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CASE REPORT

A case of anti-*N*-methyl-D-aspartate receptor encephalitis with multiple sclerosis-like demyelinated lesions

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KEYWORDS
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Neuromyelitis optica;
Brain biopsy;
Demyelination;
CSF antibody titer

Abstract
Objective: To describe an unusual case of a male patient with anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis who presented with multiple white matter lesions. Brain biopsy of the patient was performed, and follow-up evaluation of the cerebrospinal fluid (CSF) NMDAR antibody titer was implemented.
Design: Case report.
Setting: University hospital.
Patient: A 35-year-old man with anti-NMDAR encephalitis initially presented with fever and psychiatric symptoms. After an initial attack of anti-NMDAR encephalitis, 2 atypical relapses occurred, which presented with myelitis and multifocal white matter lesions; the lesions were open-ring-shaped and partially enhanced.
Intervention: Analysis of the brain biopsy specimen revealed the presence of demyelinated lesions with discrete borders. Subsequent intravenous methylprednisolone therapy resulted in improvement in the brain lesions. Prednisolone and cyclophosphamide were orally administered thereafter. Clinical progression of the disease paralleled observed changes in the CSF NMDAR antibody titer.

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Conclusion: The demyelinated lesions observed in this case were similar to lesions found in multiple sclerosis. On the basis of our finding that the clinical progression of the disease and the associated symptoms paralleled changes in the CSF NMDAR antibody titer, we speculate that the lesions formed as a result of anti-NMDAR encephalitis.

1. Introduction

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a rare, autoimmune clinical entity that can present with psychiatric symptoms, dyskinesia, decreased consciousness, and hypoventilation (Dalmau et al., 2011). It is associated with antibodies against functional NMDARs and predominantly affects young women. The first published report of anti-NMDAR encephalitis described 4 young women with ovarian teratomas (Vitaliani et al., 2005). Recently, unusual clinical courses of female patients with anti-NMDAR encephalitis have been reported (Johnston et al., 2010; Kruer et al., 2010; Lekoubou et al., 2012; Motoyama et al., 2010; Pennington et al., 2012; Yamamoto et al., 2013). Herein, we describe the unusual case of a male patient with anti-NMDAR encephalitis who presented with multiple demyelinated lesions.

2. Case report

We obtained the patient's consent by using a consent form provided by Osaka City University Hospital. A previously healthy 35-year-old man experienced headaches and fever. He visited a local hospital. Abnormal cerebrospinal fluid (CSF) findings (white blood cells, 164/μL [normal range: 0–5], primary mononuclear cells; total protein, 90 mg/dL [normal range: 10–52.6]; glucose, 56 mg/dL [normal range: 50–80]) indicated meningitis. He refused hospital admittance. Six days later, he became delirious and violent (day 1). He was then admitted to an emergency hospital, where he was diagnosed with encephalitis (day 4). Because of severe delusion, the patient was sedated and put under artificial ventilation after intubation; however, hypoventilation because of encephalitis was not apparent. He was transferred to Sakai Hospital, Kinki University Faculty of Medicine (day 7). Two courses of steroid pulse therapy (3 days × 1000 mg methylpredonisolone/day) and intravenous acyclovir (14 days × 2250 mg/day) were administered as herpes encephalitis was suspected, after which his consciousness marginally improved. CSF examination revealed pleocytosis (white blood cells, 61 cells/μL [normal range: 0–5], primary mononuclear cells; total protein, 36 mg/dL [normal range: 10–52.6]; myelin basic protein (MBP), <40 pg/mL [normal range: 0–102]; and no oligoclonal band). Blood tests revealed no autoantibodies associated with vasculitides (anti-nuclear antibody, antibodies to MPO-ANCA, PR3-ANCA, SSA, or SSB) or glutamic acid decarboxylase (GAD). He was weaned from mechanical ventilation on day 11. However, his consciousness remained mildly disturbed. Magnetic resonance imaging (MRI) on day 14 revealed a lesion in the right cerebral peduncle. Antiviral medications were discontinued because the polymerase chain reaction (PCR) (day 9) result for herpes simplex virus was negative. An additional examination of the CSF (day 4) revealed the presence of anti-NMDAR antibodies (titer=1:64). Plasmapheresis (7 times in 2 weeks) commenced on day 40, followed by oral administration of steroids, and the patient's consciousness level improved. The patient was ambulant on day 61. Two months after symptom onset, the level of anti-NMDAR antibodies in the CSF (day 81) remained weakly positive (1:4); however, follow-up MRI revealed that the right cerebral peduncle lesion had almost disappeared. On day 81, he developed sudden diplopia with abnormal movement of the right eye. MRI on this day did not show the presence of any new lesion. The CSF contained white blood cells (2.3 cells/μL [normal range: 0–5]) and protein (86 mg/dL [normal range: 10–52.6]). Because of his persistent request, he was discharged from our hospital on day 85. Thoracic, abdominal, or pelvic contrast-enhanced computed tomography revealed no evidence of tumors, and whole body MRI revealed no evidence of tumors. Furthermore, the results of serum tumor marker examinations were negative. Urologic evaluations did not detect testicular tumors (for details on the clinical course of the first attack, see Sakamoto et al., 2013, patient 4).

