

# Anti-N-methyl-D-aspartate receptor encephalitis complicating ovarian teratomas: a case report

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**A**nti-N-methyl-D-aspartate (NMDA) receptor encephalitis consists of the association of acute psychiatric disorders and seizures that are preceded by a flu-like syndrome.<sup>1</sup> Over 400 cases have been reported since the seminal description in late 2007 that led to the idea that the prevalence of this disease may be underestimated.<sup>2,3</sup> The association with teratoma was reported only 4 years ago, and the early removal of the tumor is associated with a favorable outcome in most cases.<sup>2</sup> Briefly, anti-NMDA receptor antibodies react against glutamate receptor that is located at the surface of neurons and result in an impaired glutamatergic neurotransmission.<sup>4</sup> We report the case of a woman who had “paraneoplastic” limbic encephalitis that was related to a mature ovarian teratoma.

## CASE REPORT

A 27-year-old Mauritanian woman came to our institution because of hallucinations and confusion that had been preceded by a flu-like illness 10 days earlier. Neurologic examination revealed anterograde memory deficit and trouble walking. She was taken to the reanimation department and required mechanical ventilation because

Anti-N-methyl-D-aspartate receptor encephalitis is an emerging disease that affects young women. Its diagnosis can be delayed because of the neuropsychiatric symptoms in the foreground, but early removal of the associated teratoma improves the prognosis. We report the treatment of a patient with anti-N-methyl-D-aspartate receptor encephalitis that was related to an ovarian teratoma.

**Key words:** anti-N-methyl-D-aspartate receptor encephalitis, laparoscopy, ovarian cystectomy, teratoma

of impaired vigilance with rapid worsening of the Glasgow coma score, which decreased from 10 to 6.

Blood cell count, blood electrolytes, and the brain computed tomography (CT) scan were normal. Increased fluid attenuation inversion recovery signals of both temporal lobes were seen on cerebral magnetic resonance imaging (Figure 1). Cerebrospinal fluid showed mild lymphocytosis but was sterile. Electroencephalography showed an intermittent complex partial seizure that responded well to intravenous sodium valproate, and febrile limbic encephalopathy was diagnosed. Empiric therapy that consisted of acyclovir and cefotaxime was administered. Once infection (including herpetic meningitis) had been discounted, paraneoplastic causes were explored. Screening for classic onconeural antibodies (anti-Hu, Yo, Ma2, amphiphysin, CV2/CRMP5, and Ri) was negative, but anti-NMDA receptor antibodies were found in the cerebrospinal fluid. A total body CT scan that was performed to look for a possible primary tumor revealed a 4-cm unilocular cyst on the right ovary. Ultrasound examination confirmed an anechogenic ovarian cyst with septa.

We performed laparoscopic cystectomy without cyst rupture (Figure 2). Histologic examination indicated a mature teratoma with a cutaneous component. Immunofluorescence confirmed the presence of antibodies against the NR1 and NR2B heteromers of NMDA receptor (Figure 3).

In addition to surgery, the patient received corticosteroid and intravenous immunoglobulin therapy (0.5 g/kg). She recovered rapidly and was discharged from the intensive care unit 4 days after surgery. One year after surgery, the patient had regained most of her neurologic abilities; however, attention problems remained.

## COMMENT

Antibodies against NMDA receptor were discovered more than 20 years ago,<sup>5</sup> but their pathogenic effect was not reported until 2007 by Dalmau et al.<sup>2</sup> In 2000, Gultekin et al<sup>6</sup> reported 137 patients with paraneoplastic limbic encephalitis in the English literature. In 4 cases (3%), an ovarian immature teratoma was associated. However the NMDA receptor antibodies had not been identified at that time. Thus, we can hypothesize that (1) some patients with NMDA receptor antibodies were not included in this review and (2) some patients with unknown paraneoplastic antibodies or unidentified paraneoplastic antibodies might have anti-NMDA receptor antibodies.

The anti-NMDA receptor antibodies are directed against the NR1 and NR2b heteromers of the NMDA receptor and have an antagonistic effect on the glutamate receptor.<sup>3,4</sup> This pathogenic effect reversibly affects glutamatergic neurotransmission, unlike the permanent neuronal damage that is observed in paraneoplastic neurologic syndromes that are associated with onconeural

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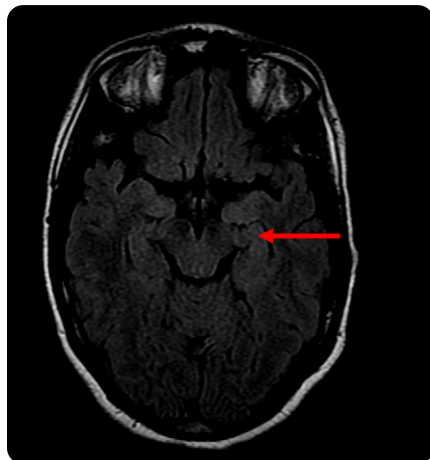
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**FIGURE 1**  
**Brain axial magnetic resonance imaging**



T2 fluid attenuation inversion recovery weighted sequence shows the hypersignal predominating in centrum semiovale (arrow).

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antibodies, which target intracellular epitopes (ie, Yo, Hu, Ma2, and amphiphysin antibodies).

NMDA receptor antibodies are supposed to result from a cross-reaction between the neuronal component of the teratoma and the central nervous system. In the present case, there was no neuronal component in the teratoma,

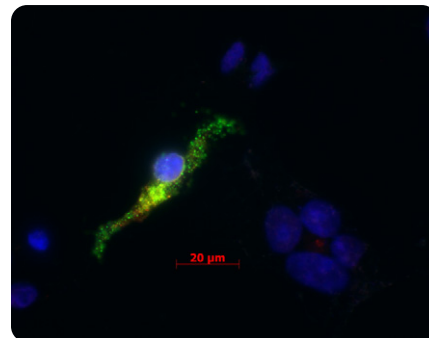
but only a cutaneous one. This could be explained by the common neuroectodermic origin of these 2 tissues, which may share some identical epitopes.

