THE JOURNAL OF
Obstetrics and Gynaecology Research

doi:10.1111/j.1447-0756.2011.01671.x J. Obstet. Gynaecol. Res. Vol. 37, No. 12: 1883–1886, December 2011

Anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian immature teratoma

Azusa Sameshima, Takao Hidaka, Tomoko Shima, Akitoshi Nakashima, Toru Hasegawa and Shigeru Saito

Department of Obstetrics and Gynecology, University of Toyama, Toyama, Japan

Abstract

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a treatment-responsive encephalitis associated with anti-NMDAR antibodies. Unlike classic paraneoplastic encephalitis, this disorder usually develops in young women with ovarian teratoma who typically present with marked neuropsychiatric symptoms, followed by prolonged respiratory failure, clouding of consciousness, and bizarre dyskinesia. This disorder is often treatable by resection of ovarian tumor and immunotherapy, but, delayed diagnosis results in a worse condition and sometimes fatal outcome. However, some gynecologists are not familiar with this disorder. When physicians encounter a female patient with encephalitis showing marked neuropsychiatric symptoms, search for an ovarian tumor should be promptly initiated. We present a case of anti-NMDAR encephalitis associated with ovarian immature teratoma. The symptoms were dramatically relieved by tumor resection and immunotherapy.

Key words: encephalitis, N-methyl-D-aspartate (NMDA) receptor, ovarian tumor, psychosis, teratoma.

Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a treatment-responsive encephalitis associated with anti-NMDAR antibodies, which bind to the extracellular conformal epitope in NR1/NR2 heteromers of the anti-NMDAR and reversibly inhibit the clustering of the anti-NMDAR on the neuronal cell membrane.[1,2]

This disorder usually develops in young women with ovarian teratoma, who typically present with neuropsychiatric symptoms, often preceded by a common cold-like illness. Most cases develop seizures, followed by prolonged respiratory failure, clouding of consciousness, central hypoventilation and bizarre dyskinesia. Delayed diagnosis of the tumor sometimes leads to a fetal outcome.

We present a case of anti-NMDAR encephalitis associated with ovarian immature teratoma, in which the symptoms were dramatically relieved by combined modality therapy.

Case Report

A 17-year-old female patient without a history of medical or psychiatric problems was admitted to a local department of psychiatry because of sudden agitation, delusion and aggressiveness, which appeared psychotic. She had been suspected common cold with low grade fever, headache and tonsillitis for one week. Despite any medication, the above symptoms persisted and gradually worsened. Two weeks after admission, the presence of lower abdominal tumor was suspected on abdominal ultrasonographic findings. Then, she was transferred to our hospital for further examination and treatment. The patient was disorientated to place and person, and appeared

Received: February 8 2011.
Accepted: April 27 2011.
Reprint request to: Associate Professor Takao Hidaka, Department of Obstetrics and Gynecology, University of Toyama, 2630 Sugitani, Toyama-shi, Toyama 930-0194, Japan. Email: hidaka@med.u-toyama.ac.jp