Four months after his initial hospitalization, the patient developed paraparesis and hypoesthesia of the lower extremities and had to be readmitted to Sakai Hospital, Kinki University Faculty of Medicine on day 141. At the time of admission, CSF examination revealed the following: white blood cells, 16 cells/μL (normal range: 0–5), mononuclear cells dominance; total protein, 85 mg/dL (normal range 10–52.6); and MBP, 1200 pg/mL (normal range: 0–102). Moreover, the anti-NMDAR antibody titer in the CSF (day 141) had increased (1:8). The immunoglobulin-G index was within normal limits and anti-aquaporin 4 (AQP4) antibodies were not detected. A T_2-weighted sagittal MRI of the thoracic spine revealed a lesion with a long vertical axis that was centered on T7 (Fig. 1A). Axial MRI showed lesions in the center of the spinal cord (Fig. 1B), while T_2-weighted axial MRI indicated lesions in the right cerebellar hemisphere (Fig. 1D and F), the left side of the pons (Fig. 1F), and around the lateral ventricles (Fig. 1C and E). MRI of the brain fulfilled the McDonald imaging criteria. The patient underwent 3 courses of steroid pulse therapy. He subsequently recovered from the paraparesis and hypoesthesia and was discharged.

Follow-up MRI, performed 4 months after the second hospitalization, revealed multiple contrast-enhanced lesions in the cerebrum on day 265. During this follow-up period, the patient developed diplopia and ptosis of the left eye and was admitted to Osaka City University Hospital on day 293. During this period of hospitalization, the patient developed fever (37.5–39.0 °C). Neurologic examination revealed disorientation and left oculomotor nerve paralysis, but no motor paralysis. Deep tendon reflexes increased in all 4 limbs, but no pathologic reflexes were elicited. No abnormality in sensory or motor coordination was detected, except for a mild right limp during normal gait. T_2-weighted axial MRI showed multiple lesions in the cerebellum, middle cerebellar

