INTERNAL MEDICINE

□ CASE REPORT □

Postpartum Anti-N-methyl-D-aspartate Receptor Encephalitis: A Case Report and Literature Review

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Abstract

We describe a 24-year-old woman with anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis that developed 3 weeks after normal delivery. She was treated with methylprednisolone, intravenous immunoglobulin, and plasmapheresis, in addition to teratoma excision. However, her recovery was slow, and dysmnesia and mental juvenility persisted even two years after onset. To date, five patients with postpartum anti-NMDAR encephalitis have been reported. All of those patients showed psychotic symptoms and were suspected of having postpartum psychosis in the early period of the encephalitis. Changes in hormonal factors, modification of immune tolerance, or retrograde infection of the ovary may be contributing factors for postpartum anti-NMDAR encephalitis.

Key words: anti-N-methyl-D-aspartate receptor encephalitis, parturition, ovarian teratoma

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Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an autoimmune limbic encephalitis induced by antibodies directed against the NR1 subunit of the NMDAR (1). Typical patients with anti-NMDAR encephalitis show nonspecific prodromal symptoms, such as a fever and headache, followed by symptoms resembling schizophrenia, and then develop generalized seizure, altered mental status, hypoventilation, autonomic instability, and characteristic movement disorders, such as orofacial-limb dyskinesia and catatonia (2-4). The majority of patients require artificial ventilation in the intensive care unit. Anti-NMDAR encephalitis was originally reported as a paraneoplastic syndrome associated with ovarian teratoma (2). However, it is now acknowledged that the spectrum of this encephalitis is much broader, as there have been many cases in women without ovarian teratoma, men, and children (5). There is also a possibility that pregnancy and/or delivery could trigger anti-NMDAR encephalitis, as several patients developed this disorder during pregnancy or in the postpartum period (6-19). We herein report a Japanese patient who developed severe anti-NMDAR encephalitis three weeks after normal delivery and discuss the pathophysiology of postpartum anti-NMDAR encephalitis.

Case Report

The patient was a 24-year-old primiparous Japanese woman with no significant medical history. She had no complications during the course of the pregnancy and gave birth to a healthy baby girl via vaginal delivery. Three weeks after delivery, she developed a depressive mood and emotional incontinence. One week later, she presented with auditory hallucination and abnormal behavior and was mandatorily hospitalized in the department of psychiatry of a general hospital. She was diagnosed with postpartum psychosis and treated with antipsychotic drugs. On the second hospital day, she presented with somnolence and unstable breathing followed by generalized seizure. On the third hospital day, she developed status epilepticus and hyperthermia

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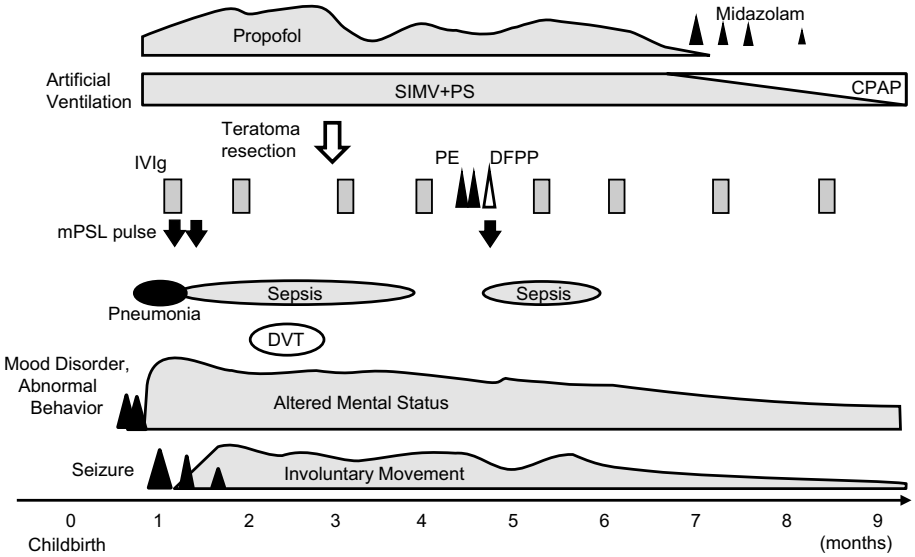