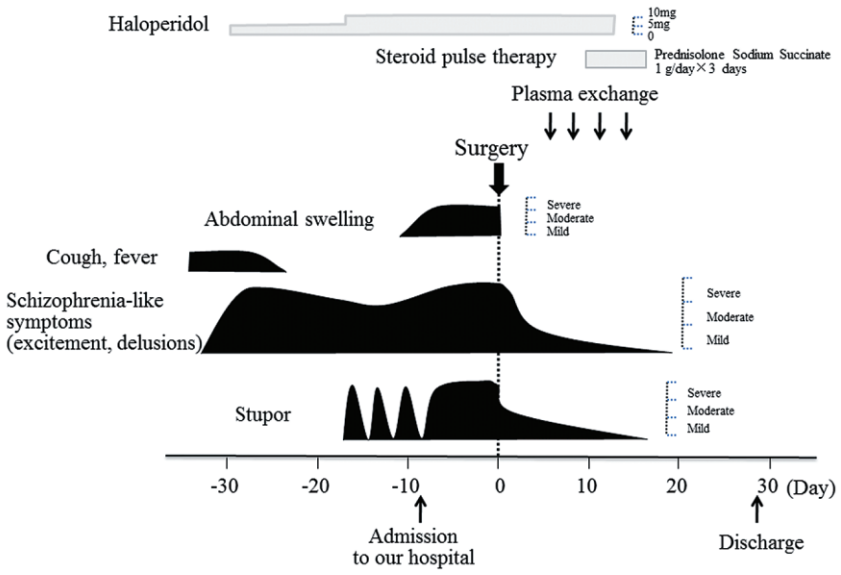


Figure 1 Clinical course of treatments and symptoms presented in this case. Steroid pulse therapy consisted of intravenous administration of glucocorticoids (prednisolone sodium succinate; 1 g/day) for three days. Surgery: right salpingo-oophorectomy.

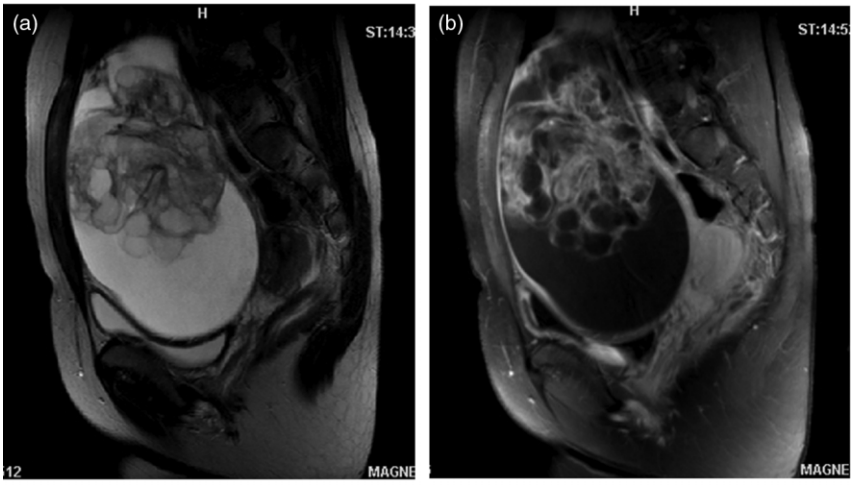
stuporous. There were no meningeal signs, and no apparent involuntary movements (Fig. 1).

On pelvic examination, the right ovary was enlarged to child head size. Abdominal ultrasonography showed right ovarian solid-cystic tumor measuring 14 × 10 cm, with multiple calcified foci. Standard blood analysis was normal. Preoperative serum tumor marker values (alpha-fetoprotein 14.2 ng/mL, CA125 72 U/mL, squamous cell carcinoma antigen 2.8 U/mL) showed slight elevation. Cerebrospinal fluid contained normal glucose and protein levels, and mononuclear cells, and showed non-specific changes. There was no serological sign of viral infection such as herpes simplex virus type 1, herpes simplex virus type 2, cytomegalovirus, varicella-zoster virus and Epstein–Barr virus. The result of serum anti-NMDAR antibody testing had not yet been identified at this point of time, however, it proved to be strongly positive postoperatively. Pelvic magnetic resonance imaging (MRI) demonstrated ovarian tumor measuring 16 × 9 cm that contained calcification, fat and an enhanced solitary portion (Fig. 2). Computerized tomography scanning did not detect any evidence of metastatic disease. Slight enlargement of the inferior horn of the right ventricle of the corpus callosum was detected by a brain MRI. single photon emission computed tomography did not show abnormal findings. The electroencephalogram was considered normal. Based on these findings, we considered the diagnosis of immature teratoma with anti-NMDAR encephalitis.