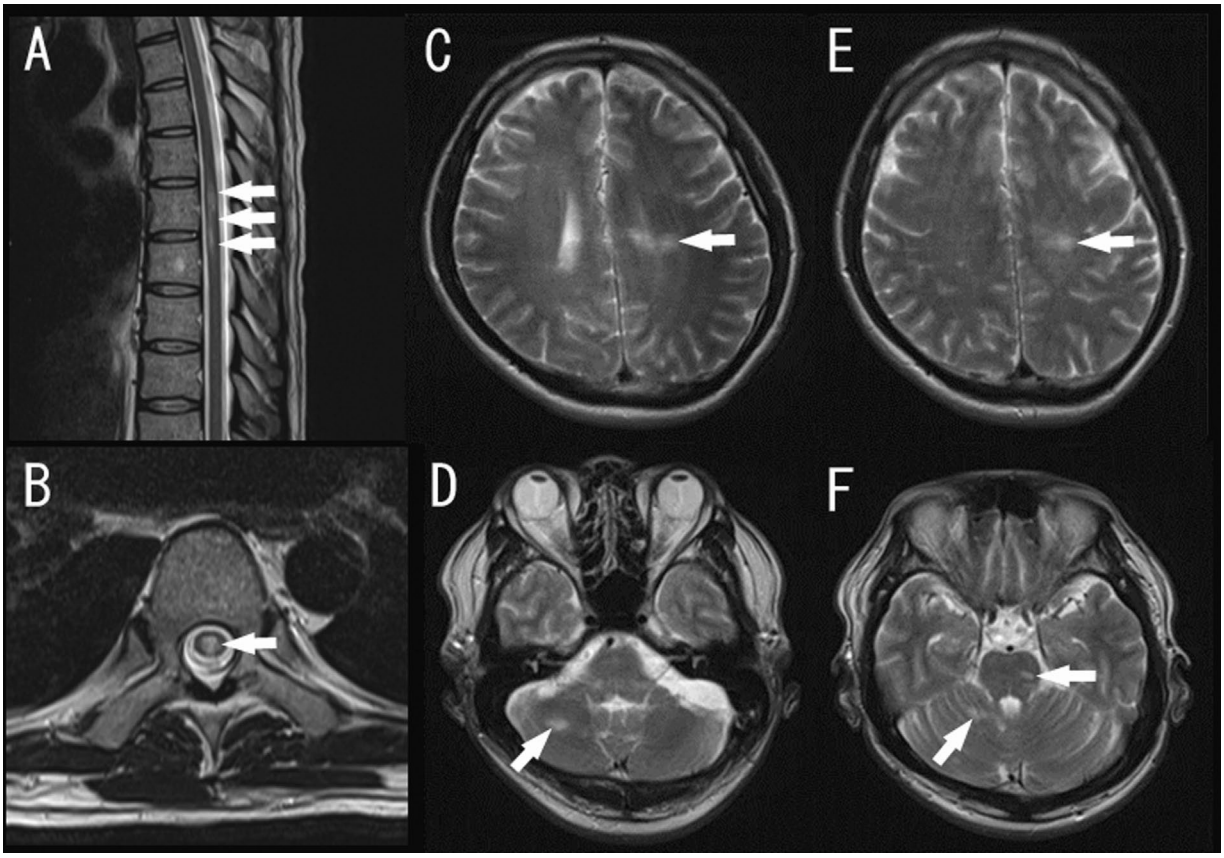

Fig. 1 MRI during the third hospitalization period. (A) Spinal MR T2WI (TR/TE=4200/89) showed a T2 high-signal lesion around the level of Th6-7 (arrow). (B) This lesion was located in the center of the spinal cord (arrow). (C and E) A T2-high signal lesion was present around the lateral ventricles (arrow). (D and F) Lesions in the right cerebellar hemisphere and the left side of the pons (arrow).

peduncle (Fig. 2A), and cerebral white matter (Fig. 2B and C), which were worse than those observed on day 265. Post-contrast T_1-weighted images demonstrated contrast-enhanced lesions at the same sites (Fig. 2D and E) as well as an open-ring-shaped and partially enhanced lesion (Fig. 2E). MRI of the spinal cord revealed that the previously observed lesions in this area had resolved and that no new lesions had formed. Blood tests revealed no increase in the inflammatory response and no autoantibodies associated with vasculitides (anti-nuclear antibody, anti-DNA antibody, antibodies to MPO-ANCA, PR3-ANCA, SSA, or SSB). CSF examination at this stage presented the following: no pleocytosis (normal range: 0–5), no oligoclonal bands, increased protein level (74 mg/dL (normal range: 10–52.6), and an immunoglobulin-G index within normal limits. Cytological examinations revealed no evidence of malignancy or other notable abnormalities. The anti-NMDAR antibody titer in the CSF (day 294) increased (1:40). However, the test results for anti-HIV antibodies, anti-AQP4 antibodies, and paraneoplastic syndrome-related autoantibodies (Ma2, Ma1, amphiphysin, CV2, Ri, Yo, and Hu) were negative, and PCR analysis of the CSF for John Cunningham (JC) virus also revealed negative results. Follow-up evaluation showed no evidence of tumors. We decided to perform an open brain biopsy because the patient presented with impaired consciousness (disorientation), and the brain lesions had worsened in a few weeks.

