Neuromyelitis Optica Preceded by HyperCKemia and a Possible Association with Coxsackie Virus Group A10 Infection

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Abstract

We report the case of a 48-year-old woman presenting with an elevated serum creatine kinase level (hyperCKemia) associated with an initial attack of neuromyelitis optica (NMO). The patient initially showed general fatigue with fever. Laboratory findings showed hyperCKemia and subsequently she developed a slight weakness of both lower limbs and reduced vision. Autoantibodies against aquaporin 4 were found in her serum, and a retrospective examination of viral titers indicated a possible coxsackie virus group A10 infection. The present case suggests that hyperCKemia-mediated disease onset is involved in some patients with NMO, and furthermore, it may be related to muscular destruction associated with viral infection.

Key words: neuromyelitis optica, hyperCKemia, aquaporin 4, viral infection, coxsackie virus


Introduction

Neuromyelitis optica (NMO) is a disease of the central nervous system (CNS) that is characterized by severe attacks of optic neuritis and myelitis (1). The presence of the circulating autoantibodies against the astrocyte water channel aquaporin (AQP) 4 is crucial in patients with NMO (2). AQP4 has been identified as the target of NMO (1), and a disturbance of water homeostasis is implicated in the development of edema in the CNS (3). Several lines of evidence indicate that the autoantibody against AQP4 plays a pivotal role in the pathogenesis of NMO (1, 2). Outside the CNS, AQP4 is also expressed in the skeletal muscles (4), and recent reports suggest that a disruption of skeletal muscle is preceded by the onset of NMO symptoms (5-8). Suzuki et al. reported the possibility that the elevated serum creatine kinase level (hyperCKemia) mediated the pathogenesis of NMO in some patients (5). Several possible mechanisms of how hyperCKemia may be involved in the pathogenesis of NMO have been proposed: (1) muscle destruction leads to the generation of AQP4 antibodies; (2) AQP4 antibodies attack AQP4-expressing tissue to cause hyperCKemia and NMO symptoms; and (3) muscle destruction activates pre-existing autoimmunity of AQP4, and as a trigger, it initiates the injury of CNS tissue.

Although the association of muscle destruction and NMO symptoms has been found in some patients with NMO, the role of hyperCKemia in the pathogenesis of NMO remains to be clarified. We herein report a patient with NMO who exhibited hyperCKemia that was related to a possible coxsackie virus group A10 infection, preceded by the onset of myelitis and optic neuritis.

Case Report

A 48-year-old woman with a past history of breast cancer developed general fatigue and a fever of 38°C. She was treated with antibiotics at a nearby clinic, and her symptoms subsequently improved; however, she showed nausea and vomiting 4 days after initial symptoms. Although she had episodes of nausea and vomiting, no neurological symptoms

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such as cranial nerve signs, weakness of limbs, and ataxia were not observed. She was referred to our hospital and underwent further examinations. Blood tests showed high creatine kinase (CK) levels 4 days after symptom onset (8,140 U/L; normal range 45-163 U/L), accompanied by a concomitant increase in the levels of lactic dehydrogenase (437 U/L; normal range 119-229 U/L), and aldolase (40.6 U/L; normal range 2.7-7.5 U/L). The serum myoglobin concentration was also elevated (153.9 ng/mL; normal range <60 ng/mL), whereas the urinary myoglobin level was normal (<10 ng/mL). However, she was neurologically asymptomatic with the exception of slight myalgia in her thighs. Chest, abdominal and pelvic computed tomography revealed no abnormal lesions related to fever or hyperCKemia. She was admitted to our hospital and subsequently given fluid therapy. Three days later, the CK levels rose to 28,750 U/L, and she experienced urinary retention and numbness in both lower limbs (Fig. 1). She was referred to our department for examination of possible myelopathy and hyperCKemia.

A neurological examination showed slight weakness in both legs. Although the deep tendon reflex was normal, a pathological reflex was identified in both lower limbs. The superficial sensation below the Th8 segment of the trunk and in both lower limbs was moderately impaired, and truncal ataxia was also found. She complained of slight myalgia in both thighs.

