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

Tadashi Doden1, Yoshiki Sekijima1,2, Junji Ikeda1, Kazuki Ozawa1, Nobuhiko Ohashi1, Minori Kodaira1, Akiyo Hineno1,3, Naoko Tachibana4 and Shu-ichi Ikeda1,2

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

(Intern Med 56: 357-362, 2017) (DOI: 10.2169/internalmedicine.56.7442)

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.

1Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, Japan, 2Institute for Biomedical Sciences, Shinshu University, Japan, 3Department of Neurology, Suwa Red Cross Hospital, Japan and 4Department of Neurology, Okaya City Hospital, Japan

Received for publication March 17, 2016; Accepted for publication June 13, 2016

Correspondence to Dr. Yoshiki Sekijima, sekijima@shinshu-u.ac.jp
eral medial temporal lobes on T2 and FLAIR imaging (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. 2). delta bursts, consistent with “extreme delta brush” (20, 21) perimposed on frontally dominant high-voltage rhythmic cephalogram (EEG) demonstrated diffuse beta activity such as 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.

Anti-NMDAR antibody was positive (×20, examined by vesicular extracellular matrix 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 Shinsyu University Hospital.

On admission, her body temperature was 38.5°C. A neurological examination showed orofacial dyskinesia and atetoid 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 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.
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-
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-

Correct para 2 and 3.

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

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

Acknowledgement

We are grateful to Dr. Katsumi Yamamoto, Dr. Sari Shimizu, and Dr. Mikito Kawamata, Department of Anesthesiology and Resuscitology, Shinshu University School of Medicine, for their advice and detailed patient management in ICU. We are also grateful to Dr. Motoki Ono, Dr. Hisanori Kobara, and Dr. Tani Shiozawa, Department of Obstetrics and Gynecology, Shinshu University School of Medicine, for their excellent surgical management.

References

1. Gleichman AJ, Spruce LA, Dalmau J, Seeholzer SH, Lynch DR. Anti-NMDA receptor encephalitis antibody binding is dependent on amino acid identity of a small region within the GluN1 amino terminal domain. J Neurosci 32: 11082-11094, 2012.
2. Dalmau J, Tuzun E, Wu HY, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 61: 25-36, 2007.
3. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 7: 1091-1098, 2008.
4. 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 10: 63-74, 2011.
5. Kayser MS, Dalmau J. Anti-NMDA receptor encephalitis, autoimmunity, and psychosis. Schizophr Res 176: 36-40, 2016.
6. Mathis S, Pin JC, Pierre F, et al. Anti-NMDA receptor encephalitis during pregnancy: a case report. Medicine (Baltimore) 94: e1034, 2015.
7. Ito Y, Abe T, Tomioka R, Komori T, Araki N. Anti-NMDA receptor encephalitis during pregnancy. Rinsho Shinkeigaku 50: 103-107, 2010 (in Japanese, Abstract in English).
8. Magley J, Towner D, Tache V, Apperson ML. Pregnancy outcome in Anti-N-methyl-D-aspartate receptor encephalitis. Obstet Gynecol 120: 480-483, 2012.
9. McCarthy A, Dineen J, McKenna P, et al. Anti-NMDA receptor encephalitis with associated catatonia during pregnancy. J Neurology 259: 2632-2635, 2012.
10. Shahani L. Steroid unresponsive anti-NMDA receptor encephalitis during pregnancy successfully treated with plasmapheresis. BMJ Case Rep 2015: bcr2014208823, 2015.
11. Kumar MA, Jain A, Dechant VE, et al. Anti-N-methyl-D-aspartate receptor encephalitis during pregnancy. Arch Neurol 67: 884-887, 2010.
12. Jagota P, Vincent A, Bhidayasiri R. Transplacental transfer of NMDA receptor antibodies in an infant with cortical dysplasia. Neurology 82: 1662-1663, 2014.
13. Chan LW, Nilsson C, Schepel J, Lynch C. A rare case of anti-N-methyl-D-aspartate receptor encephalitis during pregnancy. N Z Med J 128: 89-91, 2015.
14. Lamale-Smith LM, Moore GS, Guntupalli SR, Scott JB. Maternal-fetal transfer of anti-N-methyl-D-aspartate receptor antibodies. Obstet Gynecol 125: 1056-1058, 2015.
15. Lu J, Samson S, Kass J, Ram N. Acute psychosis in a pregnant patient with Graves’ hyperthyroidism and anti-NMDA receptor encephalitis. BMJ Case Rep 2015: bcr2014208052, 2015.
16. Yu AY, Moore FG. Paraneoplastic encephalitis presenting as postpartum psychosis. Psychosomatics 52: 568-570, 2011.
17. Koksal A, Baybas S, Muthuay Y, Altunkaynak Y, Kesek A. A case of NMDAR encephalitis misdiagnosed as postpartum psychosis and neuroleptic malignant syndrome. Neurol Sci 36: 1257-1258, 2015.
18. Shaaban HS, Choo HF, Sensakovic JW. Anti-NMDA-receptor en-
cephalitis presenting as postpartum psychosis in a young woman, treated with rituximab. Ann Saudi Med 32: 421-423, 2012.

