A Subacute Behavioral Disorder In a Female Adolescent. Autoimmune Anti-*N*-methyl-D-aspartate Receptor Encephalitis Associated with Ovarian Teratoma

To the Editor:

A 17-year-old Belgian female patient, without a history of medical or psychiatric problems, had been living in Ireland since early September 2007. Around mid-November, her teacher noticed some excitability, agitation, euphoria, and even aggressiveness. She was eventually admitted to a local psychiatric hospital on November 24, 2007, for treatment of acute hypomania. There was no history of drug abuse. Brain computerized tomography was normal. She was treated with haloperidol and aripiprazole, 10 mg/day. She was then transferred to Belgium 3 days later.

On admission to our Department of Psychiatry on November 27, she presented with disorientation in time and space and drowsiness. She lacked awareness of her behavioral problems. She was mute most of the time but not confused. There were no delusions or hallucinations. However, she claimed to be of Irish origin and to have no familial ties in Belgium. The antipsychotic treatment was withheld and her attention improved. Initially, she refused any contact with hospital staff, did not wash, and had to be prompted for eating or dressing. She had a severe short-term memory loss. From December 3, the patient had repetitive questions about the day of the week, her age, and the reasons for being admitted to hospital. The clinical picture suggested an amnesic syndrome of long duration.

Standard blood analysis was normal. Urinary tests were negative for opiates, cannabis, cocaine, and amphetamines. Brain magnetic resonance imaging (MRI) was normal. The electroencephalogram (EEG) was considered normal.

A spinal tap was performed on December 6. The cerebrospinal fluid (CSF) contained 3 mononuclear cells/μL, a normal glucose and protein level, but two specific oligoclonal immunoglobulin G (IgG) bands not present in the corresponding serum. The presence of an intrathecal immune reaction was further confirmed by the detection of free kappa chains in the CSF (1).

On December 19, a formal neuropsychological assessment showed a normal working memory but a severe impairment of visual and verbal long-term memory.

In spite of the absence of any specific treatment, the patient's cognitive status slowly improved. She became more and more alert and nosognosic of her problems. Her mood was fluctuant, and sometimes nurses found her crying alone in her hospital room.

On January 15, 2008, a formal neurological examination was normal. Her parents still found her a little apathetic and nonchalant. The patient remained amnesic from November 24 to the end of January 2008. She had no recollection of Christmas and New Years. However, she remembered her birthday on February 6. At the end of February 2008, she went on a winter holiday for 1 week. From that point, she has a full recollection of her daily life events.

In the meantime, the search for the presence of anti-Hu, anti-Yo, antiamphiphysin, and anti-voltage-gated sodium channels (anti-VGKC) antibodies was negative. The CSF and serum samples were sent to the laboratory of Professor J. Dalmau (Philadelphia) and were positive for antibodies to NR1/NR2 heteromers of the *N*-methyl-D-aspartate receptor (NMDAR), with a stronger reactivity in the CSF. A left ovarian cyst was detected on MRI scans and was removed by coelioscopy on April 17, 2008. The cyst was 54 mm in diameter (Figure 1) and contained hair, sebaceous glands, and skin components but also choroid plexus and nervous tissue with both glial fibrillary acidic protein (GFAP)-positive glial cells and neuron-specific enolase (NSE)-positive neuronal cells (Figure 2). The pathological diagnosis was a mature ovarian teratoma.

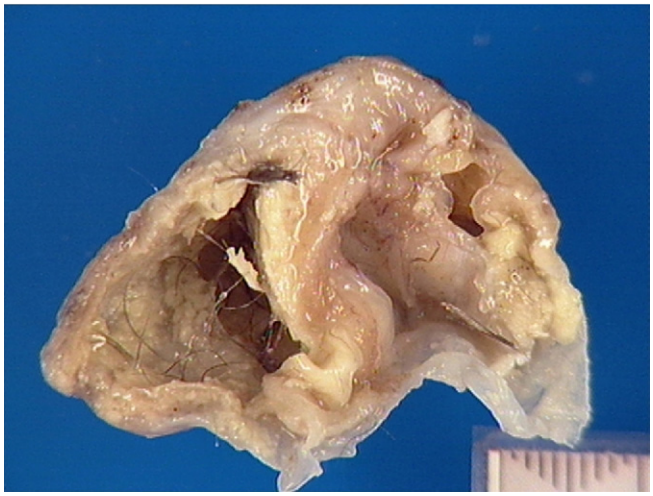

Figure 1. Macroscopic picture of the cystic tumor after incision to reveal some hair (mature cystic teratoma). A centimeter scale is visible in the lower right.