An open-brain biopsy was performed. Tissue samples were collected from the contrast-enhanced lesion in the right frontal lobe (Fig. 2F). A demyelinated lesion with discrete borders was observed (Fig. 3A–C). Bodian histochemical stain and immunostaining for phosphorylated neurofilaments demonstrated that axons were relatively preserved in the myelin-deficient lesion (Fig. 3B and C), and immunohistochemistry for MBP was negative (Fig. 3D). Scattered axonal swellings were found in the lesion (Fig. 3C). Numerous foamy macrophages and glial fibrillary acidic protein-positive (+) reactive astrocytes were observed in the lesion (Fig. 3A and E). Macrophages containing Luxol fast blue-positive particles of myelin were present (Fig. 3G). Numerous inflammatory cells were observed in the perivascular space (Figs. A.1–A.5). $CD68^+$ activated microglia and macrophages were present in the perivascular space and parenchyma (Fig. A.4). Immunohistochemistry revealed diffuse presence of AQP4 in the white matter, including in the demyelinated lesion (Fig. 3F).

After the biopsy, intravenous methylprednisolone therapy was started, which improved the symptoms of fever and left oculomotor nerve paralysis. Brain MRI revealed shrinkage of the lesions and attenuation of the contrast enhancement. After 3 additional courses of intravenous methylpredni solone therapy, treatment with oral prednisolone (30 mg/day) and cyclophosphamide (100 mg/day) was initiated; the anti-NMDAR antibody titer in the CSF subsequently decreased (1:20)

