Abstract

We report on three elderly patients with stroke-like onset of atypical Miller Fisher syndrome (MFS). The serum titer of anti-GQ1b IgG was markedly elevated in these patients. Their prognoses were sufficiently good with immunoadsorption therapy with or without intravenous immune globulin (IVIg) therapy. However, some neurological findings were not characteristic of typical MFS. Patient 1 suffered from prolonged dysesthesia in her left extremities, and Patients 2 and 3 showed no ataxia. Moreover, complete bilateral gaze limitation is rare in MFS. The sudden stroke-like onset along with the gaze limitation of these patients suggests that the unexpected elevation in the serum titer of anti-GQ1b IgG due to unknown immune dysregulation might have severely affected the third, fourth, and sixth nerves and this potent antibody rapidly attacked these nerves and induced stroke-like clinical features and complete ophthalmoplegia.

Key words: Atypical Miller Fisher syndrome, brainstem stroke, ophthalmoplegia, anti-GQ1b IgG antibody

Introduction

Miller Fisher syndrome (MFS) is generally characterized by three typical neurologic symptoms, namely, ophthalmoplegia, ataxia, and areflexia. About 20 years ago, antibodies against ganglioside GQ1b were reported to be closely associated with immune-mediated ophthalmoplegia in MFS and Guillain-Barre syndrome. However, there have recently been reports discussing some patients with ophthalmoplegia but without ataxia and areflexia. We had three elderly patients with stroke-like onset, complete ophthalmoplegia, and an elevated serum titer of anti-GQ1b antibody. Their clinical and laboratory findings were partially compatible with typical MFS, but some neurological findings were not characteristic of MFS.

Case presentation

Patient 1

A 73-year-old woman was transferred to the emergency room (ER) of our hospital with vertigo, nausea, vomiting, and dysesthesia of her left extremities. Neurological examination revealed complete bilateral gaze limitation, slight bilateral ptosis, truncal ataxia, the absence of bilateral tendon reflexes, and sensory disturbance of her left arm and leg (Figure 1). Her other cranial nerves were intact. Motor paresis was absent and her consciousness level was good. Her blood...
pressure was 162/91 mmHg, and her heart rate was 95 beats per minute with a regular rhythm. Her past and family histories were unremarkable. Four days prior to her admission, she caught a cold.

Our tentative diagnosis was brainstem infarction in spite of her good level of consciousness with areflexia. However, magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) examinations on admission showed no abnormalities. Diffusion weighted images (DWIs) indicated no acute cerebral infarction.

Laboratory findings on admission showed her blood cell counts, hepatic and renal functions, blood glucose concentration, and serum creatinine, creatine kinase (CK), and electrolyte concentrations to all be normal.

Immunologic examinations showed no abnormalities except for an elevated antinuclear factor (320 fold). The cerebrospinal fluid (CSF) was clear and showed a protein concentration of 72 mg /dl, 1 leukocyte/mm³, and a glucose concentration of 63 mg/dl. Upon diagnosis of Miller Fisher syndrome (MFS), she underwent immunoadsorption therapy seven times within two weeks. Her eye movements gradually improved after the immunoadsorption therapy and had completely recovered on discharge (Figure 1). After the patient was discharged, we were informed that her serum titer of anti-GQ1b IgG was markedly elevated (1600 fold) (Table 1).