In the experience of Dalmau et al,<sup>1</sup> the quicker the tumor is removed (<4 months after the beginning of the symptom), the fewer recurrences there are; when the tumor is not found, the prognosis is worse. Without removal, spontaneous recovery is possible; however, the symptoms last longer, and relapse is more frequent.<sup>7,8</sup> Prompt surgical treatment appears necessary in addition to intravenous immunoglobulins.

Teratomas are bilateral in 15% of cases, and can be subclinical.<sup>1</sup> If subclinical, should oophorectomy be performed if the tumor is not found in these women of reproductive age? Data on the subject are scarce, but Asai et al<sup>8</sup> suggest that cystectomy and adnexectomy result in the same neurologic prognosis after 2 years of follow-up evaluation. In the present case, we decided on cystectomy because the ovarian cyst looked like a functional one and removal was complete.

It is difficult to say whether the nonexistence of anti-NMDA receptor encephalitis before 2007 should be explained by misdiagnosis or if this entity is a new disease process. However, when we performed a PubMed search with the terms *ovarian teratoma* and *psychiatric*, 33 arti-

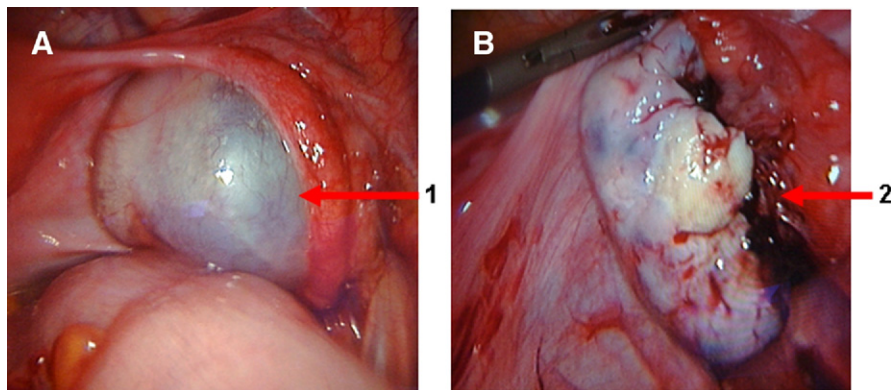
**FIGURE 3**  
**Reactivity of the patient's antibodies with the NR1 and NR2B heteromers of the anti-N-methyl-D-aspartate receptor**



Double immunolabeling of human embryonic kidney cells, which were transfected with the NR1 and NR2B heteromers of the anti-N-methyl-D-aspartate receptor and incubated with the patient's cerebrospinal fluid. The cell nucleus is stained with 4', 6-diamidino-2-phenylindole (blue). NR1 and NR2B heteromers are shown in red, and the patient's antibodies are labeled with a green fluorochrome. Colocalization of NR1 and NR2B heteromers and the patient's antibodies is yellow.

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**FIGURE 2**  
**Laparoscopic view**



Shows the **A**, right ovary before and **B**, after the cystectomy. The ovary contained a regular cyst with smooth surface (arrow 1). Cystectomy was performed; postprocedure ovary was unremarkable (arrow 2).

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cles are retrieved. Among them, 4 articles were published before 2007 (before the first description of anti-NMDA receptor encephalitis). Typically, the case report published in 1997 concerning a 15-year-old girl with an acute confused state with an immature ovarian teratoma might have been an anti-NMDA receptor encephalitis because she recovered full physical and mental faculties after salpingo-oophorectomy; anti-Yo, anti-Hu, and anti-Ri antibodies were all negative.<sup>9</sup> Consequently, misdiagnosis of anti-NMDA receptor encephalitis that complicated ovarian teratoma before 2007 is possible. However, on the basis of the rapid accrual of patients and increasing number of case reports and series reported in the neurologic literature,<sup>1,10,11</sup> we believe that anti-NMDA receptor encephalitis is an emergent treatable disease that deserves full attention from gynecologists. Gynecologists should be aware of the possibility of patient referrals

from neurologists, intensivists, and psychiatrists when a patient with a suspicious ovarian cyst and presumed anti-NMDA receptor encephalitis is referred for oophorectomy or ovarian cystectomy.

Because there may be milder cases of anti-NMDA receptor encephalitis in some women with teratomas, one could argue for systematic screening for anti-NMDA receptor antibodies in women with teratomas. Such an approach could allow the determination of the accurate prevalence of anti-NMDA receptor antibodies in women with teratomas. Anti-NMDA receptor antibodies are present both in cerebrospinal fluid and serum. Unfortunately, the screening for anti-NMDA receptor still requires a cerebrospinal fluid examination. A lumbar puncture, which is associated with a severe complication rate of 2% approximately,<sup>12</sup> must be performed. On the other hand, teratoma is the most common ovarian tumor because it accounts for 10-20% of all ovarian tumors.<sup>13</sup> Consequently, the systematic realization of a lumbar puncture in patients with ovarian teratoma is unnecessary and potentially iatrogenic. This screening must be considered only for patients with neurologic or psychiatric symptoms, even minimal. One can keep in mind that >90% of patients with this disease have pathologic electro-

encephalography. This examination may help to select patients who are eligible for anti-NMDA receptor screening. For these reasons, we believe that the systematic screening for anti-NMDA receptor in women with teratomas should be reserved for prospective studies. ■

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