Tubal Teratoma Causing Anti-NMDAR Encephalitis

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Abstract

Background: Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is considered a rare autoimmune disorder usually caused by an ovarian teratoma. The disease is clinically characterized by neuropsychiatric symptoms followed by intractable seizures and hypoventilation, and it is fatal if left untreated.

Case: We present a case of anti-NMDAR encephalitis with classical features in a young woman whose ultimate diagnosis and treatment were delayed because of multiple avoidable circumstances that were recognized only in retrospect.

Conclusion: We believe that this disorder is actually more common than reported. Anti-NMDAR encephalitis must be considered as part of the differential diagnosis in any young woman presenting with new onset psychiatric symptoms. In young women with an acute decrease in their level of consciousness, prompt and continued surveillance for the presence of an underlying tumour should be undertaken, especially when there is a delayed response to empiric treatment.

Résumé

Contexte : L'encéphalite à anticorps anti-récepteur du *N*-méthyl D-aspartate (NMDA) est considérée comme un trouble auto-immun rare qui est habituellement causé par un tératome ovarien. La maladie se caractérise, sur le plan clinique, par des symptômes neuropsychiatriques suivis de convulsions réfractaires et d'une hypoventilation; sans traitement, elle est mortelle.

Cas : Nous présentons un cas d'encéphalite à anticorps anti-récepteur du NMDA comptant des caractéristiques classiques chez une jeune femme pour laquelle le diagnostic et le traitement ultimes ont été différés en raison de multiples circonstances évitables qui n'ont été mises au jour qu'a posteriori.

Conclusion : Nous estimons que ce trouble est en fait plus courant que ce que les signalements à son égard peuvent nous porter à croire. La présence possible d'une encéphalite à anticorps anti-récepteur du NMDA doit être envisagée dans le cadre du diagnostic différentiel de toute jeune femme présentant des symptômes psychiatriques d'apparition nouvelle. Chez les jeunes femmes qui connaissent une baisse aiguë du niveau de conscience, une surveillance immédiate et continue visant à repérer la présence d'une tumeur sous-jacente devrait être mise en œuvre, particulièrement en présence d'une réaction différée au traitement empirique.

Key Words: Anti-*N*-methyl-D-aspartate receptor, encephalitis, teratoma

Competing Interests: None declared.

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INTRODUCTION

Throughout history, women have been prescribed strange therapies or sent to psychiatric institutions for conditions that were misdiagnosed and treatable. In 2005, Vitaliani et al. reported a disorder that represented a previously unrecognized form of severe, treatable, but potentially lethal paraneoplastic encephalitis.[1] Their index patients were all young women who developed prominent neuropsychiatric syndromes and who were subsequently found to have ovarian teratomas. Dalmau et al. later described the underlying pathology: an autoimmune encephalitis with antibodies directed against the NR1 and NR2 subunits of the *N*-methyl-D-aspartate receptor.[2] Eighty percent of cases occur in young women.[3] We present here the case of a woman with anti-NMDAR encephalitis and classical presenting features, whose ultimate diagnosis and treatment were delayed because of multiple avoidable circumstances that were recognized only in retrospect.[3]

THE CASE

A 26-year-old Aboriginal woman, gravida 2, para 0, presented to the emergency department in status epilepticus. She was admitted to the ICU, where she was intubated and sedated. Her medical history included obesity and remote substance abuse with alcohol and marijuana. She had previously had a miscarriage and a therapeutic abortion. A

CT scan of the head and an EEG showed no focal cause for epilepsy; a toxicology screen was negative.

Two days after admission, she was able to be extubated. She was subsequently confused and expressed herself in bizarre poses and inappropriate speech. She continued to have seizures despite administration of multiple anti-seizure medications. Repeat EEGs and imaging of the patient's head failed to provide a conclusive diagnosis or evidence of organic pathology; examination of cerebrospinal fluid showed no evidence of infection. The patient subsequently became agitated, aggressive, and emotionally labile. Anti-psychotic medications did not improve her condition, and she required chemical and physical restraints. In retrospect, her family noted that the patient had shown increasingly bizarre and abnormal behaviour before admission.

Seventeen days after admission, prompted by the patient's lack of response to conventional treatment, a serum sample was sent for assay of anti-NMDAR antibodies; the patient began empirical treatment with intravenous immunoglobulin. At 28 days after admission, the NMDAR antibody titres in serum were reported at 1:40 (normal < 1:10). CSF and further serum samples were sent for measurement of NMDAR antibodies. Because treatment with IVIg had not resulted in any substantial improvement in the patient's condition, plasmapheresis and IV prednisone were added to the treatment regimen.

