Miller Fisher Syndrome Associated with Influenza A Infection

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Abstract

A 36-year-old, previously healthy man presented with Miller Fisher syndrome (MFS) five days after he was diagnosed with an influenza A infection by a rapid antigen test. He had not received any recent vaccinations. He had no loss of consciousness. Bilateral ophthalmoplegia, blepharoptosis, areflexia, and ataxic gait were noted. One week after treatment with intravenous immunoglobulin, his ophthalmoplegia, blepharoptosis, and ataxic gait had gradually improved, and his deep tendon reflexes returned. Anti-GQ1b IgG antibodies were detected in his serum. There has been no previous report of postinfectious MFS following confirmed influenza A infection in an adult.

Key words: influenza A infection, Miller Fisher syndrome, anti-GQ1b antibody, postinfectious

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Introduction

The development of Miller Fisher syndrome (MFS) follows a wide variety of infections, including Campylobacter jejuni infection, as often described in Guillain-Barré syndrome (GBS), and upper respiratory infections (1, 2). Seasonal influenza virus infection has rarely been associated with GBS (3), and an association between seasonal influenza virus infection and MFS has not been reported in an adult. We encountered an adult case of MFS following influenza A virus infection. This is the first case of postinfectious MFS occurring in an adult following a confirmed influenza A infection to be reported in the literature.

Case Report

The patient was a 36-year-old man who visited our hospital with diplopia and gait disturbance. Five days before visiting our hospital, he displayed flu-like symptoms that were diagnosed as an influenza A infection based on a positive rapid antigen test on his pharyngeal mucus. Oseltamivir (150 mg/day for 5 days) was administered, and his temperature gradually declined. However, a day before visiting our hospital, he noticed diplopia, an inability to fully open his eyes, and gait instability. He was admitted to our hospital for detailed examinations. The patient had a history of hyperlipidemia and was being treated with antihyperlipidemic drugs. He had a 320-pack-per-year history of cigarette smoking for 16 years. At the time of hospital admission, his blood pressure was 117/77 mmHg, and his pulse was 78 beats/min. His body temperature was 36.7°C. He was alert and oriented. He had no dysarthria. His pupils were of equal sizes, at 4 mm, and were reactive to light, without any nystagmus. He had bilateral blepharoptosis and a limited lateral and downward gaze, but his other extraocular movements were of the full range. He had no muscle weakness, including the facial muscles, and his muscle tonus was normal in all limbs. He could sit without difficulty. However, his gait was wide-based and ataxic. Areflexia was present in all limbs, with no pathological reflexes. No sensory loss, including bathyanesthesia, meningeal irritation, or bladder and rectal disturbances were noted.

Blood cell counts and the results of standard serum biochemistry screening tests, including hemoglobin A1c, thiamine, cobalamin, lactic acid, pyruvic acid, thyroid function

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tests, and the anti-nuclear antibody test, were all within the normal limits. His cerebrospinal fluid contained the following: leukocytes, 1/mm³ with no mononuclear cells and 3 counts/3 mm³ polymorphonuclear leukocytes; protein, 41 mg/dL; and glucose, 61 mg/dL (plasma glucose, 111 mg/dL). The oligoclonal IgG band was negative. The serial rapid antigen test for influenza virus on admission was negative. The serum antibody titer against influenza A virus was 16-fold. Influenza A virus RNA was not detected in the cerebrospinal fluid (CSF) by the reverse transcription polymerase chain reaction (RT-PCR) method. Cultures of blood and CSF were negative. The cerebrospinal fluid cytology was class II. The serum Mycoplasma pneumoniae IgG titer detected using a fluorescent antibody was <40-fold. A culture of his stool was negative for enteric pathogens, including Campylobacter jejuni. Findings of other parainfectious evaluations, including cytomegalovirus and Epstein-Barr virus in the serum and CSF, as well as serology for human immunodeficiency virus and syphilis, were negative. The levels of anti-ganglioside IgM and IgG antibodies in his serum on admission were measured by a enzymelinked immunosorbent assay that was reported in a semi-quantitative manner (-, +, ++, ++++, ++++). IgG antibodies against GQ1b and GT1a were positive (IgG GQ1b ++, IgG GT1a ++), while IgG antibodies against GM1, GM2, GM3, GD1a, GD1b, GD3, GT1b, GA1, and Gal-C were negative. He was also negative for IgM antibodies against GM1, GM2, GM3, GD1a, GD1b, GD3, GT1a, GT1b, GQ1b, GA1, and Gal-C. Nerve conduction studies revealed normal amplitudes, latencies, and conduction velocities of the motor and sensory nerves in the upper and lower extremities, but no F waves were elicited in the left median and left posterior tibial nerves. Cranial magnetic resonance imaging including T1-, T2-, and diffusion-weighted images demonstrated no abnormalities. A whole-body evaluation for malignant tumors was negative.