Although electromyography was performed to evaluate hyperCKemia, it failed to demonstrate any myogenic changes, including the early recruitment of motor units. We found reduced recruitment patterns during voluntary contraction; however, the motor unit potentials were normal and no abnormal spontaneous activities were identified. The serum concentrations of thyroxine, thyrotoxine, and thyroid-stimulating hormone were normal, and serum antithyroglobulin and antithyroid peroxidase antibodies were negative. Furthermore, antinuclear, anti-ss-DNA, anti-ds-DNA, anti-SS-A, and anti-SS-B autoantibodies were negative. The serological tests for syphilis, human immunodeficiency virus and human T-cell lymphotropic virus 1 were also negative. No other major cause of hyperCKemia, including drug-induced hyperCKemia, was found. After the serum CK level rose to 28,750 U/L, it gradually declined and became normalized at 4 weeks after onset (Fig. 1). However, she subsequently showed a reduced visual acuity. Although her optic fundi had a normal appearance, her left visual acuity decreased to 0.15. Furthermore, the Goldmann perimetry showed left central scotoma.

Magnetic resonance imaging (MRI) of the spinal cord showed high-signal lesions on T2-weighted images (Fig. 2A-C). Contrast-enhanced MRI also showed several short enhancing lesions at C3 to Th1, Th2 to Th3, and Th11 to Th12, respectively (Fig. 2D, E). Brain MRI revealed a left optic nerve lesion (Fig. 2F-H). The cerebrospinal fluid (CSF) examination exhibited an increased protein concentration (54 mg/dL) with pleocytosis (12 cells/mm³). The myelin basic protein levels were elevated (355.3 pg/mL); however, oligoclonal IgG bands were not found in the CSF. Autoantibodies against AQP4 were found in the serum using a standard indirect immunofluorescence method. The patient was then diagnosed with NMO.

She was administered three courses of high-dose methylprednisolone (1,000 mg i.v.) for 3 days. After completion of this therapy, she was treated with oral prednisolone (50 mg/day) followed by an oral prednisolone taper. Her symptoms improved after the second round of high-dose methylprednisolone therapy, and abnormal enhancing lesions were no longer visible on the brain and spinal cord MRI.

We previously speculated that viral infection is a cause of myositis (9). Therefore, we retrospectively examined the viral titers against coxsackie virus (A4, A6, A9, A10, B1-B6 groups), echovirus (1, 6, 9 and 16), adenovirus (1 to 8, 11 and 19), Epstein-Barr virus, and parvovirus B19 (SRL, Tokyo, Japan). The results of paired viral antibodies titers exhibited that only coxsackie virus group A10 showed a four-fold rise in the convalescent phase compared with the acute phase.

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**Figure 1.** The clinical course of our patient with NMO preceded by hyperCKemia. The serum CK level gradually declined and became normalized 4 weeks after onset. The paired viral titers against coxsackie virus group A10 showed a four-fold rise in the convalescent phase compared with the acute phase.
Figure 2. Hyperintense intramedullary lesions on T2-weighted MR images of the spinal cord (day 15). Hyperintense lesions were observed in the sagittal view (A) and axial sections at the level of C6 (B) and Th12 (C). (D) Contrast-enhanced T1-weighted MRI image of the spinal cord showing multiple patchy enhancing lesions (arrows) in the cervical and thoracic spinal cord. (E) Gadolinium-enhancing intramedullary lesions (arrows) found at Th11 to Th12. Left optic nerve lesion (arrowhead) observed on axial (F), sagittal (G), and coronal (H) slices of contrast-enhanced T1-weighted MR images (day 14).

Table. Clinical Manifestations of Patients with HyperCKemia Preceding NMO

<table>
<thead>
<tr>
<th>Reference number</th>
<th>Age/ Sex</th>
<th>Symptom at onset</th>
<th>Peak CK IU/L</th>
<th>Muscular symptoms</th>
<th>Titer of anti-AQP4 antibody</th>
<th>Possible relation to viral infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>34/F</td>
<td>General fatigue</td>
<td>19,415</td>
<td>None</td>
<td>×8,192</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>67/F</td>
<td>General fatigue</td>
<td>59,660</td>
<td>ND</td>
<td>×32</td>
<td>ND</td>
</tr>
<tr>
<td>7</td>
<td>7/F</td>
<td>General fatigue, muscle pain</td>
<td>12,520</td>
<td>Muscle pain</td>
<td>×8,192</td>
<td>ND</td>
</tr>
<tr>
<td>6</td>
<td>60/M</td>
<td>Vomiting, fever</td>
<td>17,215</td>
<td>None</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>7</td>
<td>13/F</td>
<td>Myelitis episodes</td>
<td>15,818</td>
<td>Mild myalgia</td>
<td>1:500</td>
<td>ND</td>
</tr>
<tr>
<td>8</td>
<td>79/F</td>
<td>Unsteadiness, vomiting</td>
<td>30,673</td>
<td>Slight myalgia</td>
<td>×2,048</td>
<td>ND</td>
</tr>
<tr>
<td>Present case</td>
<td>48/F</td>
<td>Fever, general fatigue</td>
<td>28,750 (IU/L)</td>
<td>Slight myalgia</td>
<td>×16,384</td>
<td>Coxsackie virus group A10</td>
</tr>
</tbody>
</table>