At the last follow-up on August 19, 2008, the patient had completely recovered but remained amnesic for the period from November 24, 2007, to the end of January 2008.

Discussion. Our patient suffered from a relatively benign form of paraneoplastic anti-NMDAR encephalitis associated with an ovarian teratoma. This syndrome resembled the acute behavioral effects of the *N*-methyl-D-aspartate (NMDA) antagonist, ketamine, in humans (2).

In a first series of 12 patients described by Dalmau *et al.* (3), 11 developed generalized or partial complex seizures and 10 required mechanical ventilation because of a decreased level of consciousness. Many also presented a viral-like prodromic syndrome, abnormal dystonic or myoclonic movements, facial dyskinesias, or autonomic instability. Six patients were initially evaluated by psychiatrists and five were admitted to psychiatric units. In a very recently published series from the same group (4), most patients were women or girls (n = 91). Because of a predominant psychiatric presentation, 77 patients were initially seen by a psychiatrist. Psychiatric symptoms included anxiety, agitation, bizarre behavior, delusional or paranoid thoughts, and visual or auditory hallucinations. The 23 other patients first seen by a neurologist presented with short-term memory loss or seizures alone or associated with psychiatric manifestations. In addition, 76% of the patients suffered from seizures, 86% from dyskinesia and other movement disorders, 69% from autonomic instability, and 66% from central hypoventilation and a decreased level of consciousness. Only 7% developed a milder syndrome of seizure and psychiatric symptoms. Electroencephalogram was abnormal in almost all cases, but brain MRI showed abnormal findings in only 55% of the cases, without particular localization of the lesions. Cerebrospinal fluid pleocytosis was present in 91% of the cases and oligoclonal IgG bands were present in 66%.

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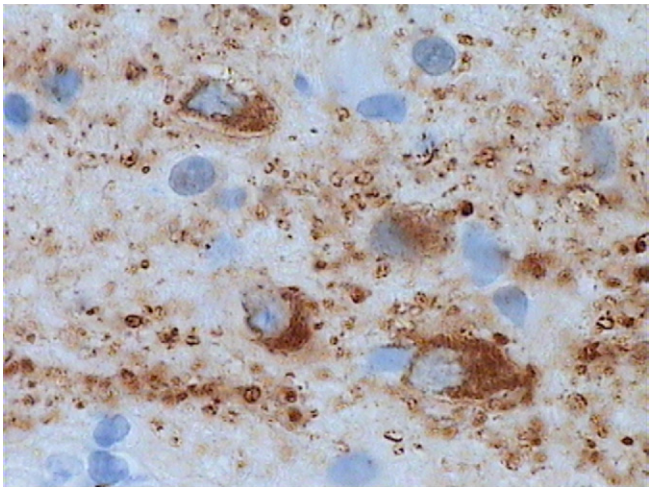

Figure 2. Presence of nervous tissue in a small fragment containing four neurons and surrounding neuropil immunostained with antineuron specific enolase antiserum.

Interestingly, anti-NMDAR encephalitis was paraneoplastic in only 59% of the cases, with a strong association with ovarian teratoma (53 out of 58 patients), and occurred in the remaining cases without associated tumors.

In our patient, memory impairment was the most conspicuous symptom. After recovery, the patient kept a persisting amnesia of the entire process, which is a characteristic feature of the anti-NMDAR encephalitis. This could indicate a predominant involvement of the medial temporal lobes, even in the absence of abnormal imaging. However, antibodies against NMDAR from such patients react preferentially with the extracellular region of the NR1 subunit, and heteromers containing NR1 are widely distributed in the brain. This may explain the large clinical spectrum of signs and symptoms observed in this disorder (4).

Our patient had a very good outcome well before the removal of the ovarian teratoma. This surprising observation has been already made in six patients reported so far (4,5) and could indicate a spontaneous regression of the immune response against the nervous tissue contained in the teratoma and against the brain itself. However, as anti-NMDAR encephalitis may be very severe and sometimes fatal and as a clear-cut neurological response to early removal of the tumor has been reported in some patients (6), search for and removal of an ovarian cyst or teratoma should be systematically performed. Most patients require intensive immunosuppressive treatment with corticosteroids, plasma exchanges, intravenous immunoglobulin, cyclophosphamide, or rituximab (4). Once improvement is noted, most patients continue to improve over weeks or months until complete recovery, and no maintenance is required (7).

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