Case Report

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Anti-N-Methyl-D-Aspartate Receptor-Related Grave but Reversible Encephalitis with Ovarian Teratoma in 2 Japanese Women Presenting with Excellent Recovery without Tumor Resection

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Acute encephalitis associated with ovarian teratoma preferentially affects young women and is characterized by acute prominent psychiatric symptoms, decreased level of consciousness, frequent seizures and central hypoventilation [1, 2]. Cases of reversible encephalitis affecting exclusively young women were reported in Japan under the name of 'acute juvenile female non-herpetic encephalitis (AJFNHE)' [3–5]. Dalmau et al. [6] recently reported that anti-N-methyl-D-aspartate receptor (NMDAR) antibody was positive in patients with acute encephalitis associated with ovarian teratoma as well as in mediastinum and grouped them in a category of NMDAR-related encephalitis. They recommended resection of the tumor for treatment [6–8], but it is not always easy for young nulligravid women to have their ovaries removed. We report NMDAR-related encephalitis in 2 patients treated without tumor resection.

Patient 1

A 28-year-old woman developed curious behavior after persistent fever for 7 days, and suddenly became convulsive. On admission, consciousness was disturbed and temperature was high. General physical examination revealed neck stiffness and Kerning sign. Blood cell counts and routine serum biochemical analyses were normal. Serological testing for antinuclear and anti-DNA antibodies, tumor markers and syphilis were negative. Her cerebrospinal fluid (CSF) showed mild pleocytosis, was negative for tubercle bacilli on culture and for herpes simplex virus (HSV)-DNA on PCR. Brain MRI showed no abnormalities. The pelvic CT showed bilateral ovarian teratoma. EEG showed diffuse delta waves with no epileptic discharges. Intravenous administration of acyclovir was continued until the result of HSV-DNA on PCR was confirmed. Administration of methylprednisolone and antiepileptic drugs was started. However, her condition worsened gradually, and she presented with stereotypic oral dyskinetic movements. She fell in hypoventilation and coma, and was put on a ventilator. Her condition began to improve and ventilatory support was withdrawn on the 50th hospital day. She was discharged 83 days after hospitalization with excellent recovery.

Antibodies to NR1/NR2B heteromers of NMDAR in the serum and CSF were positive on admission. One year after, the serum NMDAR antibodies were no longer detected. The pelvic MRI showed bilateral ovarian teratomas (fig. 1A), and the tumors did not change in size for 1 year.

Patient 2

A 33-year-old woman developed persistent fever and cried violently. High fever continued and seizure-like involuntary movements occurred. General physical and neurological examination showed neck stiffness and bilateral positive Babinski sign. The CSF showed mild pleocytosis. The pelvic CT revealed right ovarian teratoma. She received anticonvulsant medications and methylprednisolone pulse therapy. Because of hypoventilation, she was put on mechanical ventilation for 10 months. Her condition began to improve, and she was transferred for rehabilitation. Neurological examination 4 years after onset revealed excellent recovery.

The NMDAR antibodies in the CSF at the acute stage were positive. Serum NMDAR antibodies were not detected 5 years after discharge. Pelvic MRI showed right ovarian teratoma (fig. 1B), and the tumors did not change in size for 5 years.

Discussion

As to the treatment of NMDAR-related encephalitis, tumor resection was recommended [6–8], since patients with tumor resection had recovered while those without resection worsened or died [6]. In con-

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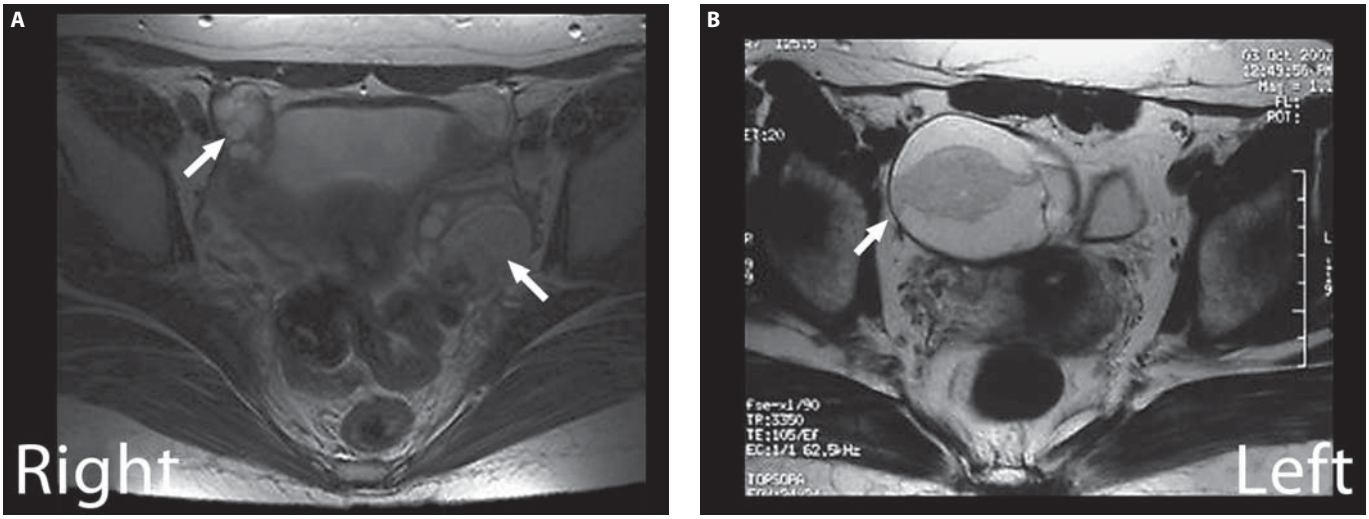

Fig. 1. Ovarian teratomas demonstrated on pelvic MRI. **A** Axial T_2-weighted fat suppression image of patient 1 one year after discharge shows bilateral ovarian cystic tumors (arrows) with the presence of fat. **B** Axial T_2-weighted image of patient 2 five years after discharge shows a right ovarian cystic tumor with the presence of a fluid level. These tumors are suspected of mature ovarian teratoma.

trast, Iizuka et al. [7] reported that patients without tumor resection had recovered though the duration of ventilatory support had been significantly longer than that of patients with tumor resection. Seki et al. [8] reported that early removal of the ovarian teratoma had resulted in prompt neurological response. Both of our patients had ovarian teratoma(s), but they finally showed excellent recovery without resection. The tumors did not change in size for year(s). These consequences suggest that tumor resection may not always be necessary though recovery may be late.

Acute onset of encephalitis after prodromal infection symptoms and spontaneous recovery associated with disappearance of the NMDAR antibodies despite the long-standing existence of ovarian teratoma(s) in the present cases and those reported by Iizuka et al. [7] remain to be clarified. Abnormal improvement reaction may be triggered by acute viral infection or other events, and autoantibodies against NMDAR may be produced temporally in these patients.

We reported 2 cases of NMDAR-related encephalitis with ovarian teratoma. They recovered without tumor resection. The timing and indication of tumor resection remain to be clarified.

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