M: male, F: female, ND: not described

We herein report a patient with NMO, whose neurological symptoms were preceded by episodes of hyperCKemia. Cases with similar features have been reported recently (5-8), but the mechanism of this coexistence remains unknown (Table). AQP4 is also expressed in fast-twitch skeletal muscle fibers (3, 10); therefore, it is suspected that anti-AQP4 antibody plays some role in the pathogenesis. The present case additionally showed a possible relationship between hyperCKemia/NMO symptoms and coxsackie virus infection, which may add an important clue to understand the cases with hyperCKemia preceding the onset of NMO.

Although the pathogenicity of anti-AQP4 antibody is well established (11), the mechanism of onset or initiation of production of anti-AQP4 antibody is still unclear. At least in some cases, pre-existing anti-AQP4 antibody may reach and attack the AQP4 molecules on astrocytes via disruption of the blood-brain barrier (BBB) due to some non-specific inflammation. This hypothesis is supported by a case with anti-AQP4 antibody seropositivity 10 years before the onset of NMO, and by the in vivo NMO models (12, 13).

Beside genetic factors, infections are known to be involved in the development of autoimmune disease (14).
Multiple mechanisms explaining how pathogens cause autoimmunity have been proposed: (1) the pathogen may carry elements that are structurally similar to the autoantigen epitope, and activated T cells cross-react with both the pathogen-derived and self-derived epitopes. These autoimmune responses are referred to as 'molecular mimicry'; (2) an inflammatory environment may cause and develop non-specific activation of autoimmune cells, namely 'bystander activation'; and (3) self-tissue destruction caused by a persistent pathogen infection may result in the release of self-peptide, and these initiations are involved in the spread of the self-reactive immune response to multiple self-epitopes. These immune responses are referred to as 'epitope spreading'. Ren et al. recently reported on the structural homology and cross-immunoreactivity between bacterial aquaporin Z and human AQP4 (15). Their findings indicate that infection affects the induction of the autoimmune response against AQP4 in NMO. Viral or bacterial infections may affect autoimmunity as a trigger, and multiple mechanisms such as molecular mimicry and epitope spreading may be intricately involved in the development of NMO.

There are several possibilities to explain the present case: (1) anti-AQP4 antibody had pre-existed in the patient, and the inflammation of viral myositis worked only as a trigger of BBB disruption; (2) the viral infection itself generated anti-AQP4 antibody by some mechanism such as molecular mimicry, and the antibody caused hyperCKemia and NMO by attacking AQP4 molecules; and (3) the viral myositis, whose inflammation involved AQP4 molecules in muscles, initiated the production of anti-AQP4 antibody and BBB disruption, thus leading to the onset of NMO.

First, the occurrence of pre-existing anti-AQP4 antibody may be less likely in all cases with hyperCKemia because the antibody was seronegative 6 months before the onset of NMO in a previous case (8). Unfortunately, in the present patient it is not known whether the AQP4 antibody had already developed prior to the episode of hyperCKemia. Second, a study of infectious serology of patients with anti-AQP4 antibody showed that various viruses were associated with exacerbations including onset (16). Coxsackie virus may trigger autoimmunity through molecular mimicry during the initiation of NMO; however, the presence of structural homology between coxsackie virus and AQP4 remains unknown. Third, muscle inflammation due to coxsackie virus infection might be caused by anti-AQP4 antibody production through epitope spreading, which in the present patient resulted in the onset of NMO. Muscle disruption mediated by viral infection might activate autoimmunity to AQP4 and subsequently cause a breakdown of the BBB through bystander activation.

The mechanisms and pathogenesis of hyperCKemia episodes in NMO patients remain unclear. However, the muscle destruction via viral infection preceding onset of NMO may play an important role in activating autoimmunity to AQP4, thus leading to development of NMO. Further studies are needed to address these issues because the above speculations are based on sparse details in only a small number of patients.

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

References