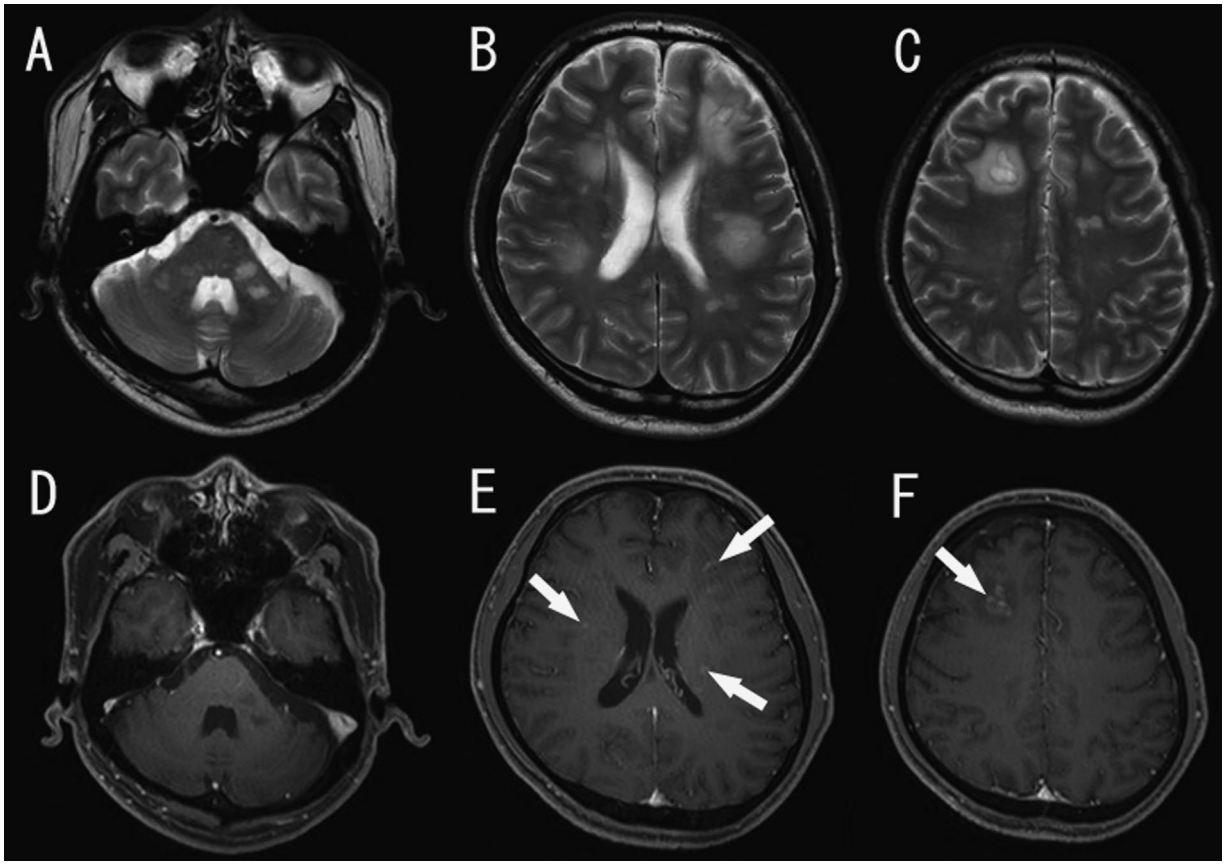

Fig. 2 MRI during the fourth hospitalization period. (A–C) T2WI (TR/TE=4000/79) multiple cerebral and middle cerebellar peduncle lesions. (D–F) A T1 contrast-enhanced image (TR/TE=5.82/2.63) showed contrast enhancement in most of the cerebrum lesions (arrow).

