Miller Fisher syndrome: a case with pattern of pure sensory polyneuropathy concomitant with anti-GQ1B antibody

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Miller Fisher syndrome is characterized by the acute onset of ophthalmoplegia, ataxia, and areflexia. Anti-GQ1b antibodies are useful markers for the differential diagnosis of Miller Fisher syndrome. We describe the case of a seven-year-old male who presented with a four-day history of diplopia and ophthalmoplegia following a febrile flu-like illness with sore throat. On examination he was found to have ataxia, areflexia and ophthalmoplegia, and a diagnosis of Miller Fisher syndrome was made after the exclusion of other conditions and concomitant with electrophysiological findings on electromyography. Although this disorder has a rare incidence, it should still be considered in the differential diagnosis in our country.

Key words: ophthalmoplegia, ataxia, areflexia, anti-GQ1b IgG antibody, electromyography.

Miller Fisher syndrome (MFS) is characterized by the acute onset of ophthalmoplegia, ataxia, and areflexia. The disorder is considered a rare variant of Guillain-Barré syndrome (GBS)[1,2]. The worldwide incidence of GBS is 1-2 per 100,000[3]. MFS accounts for up to 5% of GBS in Western countries, and 19-25% in Asian countries[4]. The diagnosis of MFS depends on the clinical characteristics of the syndrome. Although there are no specific electrodiagnostic features of the disease, various alterations on electromyography (EMG) have been reported. Since 1990, serum anti-GQ1b immunoglobulin G (IgG) antibody levels are reported for the pathophysiology of this disorder as well as the diagnosis[5].

Here we report an additional case of MFS who was diagnosed with the clinical characteristics of the syndrome and the presence of positive anti-GQ1b IgG antibodies.

Case Report

A seven-year-old male patient was admitted to the emergency department with complaint of four-day history of diplopia and three-day history of ophthalmoplegia due to bilateral third and sixth cranial nerve paralysis. He had been well until 10 days earlier, when he developed a febrile flu-like illness with sore throat. He had no history of exposure to any medications or toxic substances, tick bite, recent immunization, or head trauma. He was fully immunized.

On evaluation in the emergency department, he looked well. The following vital signs were recorded: axillary body temperature: 36.7°C, heart rate: 78 beats per minute, and blood pressure: 100/60 mm Hg. The oro-pharynx was hyperemic. There were two lymphadenopathies in the right submandibular area (size 2x1x1 cm and 1x1x1 cm) and one in the left submandibular region (size 2x1x1 cm), which were painful, hard and mobile. Neurological examination revealed bilateral ptosis and limitation of gaze in all directions due to complete palsies of both third and sixth cranial nerves. Facial paralysis was noted. There was no convincing evidence of limb weakness. Deep tendon reflexes were absent in both legs and plantar responses were flexor. Pain and light touch sensation was normal. Although

he did not complain of ataxia at the time of admission he developed ataxia on the second day of hospitalization.

Total blood cell count, erythrocyte sedimentation rate, serum biochemistry, C-reactive protein level, and creatine kinase level were in the range of normal limits, and chest radiograph was normal. A lumbar puncture revealed a sterile cerebrospinal fluid and an increased protein concentration of 219 mg/dl (normal range, 15-45 mg/dl). The cerebrospinal fluid glucose was 55 mg/dl (normal range, 5-85 mg/dl). Analysis of blood antibodies against Epstein-Barr virus, cytomegalovirus (CMV), herpes simplex virus, rubella, toxoplasma, lyme and mycoplasma pneumoniae, and analysis of cerebrospinal fluid antibodies against herpes simplex virus yielded normal results. Blood, urine, cerebrospinal fluid cultures and stool culture for Campylobacter jejuni were negative. Brain computed tomography, magnetic resonance imaging and magnetic resonance angiography were performed to rule out intracranial mass, cavernous sinus thrombosis and demyelinating disease. All of these radiological images were normal. Anti-GQ1b IgG antibody results in serum obtained immediately after admission were positive, 320 EU/ml (normal range <20 EU/ml, ELISA). EMG revealed the pattern of pure sensory polyneuropathy, which is characterized by reduced sensory nerve action potentials (SNAPs), absence of motor conduction velocity (CV), and near normal needle EMG (Table I).

