clinical diagnosis of this disease[3]. For our patient with the neuropsychiatric presentation, brain imaging came normal. EEG did not have any features suggestive of any changes. CSF analysis revealed lymphocytic pleocytosis with protein and glucose within the normal range. The autoimmune panel came strongly positive for anti-NMDA receptor, confirming the diagnosis. Teratoma or viral triggering factors were not present in our case[15,21,22].

First-line immunotherapy includes i.v. high-dose steroids (methylprednisolone) and IVIG, and/or plasmapheresis. For those who do not respond well to the first-line treatment, second-

Table 1

Case reports on nonparaneoplastic anti-NMDAR encephalitis in adolescent females.

Article	Age (years)	Symptoms	MRI	EEG	Anti-NMDAR	Management	Outcome
Chamlagain *et al.*[15]	14	Psychosis, seizure	Normal	Generalized very slow basic activity	Positive	Steroid, rituximab	Improved
Arshad *et al.*[23]	14	Sever episodic hypertension	Normal	Right hemispheric delta activity	Positive	Steroid, IVIG	Improved
Steeman *et al.*[24]	24	Psychosis, catatonia, autonomic dysfunction	Normal	Normal	Positive	Steroid, plasmapheresis, mycophenolic acid	Improved but functional deficit at 1 month
Das *et al.*[25]	12	Psychosis	T2 hypersensitivity in right hippocampus	Diffuse cortical slowing	Positive	Steroid	Improved
Day *et al.*[26]	21	Psychosis, autonomic dysfunction, seizure	Normal	NCSE	Positive	Plasmapheresis, IVIG	Cardiac arrest and death

Anti-NMDAR indicates anti-*N*-methyl D-aspartate receptor; EEG, electroencephalogram; IVIG, intravenous immunoglobulin; NCSE, nonconvulsive status epilepticus.

line immunotherapy includes targeted B-cell therapy with rituximab and cyclophosphamide (an alkylating agent which directly inhibits T-cell and B-cell proliferation). Removing the tumor is indicated in some cases[13]. Using this approach, recovery to functional independence has been documented even in patients who have been unresponsive for months[4]. Patients who are not responding to treatment may benefit from bortezomib (a proteasome inhibitor), alemtuzumab (humanized monoclonal antibody against CD52), intrathecal methotrexate, and tocilizumab (monoclonal antibody against interleukin-6 receptor). Despite extensive treatment, our patient died as a result of complications. In severe cases, this condition can cause inflammation and damage to the brainstem, leading to respiratory failure. In such cases, mechanical ventilation is required to support breathing, but it also increases the risk of complications such as ventilator-associated pneumonia, which our patient developed. Despite aggressive treatment efforts, the patient's condition worsened, and she developed septic shock which was unresponsive to vasopressor therapy. She died as a result of intractable cardiac failure. Chi *et al.*, in their study of 96 patients, mortality was 11.46%. Their study concluded GCS score 8 or less at admission, number of complications, and admission to an ICU are predictors of death. The main causes leading to death were severe pneumonia, multiple organ dysfunction syndrome, and refractory status epilepticus[5]. Our patient was admitted to the ICU with a GCS score of 8 and subsequently developed ventilator-associated pneumonia leading to cardiac failure. While the situation is complicated, prompt management of these complications can potentially improve the overall prognosis of the disease.

While comparing other reported cases of nonparaneoplastic anti-NMDAR encephalitis in adolescent females (Table 1), the sign and symptoms were typical, like psychosis, dysautonomia, and seizures, as in our case. In terms of management, four of these cases were treated in ICU. They received steroids, IVIG, plasmapheresis, rituximab, and mycophenolic acid alone or in combination. Four of them improved; however, one died of cardiac arrest. Clinical judgment and appropriate treatment are crucial in preventing complications and death.

Conclusion

A young female presenting with new onset alteration in behavior, abnormal body movement, altered sensorium, and psychiatric symptoms should raise suspicion of autoimmune encephalitis. Ruling out common differentials like viral encephalitis and tubercular meningitis, and other psychiatric diseases is also crucial; however, those investigations should not delay the diagnosis of anti-NMDA receptor encephalitis and its treatment. With a multispecialty approach, treatment is usually favorable; however, anticipation and timely management of complications are essential in reducing mortality.

Ethical approval

None.

Patient consent

Written informed consent was obtained from the parents for the publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

S.G., M.B., and S.G.: wrote the original manuscript, reviewed, and edited the original manuscript; K.B.B., P.S., A.K. and N.G.: reviewed and edited the original manuscript.

Conflicts of interest disclosure

There are no conflicts of interest.

Guarantor

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