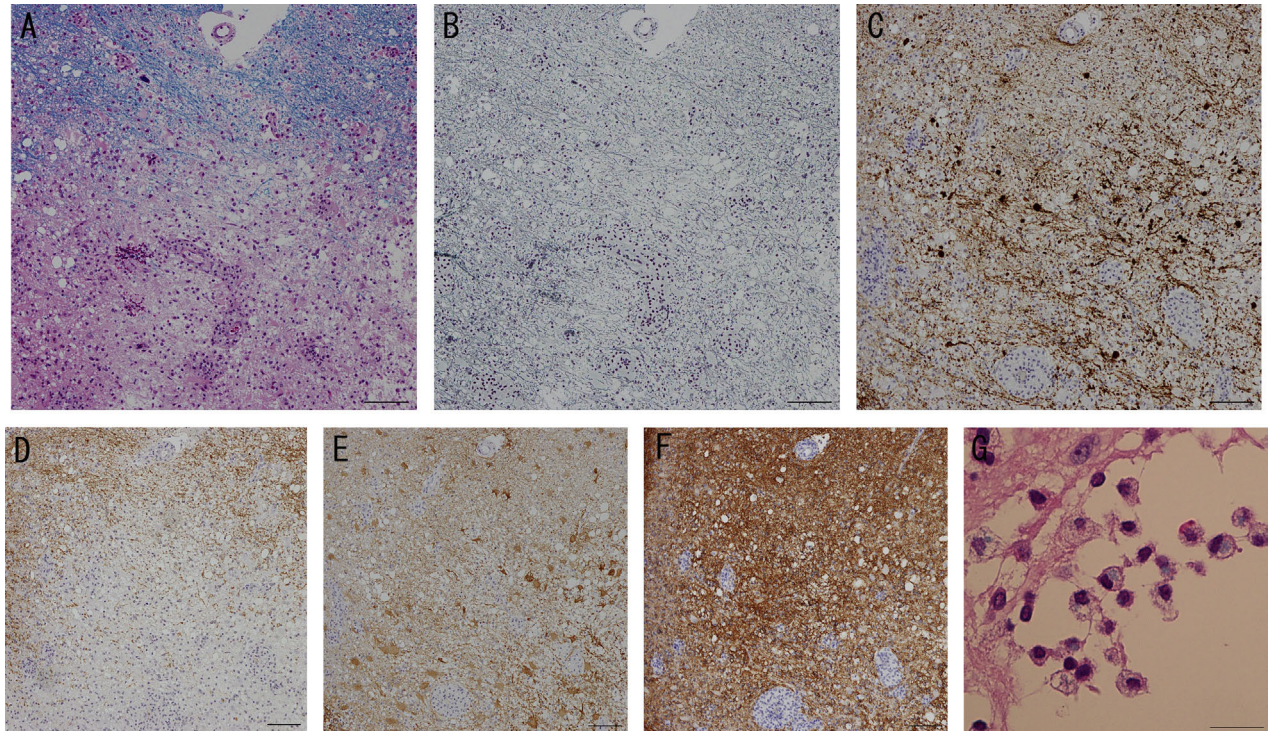

Fig. 3 Histology of brain biopsy. (A and G) Hematoxylin and eosin/Luxol fast blue (HE/LFB) staining, (B) Bodian staining, (C) immunostaining for anti-phosphorylated neurofilament, (D) myelin basic protein (MBP), (E) glial fibrillary acidic protein (GFAP), and (F) aquaporin-4 (AQP4). Scale bar=100 μm (A–F); 20 μm (G).

Table 1 The clinical characteristics of anti-NMDAR encephalitis with multiple sclerosis-like demyelinated lesions.

	Kruer et al. (2010)	Motoyama et al. (2010)	Johnston et al. (2010)	Lekoubou et al. (2012)	Pennington et al. (2012)	Yamamoto et al. (2013)	Present case
Age/sex	15/F[a]	10/F	32/F	34/F	31/F	27/F	35/M[f]
Onset	Headache Partial seizure Impaired consciousness Orofacial dykinesia	ON	Seizure Fluctuating consciousness Oral dyskinesia Catatonia Mutism	Agitation Delusion Hemiparesis Cerebellar ataxia	Myelitis	Hemiparesis Sensory disturbance	Headache Impaired consciousness Abnormal behavior Hypoventilation
Treatment	Plasmapheresis Steroid Cyclophosphamide Rituximab	Steroid	Antibiotics Acyclovir Steroid	IVIg Steroid Rituximab	Plasmapheresis Azathioprine	Acyclovir Steroid	Plasmapheresis Steroid Cyclophosphamide
Relapse	Myelitis, ON[b]	Seizure	ON Trigeminal nerve sensory disturbance	(−)	Seizure Personality change Impaired memory	Abnormal behavior Impaired consciousness Orofacial dyskinesia	Myelitis Impaired consciousness Oculomotor palsy
Tumor	(−)	(−)	(−)	(−)	(−)	(−)	(−)
MRI findings	Multifocal white matter lesions Contrast enhancement LETM[c]	Multifocal white matter lesions Leptomeningeal enhancement	Compatible with MS[e] (Fulfilled Barkhof criteria)	Multifocal white matter lesions Contrast enhancement, LETM	Multifocal spinal cord lesions Multifocal white matter lesions	Brain stem Multifocal white matter lesions	Brain stem, Cerebellar white matter lesions Multifocal white matter lesions
Anti-NMDA antibodies	CSF	CSF	NA	CSF	CSF	CSF and Serum	CSF
Pathology	Perivascular infiltration Selective demyelination (−)	NA[d]	NA	NA	NA	NA	Demyelinated lesion with discrete borders AQP4[g](+) MBP[h](−)

[a]F: female.
[b]ON: optic neuritis.
[c]LETM: longitudinally extensive transverse myelitis.
[d]NA: not available.
[e]MS: mulitiple sclerosis.
[f]M: male.
[g]AQP4: aquaporin 4.
[h]MBP: myelin basic protein.

