Psychosis: call a surgeon? A rare etiology of psychosis requiring resection

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Abstract

Objective: Anti–N-methyl-D-aspartate receptor encephalitis is a rare but emerging cause of autoimmune encephalitis. Our objective is to present a case of this rare disease while highlighting the importance of an aggressive search for underlying malignancy as well as the common mischaracterization of primary psychiatric illness that occurs in these patients.

Methods: A young Caucasian female with no known psychiatric history presented with acute onset of seizures and psychosis.

Results: Magnetic resonance imaging abdomen and pelvis showed a 6-mm ovarian teratoma which was not visualized on initial computed tomographic scans. Pathology was consistent with a mature teratoma. Both serum and cerebrospinal fluid N-methyl-D-aspartate receptor antibodies were positive.

Conclusion: An exhaustive search for underlying malignancy and specifically ovarian teratoma in young women should be completed in these patients. Diagnosis often is delayed given the prominent psychiatric manifestations and providers should be aware and strongly consider this in younger women with acute onset of neuropsychiatric symptoms.

Keywords

Anti–N-methyl-D-aspartate receptor, autoimmune encephalitis, teratoma, psychosis

Introduction

Anti–N-methyl-D-aspartate receptor (NMDA-R) encephalitis is a rare neuropsychiatric syndrome that is most common in younger adults and women with a median age of onset of 21 years.¹ Often it is preceded by a viral prodrome and typical symptoms include severe psychiatric manifestations, memory loss, seizures, decreased consciousness, autonomic dysregulation, and dyskinesia. Frequently, it is misdiagnosed as psychosis delaying the diagnosis with up to 77% of cases being seen initially by psychiatry.² Overall, nearly half of the cases are associated with malignancy. More specifically, in women over the age of 18 years, approximately 45% will have an ovarian teratoma. Herein, we describe a case of NMDA-R encephalitis which was initially diagnosed as psychosis resulting in subsequent discharge to a mental health facility. Later, she was found to have NMDA-R antibodies in her serum and cerebrospinal fluid (CSF) and a 6-mm ovarian teratoma.

Case description

A 23-year-old female with no significant past medical history presented with an acute onset of altered mental status and seizures. After stabilization, she began exhibiting hallucinations and bizarre thoughts which led to her eventual discharge to a mental health facility. She returned 72 h later with fever, tachycardia, worsening psychosis, unintelligible speech, and decreased responsiveness to external stimuli. The etiology of the fever was unclear at the time of admission. However, given her fever, tachycardia, and change in mental status, an infectious etiology was of highest concern and so she was started on broad spectrum antibiotics and acyclovir. On admission, her Glasgow Coma Scale (GCS) score was 9 and she was not alert or oriented to person.

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Despite initial interventions, her condition failed to improve and her serum NMDA antibodies increased to 1:1280. With the lack of clinical improvement and increasing antibody titer, there was concern for treatment failure or a potential residual teratoma. Repeat imaging including a positron emission tomography (PET)/CT was completed with negative results. Given this, she was started simultaneously on a combination of rituximab (375 mg/m²) and cyclophosphamide (750 mg/m²) 2 weeks after PLEX and IVIG were completed. Two months after rituximab and cyclophosphamide, significant neurologic recovery occurred and she became alert, oriented, and able to follow commands. In addition, she was weaned from the ventilator, regained her ability for fluent speech, and had resolution of her seizures. No relapses were noted and 4 months post-treatment, the only notable neurologic sequelae was short-term memory loss. In total, she received four cycles of rituximab and two cycles of cyclophosphamide with plans for further rituximab 6 months after the initial dose. Eventually, her NMDA antibodies decreased to a titer of 1:80.

**Conclusion**

NMDA-R encephalitis is an increasingly recognized disease with recent epidemiological data suggesting that it may be the second most common cause of autoimmune encephalitis. Ovarian teratomas are frequently the cause of disease in younger women and prior cases have reported improvement up to 11 months after diagnosis following teratoma removal. The search for an underlying malignancy, especially a teratoma, is paramount given the rapid and significant improvement that can occur in their clinical course.

In the setting of NMDA-R encephalitis, ovarian teratomas are common with the average size being 6 cm in prior case series with all being positive for the expression of NMDA receptors. Those with teratomas are known to have higher antibodies titers, more severe disease, and a higher likelihood of having positive serum antibodies. However, with tumor removal in the first 4 months from the development of neurologic symptoms, better outcomes as well as lower rates of relapse are noted. Even when a tumor is not found initially, it is recommended that females aged 12 years and older undergo frequent screening including MRI of the abdomen and pelvis every 6 months for 4 years after diagnosis. In our patient, the initial CT scan was negative, however; given the high suspicion for an underlying teratoma, MRI was ordered which showed a small 6 mm teratoma.

**Table 1. CSF studies.**

|                         | Value         | Normal range |
|-------------------------|---------------|--------------|
| Color/clarity           | Colorless/clear|              |
| RBC                     | 2 cells/µL    | 0–10 cells/µL|
| WBC                     | 50 cells/µL   | 0–5 cells/µL |
| Lymphocytes             | 96%           | 40%–80%      |
| Monocytes               | 4%            | 15%–45%      |
| Glucose                 | 63 mg/dL      | 40–70 mg/dL  |
| Protein                 | 30 mg/dL      | 15–45 mg/dL  |
| VDRL                    | Non-reactive  | Non-reactive |
| HSV PCR                 | Not detected  | Not detected |
| West Nile IgG           | 0.03 IV       | <1.29 IV     |
| West Nile IgG           | 0.00 IV       | <0.89 IV     |
| Enterovirus PCR         | Not detected  | Not detected |
| Varicella-Zoster PCR    | Not detected  | Not detected |

CSF: cerebrospinal fluid; RBC: red blood cells; WBC: white blood cells; HSV: herpes simplex virus; IV: intravenous; PCR: polymerase chain reaction; VDRL: venereal disease research laboratory test.

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of initial treatment. Second-line therapy includes the use of cyclophosphamide or rituximab either alone or in combination. Of those who did not improve on first-line therapy, an additional 67% improved with second-line therapy in the first 24 months. They were also noted to have reduced rates of relapse and improved outcomes compared to the non-treatment groups. In our patient, she did not initially improve despite teratoma removal and a combination of IVIG, PLEX, and steroids. Therefore, she was started on cyclophosphamide and rituximab which led to significant improvement.

NMDA-R encephalitis is an emerging cause of encephalitis, especially in younger females with an abrupt onset of neuropsychiatric symptoms. Despite the aggressive and potentially fatal nature of the disease, nearly 80% of patients will experience neurologic recovery with first-line therapy and tumor removal. Even in the setting of multiple negative imaging studies, cases have been reported where a teratoma was still the underlying etiology, and ovariectomy was done with noted patient improvement. Overall, this highlights the significance of malignancy as an underlying etiology of this disease. It is important to conduct a thorough evaluation for malignancy given the significantly improved outcomes and decreased rates of relapses when tumor resection is completed.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval
Our institution does not require ethical approval for reporting individual cases or case series.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent
Verbal informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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