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Case Report

Teratoma-negative anti-NMDA receptor encephalitis presenting with a single generalized tonic–clonic seizure

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ABSTRACT

Herein, we describe a case report of anti-NMDA receptor encephalitis characterized by a single generalized tonic–clonic seizure and predominantly psychiatric symptoms, persisting long after EEG abnormalities had resolved. We discuss common presentations of anti-NMDA receptor encephalitis and advocate for the inclusion of this disease entity in the differential diagnosis of patients presenting with one generalized tonic–clonic seizure and prominent psychiatric symptoms.

1. Introduction

Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis is an autoimmune encephalitis, which was recognized in 2007 [1]. Its etiology involves the autoimmune response against the NR1 and NR2 subunits of the NMDA receptors. Patients with anti-NMDA receptor encephalitis may experience a viral-like prodrome, followed by prominent psychiatric or neurological symptoms such as psychosis, aggression, delusions, altered mood, insomnia, memory loss, involuntary movements, seizures, repetitive behaviors, echolalia, and mutism [2]. Orofacial and lingual dyskinesia or other movement disorders and pronounced autonomic instability may occur, sometimes requiring mechanical ventilation and admission to an intensive care unit [1,3–5]. Ovarian teratomas are detected in up to 50% of female patients. Clinical recovery ensues in the majority of patients after appropriate treatment [6].

We present a case of ovarian teratoma-negative, anti-NMDA NR1 receptor encephalitis in an adult woman with predominantly psychiatric symptoms. During this patient's hospital stay, we observed no neurologic symptoms, such as autonomic dysfunction and orofacial dyskinesia. With prompt initiation of immunotherapy, the patient's EEG changes resolved early on, while her prominent psychiatric symptoms persisted for much longer.

2. Case report

A 36-year old right-hand dominant woman reportedly had one generalized tonic-clonic seizure (GTCS) lasting less than 1 minute that occurred at home. When she presented to the emergency department for seizure on July 27th, 2016 she had a six-day history of personality change, confusion, irritability, and short-term memory loss. At the emergency department, she was agitated and was treated with lorazepam and haloperidol. Apart from her agitation, her neurological and general physical examinations were unremarkable. Hematology and biochemistry panels were unremarkable. Her cerebrospinal fluid (CSF) analysis showed pleocytosis (33×10^6/L), with 50% neutrophils and 44% lymphocytes and normal glucose and protein. MRI and MR angiography including gadolinium contrast studies were normal upon admission. She was treated with intravenous acyclovir for presumed Herpes simplex encephalitis (HSV) but this was discontinued when polymerase chain reaction (PCR) was negative for HSV, Varicella Zoster Virus, and enteroviruses. On day 3 of admission, 1 g of intravenous methylprednisolone and intravenous immunoglobulin were given for 5 days to treat presumed autoimmune encephalitis. Her CSF anti-NMDA receptor NR1 antibody was positive,

Abbreviations: anti-NMDA, anti-*N*-methyl-D-aspartate; IVIg, Intravenous immunoglobulin; EEG, electroencephalogram; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; HSV, herpes simplex virus; CSF, cerebral spinal fluid; CT, computerized tomography; F/U, follow up; GTC(S), generalized tonic–clonic (seizure).

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Table 1
Autoimmune panel.

Antibodies	Results
CSF anti-NMDA NR1 antibody	Positive
Serum anti-NMDA antibody	Negative
Anti-TPO	94 IU/mL (normal: ≤34)
Anti-thyroglobulin	189 IU/mL (normal: ≤115)
Anti-ENA	Positive
Anti-SS-A/Ro	Positive
Anti-GAD-65	92 IU/mL (normal: ≤5)
Anti-voltage-gated potassium channel complex	120 pmol/L (normal: ≤69)
Antinuclear antibody	Moderately positive for speckled pattern
Anti-dsDNA	Negative
C3	1.28 g/L (normal: 0.66–1.68)
C4	0.2 g/L (normal 0.10–0.4)
Anti-Scl-70, anti-Jo-1, pANCA, cANCA, rheumatoid factor	Negative
Paraneoplastic: anti-Hu, anti-Yo, anti-Ri, anti-Ma2/Ta, anti-CV2, anti-amphiphysin	Negative