**Patient 2**

A 71-year-old man was transferred to the ER of our hospital because of the sudden onset of diplopia and dysarthria. Neurological examination on admission revealed complete bilateral gaze limitation, bilateral ptosis (prominent in the right side), bulbar palsy (dysarthria and dysphagia), and the absence of bilateral tendon reflexes (Figure 2). Motor paresis and ataxia were absent, and his consciousness level was good. His blood pressure was 146/81 mmHg, and his heart rate was 68 beats per minute with a regular rhythm. His past and family histories were unremarkable. Two weeks prior to his admission, he caught a
<table>
<thead>
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<th>Characteristics of patients</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
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<tbody>
<tr>
<td><strong>Age/Sex</strong></td>
<td>73-year-old woman</td>
<td>71-year-old man</td>
<td>76-year-old man</td>
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<tr>
<td><strong>Antecedent illness</strong></td>
<td>Fever, cough</td>
<td>Fever, cough</td>
<td>Fever, cough</td>
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<td><strong>Initial symptom</strong></td>
<td>Vertigo</td>
<td>Diplopia</td>
<td>Diplopia</td>
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<td><strong>Ptosis</strong></td>
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<td>Bilateral, severe</td>
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<td><strong>Gaze limitation</strong></td>
<td>Fixed</td>
<td>Fixed</td>
<td>Fixed</td>
</tr>
<tr>
<td><strong>Facial weakness</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td><strong>Bulbar palsy</strong></td>
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<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Tendon jerk</strong></td>
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<td>Absent</td>
<td>Absent</td>
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<tr>
<td><strong>Ataxia</strong></td>
<td>truncal ataxia</td>
<td>No</td>
<td>No</td>
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<tr>
<td><strong>Paresthesia</strong></td>
<td>Left extremities</td>
<td>No</td>
<td>No</td>
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<tr>
<td><strong>Motor paresis</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Consciousness disturbance</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Cell count (µl)/Protein (mg/dl) in cerebrospinal fluid</strong></td>
<td>1/72 (day 10)</td>
<td>1/24 (day 1)</td>
<td>0/16 (day 1)</td>
</tr>
<tr>
<td><strong>Titer of anti-GQ1b IgG</strong></td>
<td>1600</td>
<td>3200</td>
<td>800</td>
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<tr>
<td><strong>MRI/MRA</strong></td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Immunoadsorption</td>
<td>Immunoadsorption and IVIg</td>
<td>Immunoadsorption</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>good</td>
<td>good</td>
<td>good</td>
</tr>
</tbody>
</table>

MRI: magnetic resonance imaging, MRA: magnetic resonance angiography, IVIg: intravenous immune globulin

**Figure 2** (Patient 2, a 71-year-old man)

Images illustrating complete bilateral gaze limitation ophthalmoplegia and bilateral ptosis (prominent in the right side) on admission (left). After immunoadsorption and intravenous immune globulin (IVIg) therapies, his eye movements gradually improved and had completely recovered on discharge (right). Top to bottom: right gaze, left gaze, forward gaze, upward gaze, and downward gaze.
cold. Our tentative diagnosis was brainstem infarction, but MRI and MRA examinations on admission showed no abnormalities. DWIs indicated no acute cerebral infarction.

Laboratory findings on admission showed his blood cell counts, hepatic and renal functions, blood glucose concentration, and serum creatinine, CK, and electrolyte concentrations to all be normal.

Immunologic analyses showed no abnormalities. His CSF was clear and showed a protein content of 24 mg/dl, 1 leukocyte/mm$^3$, and a glucose content of 68 mg/dl. Upon diagnosis of MFS, he underwent immunoadsorption therapy six times within two weeks. After the immunoadsorption therapy, his bilateral ptosis was remarkably improved, but his eye movements were still restricted. After the additional intravenous treatment of immune globulin (IVIg), his eye movements gradually improved and had completely recovered on discharge (Figure 2). After he was discharged, we were informed that his serum titer of anti-GQ1b IgG was markedly elevated (3200 fold) (Table 1).

**Patient 3**

A 76-year-old man was admitted to our hospital because of the sudden onset of diplopia. Neurological examination on admission revealed complete bilateral gaze limitation and the absence of bilateral tendon reflexes (Figure 3). His other cranial nerves were intact. Motor paresis and ataxia were absent, and his consciousness level was good. His blood pressure was 156/77 mmHg, and his heart rate was 78 beats per minute with a regular rhythm. His past and family histories were unremarkable. One week prior to his admission, he caught a cold. MRI and MRA examinations on admission showed no abnormalities. DWIs indicated no acute cerebral infarction.

Laboratory findings on admission showed his blood cell counts, hepatic and renal functions, blood glucose concentration, and serum creatinine, CK, and electrolyte concentrations to all be normal.

Immunologic analyses showed no abnormalities. His CSF was clear and showed a protein content of 16 mg/dl, 0 leukocyte/mm$^3$, and a glucose content of 81 mg/dl. Upon diagnosis of MFS, he

![Figure 3](image-url)

*Figure 3* (Patient 2, a 76-year-old man) Images illustrating complete bilateral gaze limitation ophthalmoplegia on admission (left). After immunoadsorption therapy, his eye movements gradually improved and had completely recovered on discharge (right). Top to bottom: right gaze, left gaze, forward gaze, upward gaze, and downward gaze.
underwent immunoadsorption therapy seven times within two weeks. His eye movements gradually improved after the immunoadsorption therapies and had completely recovered on discharge (Figure 3). After he was discharged, we were informed that his serum titer of anti-GQ1b IgG was markedly elevated (800 fold) (Table 1).