At 47 days after admission, the serum titres of anti-NMDAR were reported to be 1:10 but the CSF titres were 1:40. Pelvic ultrasound showing normal findings had been performed six months before admission; a repeat ultrasound assessment was ordered but could not be carried out because of the patient's condition. However, at 53 days after admission, an MRI of the patient's abdomen and pelvis was performed using sedation and airway support. A 5.6 cm × 4.3 cm mass, highly suggestive of a teratoma, was identified in the left adnexa. The gynaecology service was consulted, and two days after the MRI, a laparoscopic left salpingectomy was performed. A 5 × 5 cm mass in the left adnexa, including the fallopian tube and omental adhesions, was removed. Both ovaries appeared normal. The final pathology report confirmed a tubal teratoma (Figures 1 and 2).

ABBREVIATIONS

CSF	cerebrospinal fluid
EEG	electroencephalography
IVIg	intravenous immunoglobulin
NMDAR	*N*-methyl-D-aspartate receptor

The patient did well postoperatively; her aggressive behaviour and mood improved significantly within weeks. She was discharged from hospital 73 days after admission. Follow-up six weeks later confirmed complete resolution of the patient's symptoms.

DISCUSSION

Patients with anti-NMDAR encephalitis develop a predictable course of illness. A viral prodrome, including mild fever, myalgia, and coryza, is often the first associated group of symptoms in 72% of patients.[2,3] Psychiatric symptoms are commonly the next manifestation, with schizophrenia-like behaviours and sudden onset of aggression or irritability being most often reported.[4] Other neuropsychiatric symptoms follow, including abnormal movements and seizures.[3–5] Patients often become non-verbal and non-responsive, leading to eventual decompensation, including hypoventilation and autonomic instability requiring ICU admission.[3–5]

Patients who present with the above symptoms are often treated empirically for a viral encephalitis or psychiatric illness. The diagnosis is often delayed because of the ambiguity of test results and the attribution of the abnormal behaviour to mental illness. EEGs do not show correlative epileptiform discharges that permit localization of a focus.[3,5] CSF analysis shows lymphocytic pleocytosis, an increased level of protein, a normal glucose level, and oligoclonal bands.[3] MRI of the brain is normal 50% of the time; however, it may show mild transient T2 hyperintensity in the medial temporal lobes, hippocampi, basal ganglia, or cortex.[3] Viral serology is negative, although there have been case reports describing serology positive for *Mycoplasma pneumonia*.[4] NMDAR antibodies are typically higher in the CSF than in the serum.

Treatment of anti-NMDAR encephalitis includes IVIg, prednisone, and plasma exchange or plasmapheresis. Patients with NMDAR encephalitis have a better prognosis if an underlying tumour is found and promptly removed.[6,7] It has also been shown that IVIg, corticosteroids, and plasma exchange all have enhanced effectiveness in treating symptoms if the underlying tumour is removed expeditiously.[3] If left untreated, this condition is fatal. Recovery commonly occurs in the reverse order of symptom presentation.[3]

Several contending factors delayed diagnosis in our case. Intractable seizures were initially misdiagnosed as acute alcohol withdrawal. Once clinical suspicion of anti-NMDAR encephalitis became high, empiric treatment was started. In our case, testing was further delayed by the

fact that NMDAR antibody testing is not readily available in our region, and samples needed to be sent to a distant laboratory. Finding the teratoma in our case proved difficult because of the patient's body habitus and our hesitation to perform a transvaginal ultrasound without patient capacity or written or verbal consent from the patient or her family. The requirement for sedation and airway support to obtain an adequate MRI study furthered delayed treatment. In addition, the patient's ovaries were normal and a tubal teratoma is a rare finding.

We suspect that anti-NMDAR encephalitis is more frequent than currently reported. The actual incidence is not known, but, on the basis of the rapid accrual of patients and increasing number of case reports, it has been suggested that anti-NMDAR encephalitis is four times more common than herpes simplex virus, varicella zoster, and West Nile encephalitis, and that it is more frequent than any known paraneoplastic encephalitis.[8] In one centre, anti-NMDAR encephalitis was found to be responsible for 86% of patients admitted to ICU with "encephalitis of unknown origin" and similar clinical features.[9] In another case series, NMDAR encephalitis was found to be responsible for 20% of ICU admissions of patients with encephalitis of unknown etiology, regardless of clinical presentation.[10] Unfortunately, this disorder is not commonly high on the list of differential diagnoses for a young woman presenting with psychiatric symptoms. Adding to this is the difficulty in establishing a firm diagnosis because of the lack of laboratory facilities capable of isolating NMDAR antibodies.

CONCLUSION

We recommend that physicians include anti-NMDAR encephalitis as part of the differential diagnosis in any young woman presenting with new onset psychiatric symptoms. In young women with an acute decrease in their level of consciousness, prompt and continued surveillance for an underlying tumour should be undertaken, especially when empiric treatment does not result in rapid improvement.

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The woman whose story is told in this case report has provided written consent for its publication.

REFERENCES

1. Vitaliani R, Mason W, Ances B, Zwerdling T, Jiang Z, Dalmau J. Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma. Ann Neurol 2005 Oct;58(4):594–604.