Figure 1. The clinical course of the patient. SIMV: synchronized intermittent mandatory ventilation, PS: pressure support, CPAP: continuous positive airway pressure, IVIg: intravenous immunoglobulin, PE: plasma exchange, DFPP: double filtration plasmapheresis, mPSL: methylprednisolone, DVT: deep vein thrombosis

and was transferred to the intensive care unit. Generalized seizure was difficult to control despite treatment with propofol and antiepileptic drugs, and respiratory depression led to tracheal intubation and artificial ventilation. She was treated with methylprednisolone (mPSL) pulse therapy at a dose of 1 g for 3 days and intravenous immunoglobulin therapy (IVIg) at a dose of 0.4 g/kg for 5 days (Fig. 1). However, her symptoms deteriorated gradually and she developed involuntary movements in the face and right upper limb. On the 16th hospital day, she was transferred to Shinshu University Hospital.

On admission, her body temperature was 38.5°C. A neurological examination showed orofacial dyskinesia and athetoid movement in the right hand even under deep sedation with propofol. She showed neither nuchal stiffness nor pathological reflexes. Laboratory tests revealed inflammatory reaction (white blood cell, 13,350/μL; C reactive protein, 4.31 mg/dL) and mild liver dysfunction (aspartate aminotransferase, 37 IU/L; alanine aminotransferase, 103 IU/L). Tests for herpes simplex, herpes zoster, and Epstein-Barr virus were negative. Autoantibodies were all negative, except for anti-thyroglobulin antibody and anti-thyroperoxidase antibody. The results of a cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis (82/μL, mononuclear cells 77/μL), a slightly elevated protein level (51 mg/dL), and a normal glucose level (73 mg/dL). Anti-NMDAR antibody was positive (×20, examined by Cosmic Corporation, Tokyo, Japan) in the CSF. Electroencephalogram (EEG) demonstrated diffuse beta activity superimposed on frontally dominant high-voltage rhythmic delta bursts, consistent with "extreme delta brush" (20, 21) (Fig. 2). Brain magnetic resonance imaging (MRI) showed slightly increased signal intensity with swelling in the bilateral medial temporal lobes on T2 and FLAIR imaging (Fig. 3A). Abdominal computed tomography (CT) revealed a right ovarian cystic tumor with small calcifications (Fig. 4A). Based on the characteristic clinical findings and positivity for anti-NMDAR antibody, a diagnosis of anti-NMDAR encephalitis associated with a right ovarian tumor was made.

She underwent laparoscopic removal of the ovarian tumor on the 56th hospital day. A pathological examination showed a mature cystic teratoma (Fig. 4B) consisting of stratified squamous epithelium with cutaneous appendage, neural tissue with choroid plexus, adipose tissue, bone, cartilage, and intestinal structure with goblet cells. In addition to resection of the teratoma, she was treated with IVIg, mPSL pulse therapy, plasma exchange (PE), and double filtration plasmapheresis (DFPP); however, her involuntary movements, higher brain dysfunction, and autonomic dysfunction were prolonged. We could not perform further intensive immunosuppressive therapy, such as rituximab and cyclophosphamide, due to repetitive severe infections, including pneumonia and sepsis (Fig. 1). The titer of anti-NMDAR antibody in CSF decreased to "×1" after teratoma resection and PE/DFPP (approximately 4 months after onset). After the fifth IVIg, her involuntary movements and respiratory failure improved gradually, and she was transferred to rehabilitation hospital eight months after onset (Fig. 1). At the time of transfer, she was still in a bedridden state and had severe cognitive dysfunction. Brain MRI 8 months after onset showed an almost normal appearance with no abnormal signals or brain atrophy. Her neurological condition continued to improve after transfer, and she achieved independent gait and verbal communication at 12 months after onset. Neither brain atrophy nor abnormal signals were revealed on MRI (Fig. 3B), but her memory disturbance and mental juvenility persisted even two years after onset.