The patient was treated with intravenous immunoglobulin (25 g/day for 5 days). On the seventh hospital day, his gait ataxia and blepharoptosis disappeared, and his deep tendon reflexes returned. The diplopia also improved, with improvement of the gaze limitation in the lateral and downward directions. On the 18th hospital day, he was discharged with a mild gaze limitation to the lateral side, and at the 1-month follow-up evaluation, his eye movement had fully recovered.

Discussion

MFS is known as a variant of GBS, accounting for 5% to 10% of cases, with higher incidences reported in Asian populations: 19% in Taiwan (4) and 25% in Japan (5). It is characterized by the triad of ophthalmoplegia, ataxia, and areflexia (6) and is strongly associated with anti-GQ1b antibodies (7). The present patient exhibited the classical triad of MFS and was anti-GQ1b antibody-positive. The absence of F waves on neurophysiological studies was also consistent with MFS (8). Mori et al. noted in their study that 76% of 50 MFS patients had antecedent respiratory symptoms, and the median interval between the onset of antecedent infection and neurological symptoms was 8 days (range, 1 to 30 days) in their report (5). The time interval between the onset of MFS and that of influenza infection in the present case was 4 days, which was consistent with their report.

The most frequent inciting pathogen in GBS is Campylobacter jejuni, which has been reported in as many as 30% of cases of GBS (9). In contrast, in MFS, Mori et al. reported that respiratory symptoms preceded neurological onset in 76% of cases, with gastrointestinal symptoms in only 4% of patients (5). MFS has also been associated with infection due to Campylobacter jejuni (10, 11), Mycoplasma pneumoniae (12), Hemophilus influenzae (13), Epstein-Barr virus (14), cytomegalovirus, varicella-zoster virus (15), human immunodeficiency virus (16), and Helicobacter pylori (17). However, a large prospective case-control serological study showed the associated infective agents to remain unknown in the majority of cases (2). Recently, the cases of a 17-month-old boy with MFS following a pandemic H1N1 influenza A infection (18), a 39-year-old woman with acute ophthalmoplegia following influenza A infection (19), and two children with an impaired ocular movement (20) following influenza A infection were reported. However, anti-GQ1b antibodies were not detected (18) or not demonstrated (19, 20) in their serum. There has been no previous report of an adult patient in whom the presence of anti-GQ1b antibodies was confirmed showing MFS associated with influenza A infection. It remains possible that other infectious agents may have triggered the MFS. However, in the present case, the cause of his MFS was considered to have been an influenza A infection based on the positive rapid antigen test result, the efficacy of oseltamivir for his upper respiratory tract symptoms, and the absence of any abnormalities on whole body evaluation for foci of infection.

The pathogenesis of MFS is considered to partly be associated with anti-GQ1b antibodies that affect the paranodal region of the extramedullary portion of the oculomotor, trochlear, and abducens nerves, in which the ganglioside GQ1b is abundant, supplying extraocular muscles (21). The leading pathogenic concept in postinfectious MFS, as in GBS, is molecular mimicry (10). With respect to Campylobacter jejuni, considerable information now supports the principle of molecular mimicry between GQ1b/GT1a antibodies and Campylobacter jejuni lipopolysaccharide and lipo-oligosaccharide as central to the induction of this response (10, 11, 22). Although data that support the molecular mimicry hypothesis in MFS, similar to GBS, after viral infections (including influenza) are sparse (3), a relationship between anti-GQ1b antibodies and herpes simplex virus type 1 (HSV-1) has been previously reported (23). In that article, a patient with overlapping GBS and Bickerstaff’s brainstem encephalitis associated with HSV-1 infection was reported, and the authors discussed the possibility of molecular mimicry between HSV-1 and ganglioside GQ1b. In the present
case, anti-GQ1b antibodies may also have developed after the antecedent influenza A infection.

The present case is, to the best of our knowledge, the first report of an adult case of MFS following upper respiratory tract symptoms due to influenza A infection, and our findings suggest that there may be an association between anti-GQ1b antibodies and influenza A infection.

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

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