**Discussion**

Patient 1, a 73-year-old woman, had opthalmoplegia, the loss of deep tendon reflexes, and truncal ataxia, but the associated refractory dysesthesia of her left extremities persisted for a long time. Four days prior to her admission, she caught a cold. Patient 2, a 71-year-old man, had opthalmoplegia, bulbar palsy, and the loss of tendon reflexes but no ataxia. Two weeks prior to his admission, he caught a cold. Patient 3, a 76-year-old man, also had opthalmoplegia and the loss of tendon reflexes but no ataxia. He caught a cold one week prior to his admission. The serum titer of the anti-GQ1b antibody was markedly elevated in all three of these patients. Their prognoses were sufficiently good with immunoadsorption therapy with or without IVIg therapy. The clinical and laboratory findings were partially compatible with those of typical MFS, but some neurological findings were not characteristic of MFS. Patient 1 suffered from prolonged dysesthesia in her left extremities, and Patients 2 and 3 showed no ataxia. Moreover, complete bilateral gaze limitation is rare in MFS.

Suzuki et al. reported that the titer of serum IgG to GQ1b was elevated in some patients with opthalmoplegia from an undetermined cause. They described a 56-year-old woman with bilateral abducens palsy and areflexia but without ataxia, and a 62-year-old woman with painful lateral opthalmoplegia but without areflexia or ataxia. Suzuki et al. referred to these two patients using the term “atypical Fisher syndrome”.

Yuki et al. discussed 21 patients with acute opthalmoplegia (without ataxia) associated with anti-GQ1b antibodies, and suggested that these patients might be suffering from a mild form of MFS or a regional variant of Guillain-Barre syndrome. Deep tendon reflexes were normal in nine cases, fast in one case, reduced in eight cases, and absent in three cases. Eight patients showed paresthesia in their arms, legs, palms, hands, and fingers. Only one patient developed complete bilateral gaze limitation similar to that of our three patients.

The clinical, laboratory, and radiological findings of our patients indicate that they developed “atypical Fisher syndrome”. We also observed the sudden stroke-like onset of neurologic symptoms in our patients. Patient 1 was transferred to our hospital because of the sudden onset of vertigo associated with nausea, vomiting, opthalmoplegia, and dysesthesia of her left extremities. Patient 2 was also transferred to our hospital because of the sudden onset of opthalmoplegia and ptosis, which is associated with bulbar palsy. Patient 3 was admitted to our hospital because of the sudden onset of diplopia. In these patients, MRI and MRA examinations revealed no remarkable findings in the brain (including the brainstem). Stroke-like clinical features and complete opthalmoplegia were the clinical manifestations in our patients.

There are only a few reports on MFS mimicking stroke. Cher and Merory reported on a 66-year-old male with a 5-year history of rheumatoid arthritis (RA) who suddenly developed horizontal diplopia and frontal headache while driving. On admission to the hospital, neurological examination revealed opthalmoplegia with dissociated nystagmus, truncal ataxia, the absence of deep tendon reflexes, and sensory loss of vibration in his lower limbs and from his trunk to his lower thorax. The patient responded to plasma exchange therapy. Cher and Merory suggested one possible mechanism of the sudden onset of these symptoms: immune dysregulation from the long-term administration of the steroid prednisolone (5 mg daily) and methotrexate (10 mg weekly) to treat RA induced the sudden decompensation of progressive ocu lomotor
weakness. Of particular relevance to our cases is the long-term administration of low-dose methotrexate, which has been shown to increase the number of T-4 (helper) cells and decrease the number of T-8 (suppressor) cells. Immune dysregulation from impaired T-suppressor cell function might induce acute inflammatory demyelination of the third nerve. Bourke et al. reported on a case of sudden onset MFS in a 77-year-old woman. They stated that the diagnosis of sudden onset MFS was confirmed by the presence of serum IgG to ganglioside GQ1b, and thus, atypical MFS should be included in the differential diagnosis of brainstem stroke.

The sudden stroke-like onset along with complete ophthalmoplegia of our patients suggests that the unexpected elevation in the serum titer of anti-GQ1b IgG due to unknown immune dysregulation might have severely affected the third, fourth, and sixth nerves and this potent antibody rapidly attacked these nerves and induced stroke-like clinical features and complete ophthalmoplegia.

References