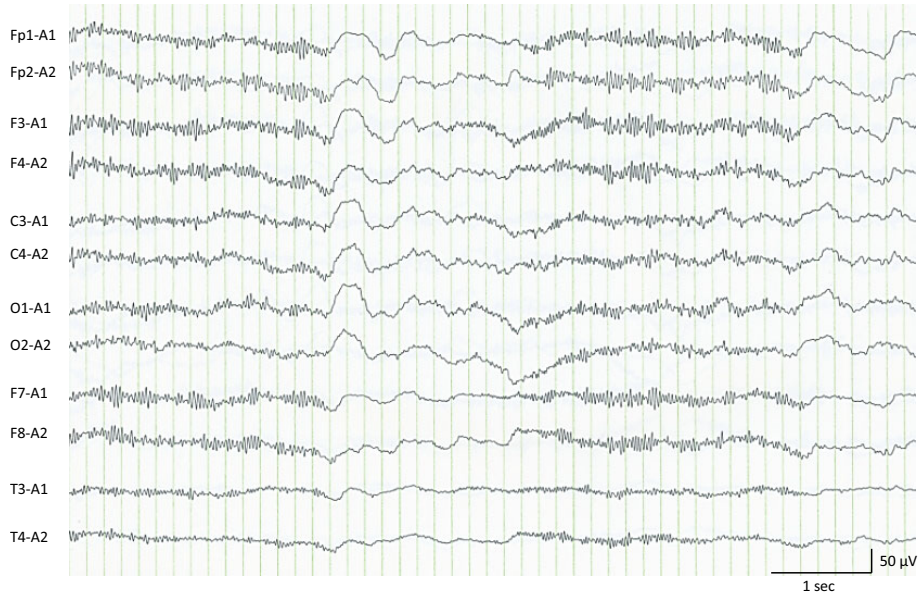

Figure 2. **Electroencephalogram of the patient. Diffuse beta activity superimposed on frontally dominant high-voltage rhythmic delta bursts was observed.**

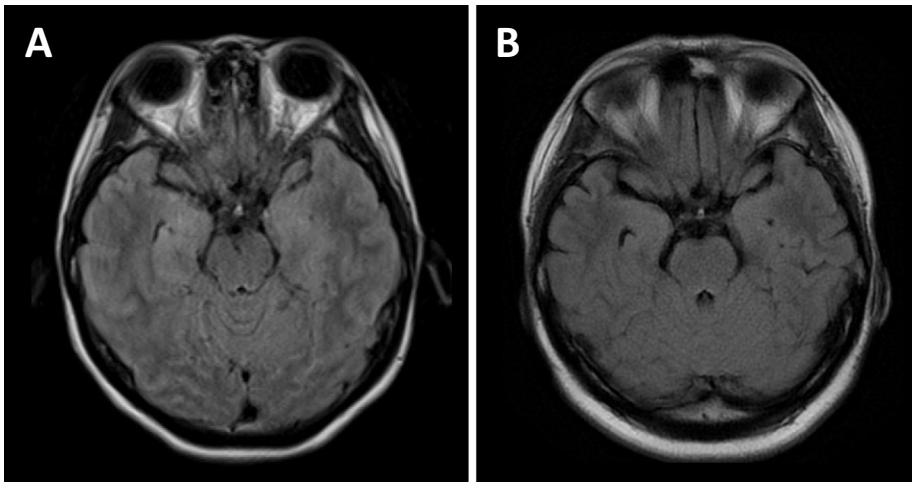

Figure 3. **Brain magnetic resonance image (MRI) of the patient (FLAIR image, axial view). (A) MRI performed at 1 month after onset. High signal intensity and slight swelling were seen in the bilateral medial temporal lobes. (B) MRI performed at 2 years after onset. Abnormal signal intensity in the bilateral medial temporal lobes disappeared without brain atrophy.**

Discussion

Ovarian teratoma is the most common associated tumor of anti-NMDAR encephalitis in female patients and contains antigenic neural tissue. In addition, the majority of patients have a history of prodromal flu-like symptoms, including headache, fever, nausea, vomiting, diarrhea, or upper respiratory tract symptoms. Therefore, the combination of ectopic expression of NMDAR, especially the NR1 subunit contained in the teratoma, and the adjuvant effect of the prodromal flu-like syndrome is thought to contribute to initiation of the immune response and production of pathogenic antibodies (3). The present case involved an ovarian teratoma with the development of anti-NMDAR encephalitis three weeks after delivery without prodromal flu-like symptoms. Therefore, anti-NMDAR encephalitis may have been triggered by normal vaginal delivery in our patient.

