CASE REPORT

A Case of Anti-aquaporin-4 and Anti-glutamate Receptor Antibodies Positive Myelitis Presented with Modest Clinical Signs

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We present a case of anti-aquaporin-4 antibody-positive myelitis, which suggests the high-risk syndrome of neuromyelitis optica, whose modest clinical signs were in conspicuous contrast to the extensive spinal cord lesions demonstrated on magnetic resonance (MR) imaging. Follow-up MR imaging showed marked improvement of lesions. Interestingly, an anti-glutamate receptor antibody, which has been suggested to cause dysfunction of N-methyl-D-aspartate receptor on neuron, was detected in the cerebrospinal fluid of the patient. We discuss the case and related literature.

Keywords: *amnesia, aquaporin-4, autoantibody, glutamate receptor, neuromyelitis optica*

Introduction

Myelitis with long spinal cord lesions extending more than 3 vertebral bones has recently been recognized as the high-risk syndrome of neuromyelitis optica (NMO).¹ NMO is a severe inflammatory demyelinating disorder that preferentially affects the optic nerves and spinal cord. The demonstration of antibody against water channel protein aquaporin-4 (AQP-4) in this syndrome underlies the view of this entity as an independent autoimmune disease.² The clinical presentation of NMO is generally severe because of its extensive spinal cord lesions.¹

We experienced a case of anti-AQP-4 antibody-positive myelitis with long spinal cord lesions that showed very modest clinical signs. Interestingly, anti-glutamate receptor antibody was found in the patient's cerebrospinal fluid (CSF).

Case Report

The patient was a 39-year-old woman with unremarkable medical history except for severe anterograde amnesia that was unresponsive to corticosteroid therapy. She also showed mild Hashimoto thyroiditis that did not require medication. We examined the patient to re-explore her amnesia, which had lasted 30 months. Neurological exami-

nation demonstrated difficulty with delayed recall tasks. Magnetic resonance (MR) imaging of the brain disclosed lesions at the left caudate and left putamen. She was hospitalized in our department 3 weeks later.

On admission, the patient's consciousness was clear, but she was unable to maintain short term memory longer than 10 min. Neurological examination demonstrated faint exaggeration of the deep tendon reflex in her left upper and lower extremities and slight instability in tandem gait.

Neuropsychological examination disclosed severe impairment of the patient's short-term memory, demonstrated on Wechsler Memory Scale-Revised and by delayed reproduction task on Rey's Osterrieth Complex Figure. Other categories of cognitive function were not affected.

Two months later, MR imaging of the brain showed total disappearance of the lesions at the basal ganglia but a new lesion at left caudate body on T₂-weighted (T₂WI) and fluid-attenuated inversion-recovery (FLAIR) imaging. There was no contrast-enhanced lesion.

Laboratory findings were unremarkable except for the presence of thyroid peroxidase antibody. Antinuclear, anti-neuronal, and anti-SS-A and SS-B antibodies were not detected. Although the level of thyroid-stimulating hormone was high, the concentration of thyroid hormone remained in normal range, and the clinical condition was similar to that 3 years previously. Examination of the CSF showed normal cell count (5/3 μ L), mild elevation of pro-

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tein (47 mg/dL), and IgG (9.3 mg/dL). The IgG index read 0.91, and oligoclonal band was positive. CSF cytology was compatible with inflammation. Electroencephalographic and visual findings of evoked potential were unremarkable. No sign of malignancy was detected on extensive exploration with serum tumor markers and computed tomographic (CT) scan.

In accordance with her clinical history and repeated occurrence of multiple central nervous system lesions, we considered diagnosis of multiple sclerosis (MS). For thorough investigation of latent lesions, we performed MR imaging of her spinal cord, which demonstrated cervical and thoracic cord lesions that extended over more than 3 vertebral segments, involved gray and white matter, and were accompanied by cystic changes (Fig. 1 A–D). Because longitudinal continuous lesions extending more than 3 vertebral segments are highly specific to NMO, we tested her serum for anti-AQP-4 antibody³ and found it.

Exploring the etiology of the patient's amnesia, we checked for the presence of voltage-gated potassium channel (VGKC) and glutamate receptor $\epsilon 2$

subunit (GluR $\epsilon 2$). VGKC antibody was not detected, and anti-GluR $\epsilon 2$ antibody was found to be positive not in the serum but in the cerebrospinal fluid.

We treated the patient with intravenous methylprednisolone (1000 mg/day for 3 days per week), and the spinal cord lesions responded well. Except for cystic lesions, the cervical and thoracic spinal cord lesions disappeared almost completely after therapy. MR imaging with contrast enhancement showed no lesions. The neurological signs, modest hyper-reflexia in her left side, and unsteady tandem gait also disappeared. However, the patient's amnesia remained unchanged. She was discharged after introduction of subcutaneous injection of interferon-beta.