Intravenous administration of haloperidol (10 mg/day) did not improve and the symptoms worsened daily. On day 6 of hospitalization, she underwent exploratory laparotomy and right salpingo-oophorectomy (Fig. 3), which demonstrated grade 2 immature teratoma, International Federation of Gynecology and Obstetrics stage 1a. After surgery, consciousness level improved remarkably, but her psychotic behavior, such as excitement, stupor and dismissive behavior, was not completely relieved. Then, four consecutive plasma exchanges were performed from day 6 to day 15, and subsequently, steroid pulse therapy; intravenous administration of glucocorticoids (prednisolone sodium succinate; 1 g/day) on day 10 to day 12. Eventually, her psychotic behavior and all neurological symptoms were completely resolved, and she was discharged home on day 29 (Fig. 1). At the last follow up 10 months postoperatively, she had completely recovered and there were no signs of recurrent neurologic symptoms.

Discussion

Ovarian teratoma-associated encephalitis was first described by Nokura *et al*. and Okamura *et al*. independently in 1997.[3,4] In the first series of 12 patients described by Dalmau *et al*.,[1] 11 developed generalized or partial complex seizures and 10 required mechanical ventilation because of decreased consciousness level. Many patients also presented a viral-like prodromic



T1-weighted MRI with Gd-DTPA enhancement

T1-weighted fat suppressed image

Figure 2 Pelvic magnetic resonance imaging (MRI): (a) enhanced T1-weighted MRI and (b) T1-weighted fat suppressed image. An ovarian tumor with calcification, fat and markedly enhanced solid portion was demonstrated on T1-weighted MRI with gadolinium- diethylenetriamine penta-acetic acid (Gd-DTPA) enhancement. T1-weighted hyperintensity in the tumor was suppressed in T1-weighted fat suppressed image, indicating the presence of fat, compatible with ovarian teratoma.

Figure 3 Macroscopic findings of the ovarian tumor. The ovarian tumor contained a solid component, including hair, sebaceous glands, and skin components; however, the choroid plexus and nervous tissue were not clear.

syndrome, abnormal dystonic or myoclonic movements, facial dyskinesia or autonomic instability. They also presented with prodromal headache, fever, or a viral-like process, followed in a few days by a multistage progression of symptoms that included prominent psychiatric manifestations, insomnia, memory deficits, seizures and dyskinesias.[1,2,5]

The pathogenesis remains unknown; however, a recent study demonstrated that it was associated with anti-NMDA receptor antibodies in serum and cerebrospinal fluid that bind to rat hippocampus and the teratoma,[1,6,7] and that the antibodies reversibly inhibit the clustering of the NMDA receptor on the neuronal cell membrane.[2] Dalmau *et al*. also demonstrated the expression of anti-NMDA receptor antibody in the resected ovarian tumor tissue specimen.[1] In this case, we obtained the permission for immunohistochemical analysis of the surgical specimen from the patient and the Institutional Review Board of Toyama University, and performed immunohistochemical studies as reported; however, we could not demonstrate the reactivity of anti-NMDA receptor antibody clearly. Instead, the result of serum anti-NMDAR antibody testing proved to be strongly positive postoperatively. Furthermore, we have examined the anti-NMDAR antibody using mutant NMDAR over-expressing cells. NMDA is toxic to the host cells, therefore, mutated NMDAR-expressing vector was transfected. These cells are very useful to detect NMDAR (manuscript in preparation). Interestingly, anti-NMDAR antibody was detected before the operation, but this antibody was disappeared after operation and plasma exchange therapy.