With regard to the relationship between anti-NMDAR encephalitis and pregnancy/delivery, 10 patients developed anti-NMDAR encephalitis during pregnancy (6-15), and 5 patients developed the disease during the postpartum period (16-19). One of the major immunological modifications during pregnancy is the Th1/Th2 shift, due to the progressive increases in levels of progesterone and estrogen during pregnancy, which suppress Th1 cytokines and stimulate Th2-mediated immunological responses as well as antibody production (22). Therefore, Th1-mediated diseases, such as rheumatoid arthritis and multiple sclerosis, tend to improve during pregnancy and worsen during the postpartum pe-

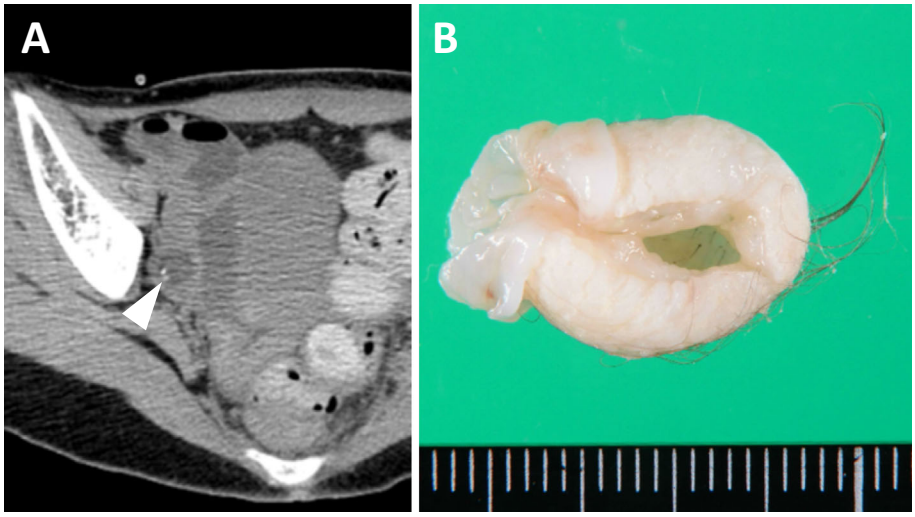

Figure 4. **The radiological and pathological findings of the ovarian teratoma. (A) Computed tomography of the pelvis showed a cystic tumor (1.5 cm in maximal diameter) with small calcifications adjacent to the right ovary. (B) Gross pathology of the encapsulated ovarian teratoma containing hair.**

riod (23, 24). In contrast, Th2-mediated diseases, such as systemic lupus erythematosus, tend to worsen during pregnancy (25). However, recent studies have shown that annualized relapse rate of neuromyelitis optica (NMO) tends to decrease in the first half of pregnancy and increase after the pregnancy (26, 27), although NMO is a Th2-mediated disease. In myasthenia gravis, worsening of symptoms is more likely during the first half of pregnancy and postpartum (28). Therefore, the influence of pregnancy and delivery on patients with immunological disorders should be analyzed with respect to each disease. With regard to anti-NMDAR encephalitis, the precise immunopathogenesis remains to be elucidated, although B cells, but not T cells, have been proposed to be involved (29). Therefore, further investigations regarding the immunopathogenesis of the disease, including the Th1/Th2 balance and cytokine dynamics, and large-scale epidemiological surveys are necessary to determine the effects of pregnancy and delivery on anti-NMDAR encephalitis.

Several hypotheses have been proposed to explain the pathomechanism of anti-NMDAR encephalitis associated with pregnancy and/or delivery. It was demonstrated that markedly increased estrogen promotes formation of autoreactive lymphocytes through rapid maturation of B cells and secretion of interleukin-10 during pregnancy (30, 31), which may facilitate the production of anti-NMDAR antibody and/or its crossing of the blood-brain barrier, thereby contributing to the development of anti-NMDAR encephalitis (3). Indeed, symptomatic recovery seemed to accelerate after giving birth in three patients with anti-NMDAR encephalitis (11). In contrast, the maternal immune system is modified to allow immune tolerance to fetal antigens during pregnancy. Yu et al. hypothesized that pregnancy-induced modulation of the immune system may contribute to the occurrence of postpartum anti-NMDAR encephalitis by a breakdown in tolerance to self-antigens (16).