and a diagnosis of anti-NMDA receptor encephalitis was made (Table 1). Serum anti-NMDA receptor antibody was negative while it was positive for anti TPO, anti-thyroglobulin antibody, anti-ENA, anti-SS-A/Ro, anti-GAD-65, and anti-voltage-gated potassium channel complex antibody. Paraneoplastic screening was negative for antibodies against Hu, Yo, Ri, Ma2/Ta, CV2, and amphiphysin. EEG showed mild diffuse slowing on the day of admission. On her last day of steroid and IVIg treatment, her EEG had worsened and was characterized by persistent diffuse delta waves. No epileptiform activity or classic delta brushes were seen at any point. Twenty-three days after methylprednisolone and IVIg treatment, she was treated with 4 doses of 540-mg rituximab weekly due to persistent psychiatric symptoms. During her treatment with rituximab, 100 mg of lamivudine once daily was given for prophylaxis of hepatitis B virus reactivation due to her serum hepatitis B core antibody positivity. After her third dose of rituximab, EEG was performed and showed mild improvement. Ovarian teratoma or other tumors were ruled out with CT chest, abdomen, and pelvis. During her hospital stay, she did not develop seizures, focal neurological signs, dyskinesia, or autonomic instability. At 2 months after initial immunotherapy, she continued to have fluctuating psychiatric symptoms including confusion, paranoia, euphoric mood, anxiety, insomnia, impulsivity, and aggressive behavior, requiring treatment with quetiapine, haloperidol, risperidone, and loxapine. She was transferred to a rehabilitation facility and then discharged home 5 months after presentation. The patient slowly returned to baseline with tapering doses of antidepressants and antipsychotics. She was symptom-free at 7.5 months and was discharged from neurological care at 12 months after initial presentation.

3. Discussion

We presented a female patient with anti-NMDA receptor encephalitis who had a single GTCS plus florid psychiatric symptoms. Her psychiatric symptoms resolved at 7.5 months after presentation. A case series by Viaccoz et al. showed that adult female patients were less likely than males to present initially with one seizure (14% vs. 61.5%) [7]. Reported cases of patients presenting with one seizure at onset are shown in Table 2. Studies documenting the time of resolution of psychiatric symptoms in patients with one seizure, as their presenting complaint is lacking. In Viaccoz's series, patients with seizure onset subsequently developed psychiatric symptoms lasting 3 to 12 months, suggesting that recovery time in patients presenting with or without seizure at onset can be similarly very variable. In anti-NMDA receptor-positive male patients, seizures at onset were likely to be focal seizures (unilateral paresthesia or unilateral motor), whereas in female patients, seizures at onset were more likely to be generalized [7]. Seizures at onset are followed by psychiatric manifestations more rapidly in females than males (median 2 vs. 12 days). Common psychiatric manifestations included hallucinations, anxiety, aggressiveness, confusion, and anterograde amnesia. These data suggest a possible role of sex hormones in modulating seizure onset and semiology in patients with anti-NMDA receptor encephalitis. In addition, the frequency of seizure at disease onset decreases with age [8]. Dalmau's group analyzed 571 patients with anti-NMDA encephalitis and showed only 4% (23 patients) had isolated psychiatric symptoms [2]. Were with isolated psychiatric episodes, 83% of these patients treated with immunotherapy had full or substantial recovery by 24 months after initial presentation. Clinical data of selected cases identified in the literature of patients presenting with only psychiatric symptoms are shown in Table 3. These data suggest that most of these patients make full recovery with immunosuppressive therapy.

During her hospital stay, our patient showed prominent psychiatric symptoms with no autonomic instability, which is commonly found in other patients with anti-NMDA receptor encephalitis. Patients often complain of viral-like symptoms such as headache, fever, nausea, vomiting, diarrhea, and rhinitis lasting up to 1 week. This may be followed by psychiatric features such as cognitive dysfunction, psychosis or mood changes. Other characteristics of anti-NMDA encephalitis include seizures, abnormal movements, dysautonomia, hypoventilation and death if left untreated. Labate et al. reported a case of a 26-year-old female with an ovarian teratoma-positive anti-NMDA receptor encephalitis presented with a combination of febrile GTC seizures, versive motor focal seizures with secondary generalization, and psychogenic hyperkinetic movements [10]. This patient required mechanical ventilation and was treated with steroids and IVIg two weeks after admission. This presentation contrasts with our patient described herein who was

Table 2
Anti-NMDA patients presenting with one seizure at onset.