Patients may require intensive care support for several weeks or months, followed by a multidisciplinary team including physical rehabilitation and psychiatric management of protracted behavior symptoms. The latter include symptoms of frontal lobe dysfunction that progressively improve over months.[2,8–10]

Dalmau *et al*. analyzed 100 patients with anti-NMDAR encephalitis and showed that 58 of 98 patients

had a tumor (mature teratoma of the ovary, 35 cases; immature teratoma of the ovary, 15 cases; other tumors, 8 cases). All but one of these patients developed neurological symptoms before the diagnosis of the tumor. In six patients, the tumor was diagnosed after recovery from the encephalitis; however, two died before tumor assessment.[2]

Removal of the tumor together with immunotherapy including glucocorticoids, intravenous immune globulin, and plasma exchange often result in rapid improvement.[11] Delayed diagnosis of the tumor sometimes leads to a fetal outcome.[1,2,8,12–14] In our case, almost all of the symptoms were rapidly relieved by removal of tumor, but not completely. Therefore, we added immunotherapy including plasma exchange and glucocorticoids, and the patient then completely recovered.

In conclusion, if ovarian tumor, mainly teratoma, is detected in a patient demonstrating psychotic symptoms, including anxiety, agitation, bizarre behavior, delusional or paranoid thoughts, and visual or auditory hallucinations, gynecologists should remember anti-NMDAR encephalitis as differential diagnosis. Then, the removal of the tumor followed by immunotherapy should be performed as early as possible.

References

1. Dalmau J, Tuzun E, Wu HY *et al*. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol* 2007; **61**: 25–36.
2. Dalmau J, Gleichman AJ, Hughes EG *et al*. Anti-NMDA-receptor encephalitis: Case series and analysis of the effects of antibodies. *Lancet Neurol* 2008; **7**: 1091–1098.
3. Nokura K, Yamamoto H, Okawara Y, Koga H, Osawa H, Sakai K. Reversible limbic encephalitis caused by ovarian teratoma. *Acta Neurol Scand* 1997; **95**: 367–373.
4. Okamura H, Oomori N, Uchitomi Y. An acutely confused 15-year-old girl. *Lancet* 1997; **350**: 488.
5. 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**: 63–74.
6. Moscavitch SD, Szyper-Kravitz M, Shoenfeld Y. Autoimmune pathology accounts for common manifestations in a wide range of neuro-psychiatric disorders: The olfactory and immune system interrelationship. *Clin Immunol* 2009; **130**: 235–243.
7. Tachibana N, Shirakawa T, Ishii K *et al*. Expression of various glutamate receptors including N-methyl-D-aspartate receptor (NMDAR) in an ovarian teratoma removed from a young woman with anti-NMDAR encephalitis. *Intern Med* 2010; **49**: 2167–2173.
8. Iizuka T, Sakai F, Ide T *et al*. Anti-NMDA receptor encephalitis in Japan: Long-term outcome without tumor removal. *Neurology* 2008; **70**: 504–511.
9. Zandi MS, Irani SR, Follows G, Moody AM, Molyneux P, Vincent A. Limbic encephalitis associated with antibodies to the NMDA receptor in Hodgkin lymphoma. *Neurology* 2009; **73**: 2039–2040.
10. Novillo-López ME, Rossi JE, Dalmau J, Masjuan J. Treatment-responsive subacute limbic encephalitis and NMDA receptor antibodies in a man. *Neurology* 2008; **70**: 728–729.
11. Asai S, Ishimoto H, Yabuno A, Asada H, Seki M, Iwata S. Laparoscopic cystectomy of ovarian teratoma in anti-NMDAR encephalitis: 2 case reports. *J Minim Invasive Gynecol* 2011; **18**: 135–137.
12. Seki M, Suzuki S, Iizuka T *et al*. Neurological response to early removal of ovarian teratoma in anti-NMDAR encephalitis. *J Neurol Neurosurg Psychiatry* 2008; **79**: 324–326.
13. Florance NR, Davis RL, Lam C *et al*. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. *Ann Neurol* 2009; **66**: 11–18.
14. Niehusmann P, Dalmau J, Rudlowski C *et al*. Diagnostic value of N-methyl-D-aspartate receptor antibodies in women with new-onset epilepsy. *Arch Neurol* 2009; **66**: 458–464.