One month later, the patient's short term memory started to improve, and follow-up examination 5 months later demonstrated that her memory function had returned to a normal level. Six months later, MR imaging study showed further improvement of the spinal cord lesions and almost complete disappearance of the cystic lesions (Fig. 2 A–D).

Fig. 1. Magnetic resonance (MR) imaging of the spinal cord, T₂-weighted image. **A)** Sagittal image of cervical cord shows longitudinal cord lesion extending over more than 3 vertebral bodies. **B)** Sagittal image of thoracic cord discloses long cord lesion with cystic change. **C)** Axial image of cervical cord depicts a central cystic lesion and surrounding lesion with T₂ high intensity. **D)** Axial image of thoracic cord lesion shows marked cystic change with surrounding T₂ high intensity lesion distributed on the right side.

Fig. 2. Magnetic resonance (MR) imaging of the spinal cord, T₂-weighted image, 6 months after treatment with interferon β . **A)** Sagittal image of cervical cord. **B)** Sagittal image of thoracic cord. **C)** Axial image of cervical cord. **D)** Axial image of thoracic cord. Note cystic lesions depicted in Fig. 1 completely disappear at the cervical cord, and there is marked shrinkage at the thoracic cord without atrophic change.

Discussion

The diagnosis of myelitis was unexpected because the patient showed only faint clinical signs suggesting the condition. However, MR imaging of the spinal cord demonstrated florid expression of lesions at both the cervical and thoracic cords. The long cord lesions that extended more than 3 vertebral segments and brain lesions that did not meet the radiological criteria for MS steered us toward the diagnosis of NMO. However, because we could not demonstrate optic neuritis, we could not diagnose NMO. Rather, because of the presence of both anti-AQP-4 and longitudinally extended spinal cord lesions, we considered the case to be at an early stage of and highly likely to develop into NMO, i.e., the high-risk syndrome of NMO. Applying a more sensitive AQP-4 assay system, Takahashi's group recently reported sensitivity of 85% and specificity of 100% for anti-AQP-4 antibody assay for the high-risk syndrome.¹

The most interesting aspect of this case is the marked discrepancy between the extent of the spinal cord lesions and the severity of its clinical signs, which rated 1.0 on the expanded disability status scale (EDSS). The attacks of NMO are generally considered more severe than those typical of MS, and this was underscored in the diagnostic criteria

proposed in 1999.⁴ Our case revealed marked swelling of the spinal cord and cystic lesions compatible with severe inflammation. These MR findings suggest severe neurological deficit. In accordance with this idea, a recent study shows that data from 21 anti-AQP-4 antibody-positive cases distributed from 3.5 to 6.5 on EDSS,¹ which means the severity of our case must therefore be considered exceptionally mild.

The case presented here showed anti-GluR ϵ 2 antibody intrathecally. GluR ϵ 2 is a subunit of N-methyl-D-aspartate (NMDA) receptor, which is predominantly expressed at the hippocampus and forebrain and is involved in memory function. The amnesia of our patient appears compatible with the diagnosis of limbic encephalitis associated with anti-GluR ϵ 2 antibody. Although a recent study demonstrated that some cases of paraneoplastic limbic encephalitis are associated with anti-GluR ϵ 2 antibody,⁵ absence of findings suggesting malignancy did not support diagnosis of paraneoplastic syndrome in our case. The diagnosis of Hashimoto encephalopathy, a still controversial entity, is not consistent with our case because the anterograde amnesia did not respond to corticosteroid therapy.⁶

The reversibility of the amnesia suggests that the antibody is functionally active during episodes of myelitis. An NMDA receptor presents diffusely in

the gray matter of the human spinal cord.⁷ Although the localization of NMDA receptor subtypes in the human spinal cord is still under debate, the existence of GluR ϵ 2 has, in fact, been shown in rodents.⁸ It is well established that glutamate receptors, especially NMDA receptors, play a pivotal role in glutamate-induced necrotic neuronal death.⁹ Recently, Misu and colleagues demonstrated the disappearance of astroglia in spinal cord lesions of NMO.¹⁰ Because astroglia are involved in glutamate uptake by glutamate transporters, the loss of astroglia could influence glutamate homeostasis and cause excitotoxicity.¹¹ If we consider that extensive inflammation with edema and necrosis with cystic changes or cavitation were commonly observed in spinal cord lesions occurring with NMO and that glutamate receptor is related to the induction of necrosis, then the remarkable discrepancy between neurological signs and severity of spinal cord lesions in this case suggests that the anti-glutamate receptor antibody might act protectively against myelitis. The shrinkage of the cavitory lesion without spinal cord atrophy on MR imaging might suggest that the nature of the lesion in our case is not cyst associated with pure necrosis but predominantly edema, though we cannot thoroughly exclude the possibility of imprecise estimation of the size of edema resulting from partial volume effect on MR imaging. This observation is consistent with our view that necrosis was halted by an unknown mechanism. The differential diagnosis of spinal cord lesion is syringomyelia and spinal cord tumors. Since the best way to treat NMO has not been established, further progress will be expected.

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