Age (yrs.)/Sex	Clinical features	Therapy	Recovery	Reference
28/M	Focal seizure (right paresthesia), then anxiety, aggressiveness, confusion, mutism, anterograde amnesia	Steroids, then IVIg, then rituximab, then mycophenolate mofetil	Full at 12 months F/U	[7]
18/M	Focal seizure (motor, secondarily generalized), then anterograde amnesia, ICU admission	None	Full at 3 months F/U	[7]
21/M	Focal seizure (motor), then ataxia, hallucinations, limb dyskinesia, confusion, anterograde amnesia	Steroids, then IVIg, then rituximab, then mycophenolate mofetil	Full at 6 months F/U	[7]
75/M	Focal seizure (motor, left hemiparesia), then hypersexuality, auditory, hallucinations, rigidity, confusion, anterograde amnesia	Steroids, then IVIg, then rituximab, then mycophenolate mofetil	Full at 12 months F/U	[7]
32/M	GTCS, then hallucinations, anterograde amnesia, anxiety	Steroids, then IVIg	Residual psychosis and amnesia at 12 months F/U	[7]
20/M	GTCS, then aggressiveness, stupor and prostration, visual hallucinations, anterograde amnesia	Steroids, then IVIg, then rituximab, then mycophenolate mofetil	Residual anterograde amnesia at 12 months F/U	[7]
17/M	GTCS, then emotionally labile, bizarre behaviors, hypersexuality, aggression, disinhibition	steroids, then plasma exchange. At relapse, treated with plasma exchange, IVIg, rituximab, cyclophosphamide, methotrexate	Relapse at 10 months, then made full recovery	[9]

Table 3
Anti-NMDA patients presenting with only psychiatric symptoms.

Age(yrs.)/Sex	Clinical features	Tumor	Therapy	Recovery	Reference
13/F	Delusions, mania, suicidality	Yes	Steroids, then IVIg	Full at 24 months F/U	[2]
18/F	Delusions, auditory/visual hallucinations	Yes	Steroids and IVIg	Full at 34 months F/U	[2]
19/M	Aggression, delusions, mania	No	Steroids, then azathioprine	Full at 25 months F/U	[2]
20/F	Delusions, depression	No	Steroids and IVIg, then rituximab, then mycophenolate mofetil	Full at 37 months F/U	[2]
46/F	Aggression, auditory/visual hallucination, delusions	No	Unknown	No improvement at 4 months F/U	[2]
2/F	Violent behaviors, agitation, staring spells	No	Steroids and plasma exchange, then rituximab	Marked improvement after seventh plasma exchange	[9]

teratoma-negative, presented with only one GTCS of unknown onset, and did not demonstrate hyperkinetic movements. We believe that the early provision of immunotherapy (day 3 of admission) in our patient may have prevented her from developing hyperkinetic movements and dysautonomia. Approximately 75% of patients with anti-NMDA receptor encephalitis achieve substantial or even full recovery [6]. Good prognostic factors in anti-NMDA receptor encephalitis include early diagnosis and intervention, presence and removal of ovarian teratoma, good response to first-line immunotherapy, and absence of autonomic dysfunction [3,8].

There are currently no established treatment guidelines for anti-NMDA receptor encephalitis. Level IV evidence shows that early diagnosis and treatment with first-line immunotherapy, including corticosteroids and intravenous immunoglobulin and teratoma resection are important factors for remission [6]. Women with teratoma-negative disease tend to be more resistant to first-line immunotherapy. Rituximab and cyclophosphamide alone or in combination are considered second-line treatment and have been shown to have a higher response rate in teratoma-negative disease than teratoma-positive disease. Treatment should be continued until substantial recovery occurs and may take up to 18 months [8].

4. Conclusions

This case highlights the importance of including anti-NMDA receptor encephalitis in the list of differential diagnosis when a patient presents with a single GTC seizure at onset plus psychiatric symptoms. Immunotherapy should be promptly initiated if autoimmune disease is suspected and after infection has been excluded to prevent negative long-term cognitive sequelae.

Conflict of interest

None.

Ethical statement

Informed consent was obtained to proceed with this case report.

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