19. Bergink V, Arangue T, Titulaer MJ, Markx S, Dalmau J, Kushner SA. Autoimmune encephalitis in postpartum psychosis. Am J Psychiatry 172: 901-908, 2015.

20. Schmitt SE, Paragon K, Frechette ES, Hirsch LJ, Dalmau J, Friedman D. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology 79: 1094-1100, 2012.

21. VanHaerents S, Stillman A, Inoa V, Searls DE, Herman ST. Early and persistent ‘extreme delta brush’ in a patient with anti-NMDA receptor encephalitis. Epilepsy Behav Case Rep 2: 67-70, 2014.

22. Doria A, Iaccarino L, Arienti S, et al. Th2 immune deviation induced by pregnancy: the two faces of autoimmune rheumatic diseases. Reprod Toxicol 22: 234-241, 2006.

23. Østensen M, Forger F, Nelson JL, Schuhmacher A, Hebisch G, Villiger PM. Pregnancy in patients with rheumatic disease: anti-inflammatory cytokines increase in pregnancy and decrease post partum. Ann Rheum Dis 64: 839-844, 2005.

24. Vukusic S, Hutchinson M, Houns M, et al. Pregnancy and multiple sclerosis (the PRIMS study): clinical predictors of post-partum relapse. Brain 127: 1353-1360, 2004.

25. Petri M. Prospective study of systemic lupus erythematosus pregnancies. Lupus 13: 688-689, 2004.

26. Bourre B, Marignier R, Zephir H, et al. Neuromyelitis optica and pregnancy. Neurology 78: 875-879, 2012.

27. Kim W, Kim SH, Nakashima I, et al. Influence of pregnancy on neuromyelitis optica spectrum disorder. Neurology 78: 1264-1267, 2012.

28. Ferrero S, Esposito F, Bianchi M, Bentivoglio G, Ragai N. Myasthenia gravis during pregnancy. Expert Rev Neurother 8: 979-988, 2008.

29. Tüzün E, Zhou L, Baehring JM, Bannykh S, Rosenfeld MR, Dalmau J. Evidence for antibody-mediated pathogenesis in anti-NMDAR encephalitis associated with ovarian teratoma. Acta Neuropathol 118: 737-743, 2009.

30. Zen M, Ghirardello A, Iaccarino L, et al. Hormones, immune response, and pregnancy in healthy women and SLE patients. Swiss Med Wkly 140: 187-201, 2010.

31. Pevia E, Zouali M. Spotlight on the role of hormonal factors in the emergence of autoreactive B-lymphocytes. Immunol Lett 101: 123-143, 2005.