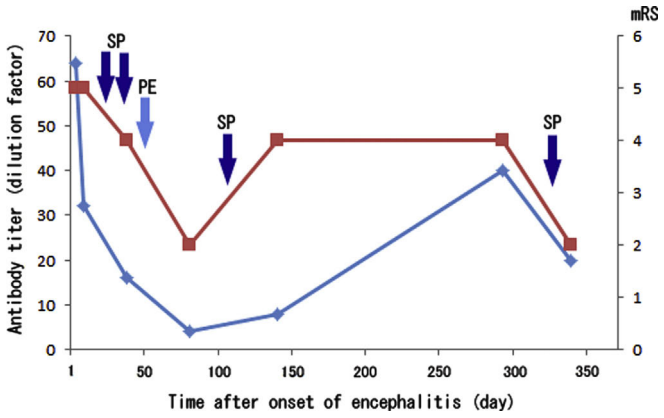

Fig. 4 Time course of the clinical severities and CSF NMDAR antibody titers. The Modified Rankin Scale scores (mRS, red line) paralleled changes observed in the CSF NMDAR antibody titers (blue line). Arrow: mPSL pulse (SP), plasmapheresis (PE). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

on day 340. The patient was discharged after his symptoms significantly improved on day 349.

3. Comment

We describe the unusual case of a male patient with anti-NMDAR encephalitis who presented with multiple sclerosis (MS)-like demyelinated lesions. To the best of our knowledge, a similar case, supported by immunohistochemical results, has not been previously reported. Six female patients with multiple demyelinating lesions of the cerebral and spinal cord due to anti-NMDAR encephalitis have been reported thus far (Table 1); however, our patient is only the second case showing pathological findings. In addition, this is the first patient in whom the anti-NMDAR antibody titers in the CSF and the clinical severity were serially determined during the recurrent disease course. In 3 of the 6 reported female cases, the presence of optic neuritis complicated the differentiation of an NMDAR-related condition from MS and neuromyelitis optica (NMO) (Johnston et al., 2010; Kruer et al., 2010; Motoyama et al., 2010). MRI analysis detected multiple lesions of acute disseminated encephalomyelitis (ADEM) at the time of onset in one of these cases (Lekoubou et al., 2012), whereas MS or myelitis occurred before the onset of encephalitis in the other cases (Pennington et al., 2012; Yamamoto et al., 2013). Common characteristics in these cases, except the case with ADEM-like presentation (Lekoubou et al., 2012), included polyphasic progression that was responsive to immunosuppressive therapy and the absence of tumors.

Analysis of the brain biopsy in our case revealed clear demyelinating borders of the myelin sheath. In addition, a low intensity of MBP antibody staining in the same area was further indicative of demyelination. A low level of AQP4 antibody staining, suggestive of NMO (Misu et al., 2007), was not observed. Pathologically, the findings of this case were more indicative of MS than of NMO. In a case of NMO reported by Kruer et al. (2010), no marked demyelination was observed, which suggests that the pathological characteristics of their patient and that of our patient were different. Many unknown aspects of the polyphasic clinical course as well as lesions in the brain and the spinal cord are caused by anti-NMDAR encephalitis. Kruer et al. (2010) speculated that an epitope spread, which occurs after anti-NMDAR encephalitis, causes seronegative NMO. While the present case was pathologically negative for NMO, the pattern of demyelination was more similar to that observed in MS. The clinical progression and the associated symptoms of our case paralleled changes observed in CSF NMDAR antibody titers (Fig. 4; (Martinez-Hernandez et al., 2011). We could not determine whether the patient had MS after anti-NMDAR encephalitis, because he responded well to steroid therapy—a therapy usually insufficient to treat anti-NMDAR encephalitis. However, absence of an oligoclonal band as well as fever and impaired consciousness in our patient during his third admission to hospital were atypical of MS. Additionally, since the CSF titers of anti-NMDAR antibodies decreased after steroid therapy, which subsequently reduced the severity of the disease, we speculate that the patient had an atypical form of recurrent anti-NMDAR encephalitis.

Conflict of interest

The authors declare no potential conflicts of interest related to the research, authorship, and/or publication of this article.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.msard.2013.09.005.

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