Figure 1. Laparoscopic image of the left fallopian tube

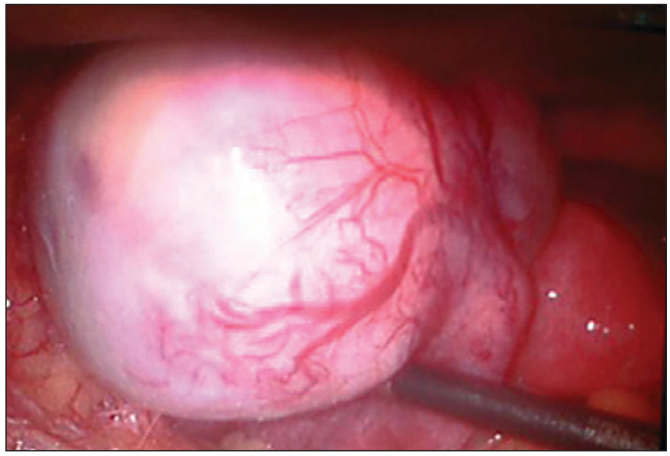
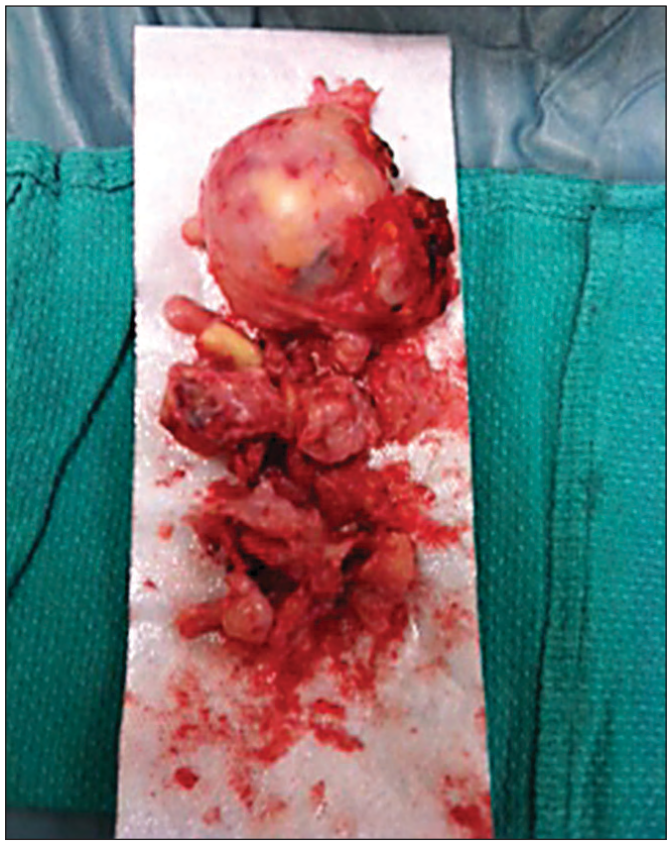


Figure 2. Left fallopian tube with teratoma. The teratoma was morcellated in a bag to facilitate removal from the patient's abdomen.



2. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008 Dec;7(12):1091–8.

3. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 2011;10(1):63–74.

4. Gable MS, Gavali S, Radner A, Tilley DH, Lee B, Dyner L, et al. Anti-NMDA receptor encephalitis: report of ten cases and comparison with viral encephalitis. Eur J Clin Microbiol Infect Dis 2009;28(12):1421–9.

5. Mann A, Machado NM, Liu N, Mazin AH, Silver K, Afzal KI. A multidisciplinary approach to the treatment of anti-NMDA-receptor antibody encephalitis: a case and review of the literature. J Neuropsychiatry Clin Neurosci 2012;24(2):247–54.

6. Seki M, Suzuki S, Iizuka T, Shimizu T, Nihei Y, Suzuki N, et al. Neurological response to early removal of ovarian teratoma in anti-NMDAR encephalitis. J Neurol Neurosurg Psychiatry 2008;79(3):324–6.

7. Iizuka T, Sakai F, Ide T, Monzen T, Yoshii S, Iigaya M, et al. Anti-NMDA receptor encephalitis in Japan: long-term outcome without tumor removal. Neurology 2008;70(7):504–11.

8. Peery HE, Day GS, Dunn S, Fritzler MJ, Pruss H, De Souza C, et al. Anti-NMDA receptor encephalitis. The disorder, the diagnosis and the immunobiology. Autoimmun Rev 2012;11(12):863–72.

9. Pruss H, Dalmau J, Harms L, Holtje M, Ahnert-Hilger G, Borowski K, et al. Retrospective analysis of NMDA receptor antibodies in encephalitis of unknown origin. Neurology 2010;75(19):1735–9.

10. Davies G, Irani SR, Coltart C, Ingle G, Amin Y, Taylor C, et al. Anti-N-methyl-D-aspartate receptor antibodies: a potentially treatable cause of encephalitis in the intensive care unit. Crit Care Med 2010;38(2):679–82.