Table shows the clinical characteristics of patients with anti-NMDAR encephalitis that developed during the postpartum period (16-19). All of the patients showed psychotic symptoms, including anxiety, delusions, bizarre behavior, insomnia, agitation, irritability, hallucinations, psychomotor excitement, confusion, and depression, and were suspected of having postpartum psychosis in the early period of the encephalitis. Three patients, including the patient described here, had ovarian teratoma. The patient reported by Koksal et al. showed dramatic improvement shortly after teratoma resection (17). In contrast, the patient reported by Yu et al. showed little improvement following tumor resection, mPSL, and PE, but improved dramatically shortly after rituximab administration (16). Rituximab was also very effective in a patient with postpartum anti-NMDAR encephalitis without teratoma (18). Our patient showed very slow improvement after tumor resection, which may have been caused by the delay in surgical resection and hesitation to perform aggressive immunosuppressive treatment, such as rituximab, due to recurrent severe bacterial infections. Severe bacterial infections and deep vein thrombosis are complications which occur frequently in patients with severe anti-NMDAR encephalitis. Management of these complications is crucial and has a considerable effect on the prognosis of anti-NMDAR encephalitis.

To our knowledge, there are no obvious differences in the clinical characteristics of patients between anti-NMDAR encephalitis associated with pregnancy, associated with delivery, and with no pregnancy/delivery association. However, Bergink et al. recently screened 96 consecutive patients with postpartum psychosis and 64 healthy postpartum women and found 2 patients with postpartum psychosis positive for anti-NMDAR antibody (19). Both patients recovered after treatment with lithium, lorazepam, and antipsychotic agents, and remission was sustained, despite the absence of any immunosuppressive treatment (19), suggesting that mild anti-

Table. Clinical Characteristics of Postpartum Anti-NMDAR Encephalitis.

Age	Number of delivery	Type of delivery	Interval between delivery and onset	Symptoms	Tumor	Treatment	Outcome / Sequelae	Reference
29	first	normal vaginal	8 to 9 weeks	memory difficulty, headache, anxiety, delusion, IVM, GTCS, catatonia	Rt. ovarian immature teratoma	teratoma resection, mPSL, PE, rituximab	dramatic improvement / poor short-term memory	16
25	unknown	normal vaginal	3 months	insomnia, agitation, irritability, delusion, hallucination, psychomotor excitement, confusion, generalized seizure	Rt. ovarian cystic teratoma	IVIg, mPSL pulse, teratoma resection	dramatic improvement / minimal behavioral changes	17
25	unknown	normal vaginal	2 months	bizarre behavior, GTCS, status epilepticus, hypoventilation	not found	mPSL pulse, PE, rituximab	dramatic improvement after rituximab / no sequelae	18
31	first	normal vaginal	1 week	mania, delusions of grandeur, bizarre behavior	not found	haloperidol, olanzapine, lorazepam, lithium	improved within 34 days / no sequelae	19
25	third	normal vaginal	3 weeks	paranoid delusion, auditory hallucination	not found	haloperidol, lorazepam, lithium	improved within 3 months / minor mood instability	19
24	first	normal vaginal	3 weeks	depression, abnormal behavior, GTCS, hypoventilation, IVM, catatonia	Rt. ovarian mature teratoma	mPSL, IVIg, teratoma resection, PE, DFPP	gradual improvement / higher brain dysfunction	present case

IVM: involuntary movement, GTCS: generalized tonic-clonic seizure, Rt.: right, mPSL: methylprednisolone therapy, PE: plasma exchange, IVIg: intravenous immunoglobulin therapy, DFPP: double filtration plasmapheresis

NMDAR antibody encephalitis may be underdiagnosed among a cohort of postpartum psychosis patients.

The authors state that they have no Conflict of Interest (COI).

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