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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

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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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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.

place, or time. The remainder of the neurologic examination was notable for fast unintelligible speech, inability to follow commands, and decreased responsiveness to external stimuli except pain. She initially was spontaneously moving all four extremities, had no significant cranial nerve abnormality, normal muscle tone, and 2+ symmetric reflexes bilaterally in upper and lower extremities. Imaging including magnetic resonance imaging (MRI) of her head and computed tomographic (CT) scans of her chest, abdomen, and pelvis were negative. An extensive infectious work-up was negative, however; her lumbar puncture did show a lymphocytic pleocytosis (Table 1). Continuous electroencephalogram monitoring was obtained and notable for severe generalized slowing and 2–3 Hz rhythmic delta activity with 15–18 Hz sharply contoured beta activity overlying delta activity consistent with extreme delta brushing. Additional evaluation was notable for positive serum NMDA antibodies (1:320) and CSF NMDA antibodies (1:80). Given these results, further imaging studies were completed to evaluate for teratoma, and an MRI abdomen and pelvis revealed a 6-mm right ovarian teratoma. At that time, high-dose methylprednisolone 1 g/day and plasma exchange (PLEX) were initiated. The patient was taken for definitive surgical therapy the next morning. Post-operatively, she was continued on methylprednisolone for a total of 5 days with five treatments of PLEX. She continued to decline with worsening mental status, loss of response to pain, and respiratory failure requiring intubation. GCS score at this time had now decreased to 3. She then began treatment with intravenous immunoglobulin (IVIG) for five doses. There was no response to IVIG, and both her respiratory and neurologic status remained unchanged. No testing was completed looking for genetic abnormalities or variations in her Cytochrome P450 system. Her final pathology was consistent with a mature teratoma.

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/m^2) and cyclophosphamide (750 mg/m^2) 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.[3] 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.[4] 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.[5] Those with teratomas are known to have higher antibodies titers, more severe disease, and a higher likelihood of having positive serum antibodies.[5,6] 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.

Beyond surgical removal of the tumor, treatment consists of immunosuppression. There are no randomized controlled clinical trials addressing this issue, but large observational and retrospective studies have outlined treatments. First-line therapy consists of steroids, IVIG, and PLEX, either alone or in combination as well as tumor removal as indicated. Yet, even in the setting of tumor removal, first-line therapy was noted to only have a 53% improvement rate within 4 weeks

of initial treatment.[7] Second-line therapy includes the use 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.[2] Even in the setting of multiple negative imaging studies, cases have been reported where a teratoma was still the underlying etiology, and ovarectomy was done with noted patient improvement.[4] 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

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Ethical approval

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Informed consent

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