He received a course of intravenous immunoglobulin (IVIG), 400 mg/kg daily for five days, and B complex vitamins were added to this therapy. After one week, his external ocular movements ameliorated. A month later diplopia and ptosis resolved, and after two months deep tendon reflexes of both legs could be elicited and he had no ataxia.

Table I. Nerve Conduction Velocities and Needle Electromyography of the Patient

EMG time from onset	At the time of diagnosis	At three months
Motor conduction		
Median nerve		
Distal latency (msec)	3.2	2.6
Amplitude (mV)	8	7.6
CV (m/sec)	45	56
Ulnar nerve		
Distal latency (msec)	2.9	2.3
Amplitude (mV)	6.7	6.3
CV (m/sec)	47	58
Peroneal nerve		
Distal latency (msec)	3.1	3.25
Amplitude (mV)	4.9	5.8
CV (m/sec)	42	50.6
Posterior tibial nerve		
Distal latency (msec)	3.4	2.9
Amplitude (mV)	4.9	5.3
CV (m/sec)	43	48
Sensory conduction		
Median nerve		
Amplitude (μV)	2.2	5.3
CV (m/sec)	32	51.3
Ulnar nerve		
Amplitude (μV)	NR	12
CV (m/sec)	NR	51.8
Sural nerve		
Amplitude (μV)	NR	18
CV (m/sec)	NR	49
Needle EMG		
Fibs/PSW	negative	negative
MUP	normal	normal

EMG: Electromyography. NR: No response. Fibs: Fibrillation potentials. PSW: Positive spike and waves. CV: Conduction velocity. MUP: Motor unit potentials.

Discussion

Miller Fisher syndrome is a clinical variant of GBS. The classical triad of symptoms consists of ataxia, areflexia and ophthalmoplegia; however, other cranial nerves can be involved. Both GBS and MFS have similar findings such as increased cerebrospinal fluid protein with mild or absent pleocytosis, responsiveness to immune modulatory therapies, and association with infections including upper respiratory tract viruses and enteritis due to Clostridium jejuni[6]. Prognosis in MFS is generally better compared to GBS, and complete recovery occurs by six months in most patients[4].

Miller Fisher syndrome is considered to be a post-infectious autoimmune illness. As is the case in GBS, a wide range of pathogens, including C. jejuni, Haemophilus influenzae, Streptococcus pyogenes, Staphylococcus aureus, Mycoplasma pneumoniae, Coxiella burnetii, CMV, Epstein-Barr virus, varicella-zoster virus and mumps virus have been reported as antecedent infectious agents in MFS. A study on the antecedent infectious agents in MFS showed that 18% of patients with MFS were seropositive for recent C. jejuni infection, and that the frequency was lower than that of patients with GBS (31%)[2,7].

The diagnosis of MFS is based on the presence of the clinical triad of ataxia, areflexia ophthalmoplegia[1]. Increased cerebrospinal fluid protein levels and the presence of anti-GQ1b antibody in the serum are important laboratory results to support the diagnosis of MFS[8,9].

Chiba et al.[8] first reported that six patients with MFS had anti-GQ1b IgG antibody during the acute phase of disease. Other studies confirmed this strong association. Peripheral nerves contain gangliosides which are complex glycosphingolipids. Gangliosides are attractive potential antigenic targets in peripheral neuropathies. Immunohistochemical studies have revealed GQ1b epitope staining in the paranodal regions of the extramedullary portions of the human third, fourth and sixth cranial nerves; it has also been revealed that ganglioside composition showed higher percentage of GQ1b in the optic nerve and all three ocular motor nerves. The correlation between anti-GQ1b antibody and acute ophthalmoplegia has been shown in typical MFS, in atypical (without ataxia) MFS, in GBS with ophthalmoplegia, and in Bickerstaff brainstem encephalitis (BBE)[7]. For this reason, anti-GQ1b antibodies have been implicated in the pathogenesis of the external ophthalmoplegia[8]. Most of the MFS patients have anti-GQ1b IgG autoantibody and it is very specific for MFS. During the acute phase of disease, more than 90% of MFS patients have anti-GQ1b IgG in the serum, with antibodies to GT1a, GD1b, and GD3 present to a lesser degree[10]. At the time of clinical presentation, antibody titers reach the highest level and decrease rapidly at the recovery[11]. The diagnosis of our case became definite with the positive antibody results in the early period of the disease.

Because of the rarity of MFS, there has been no electrodiagnostic study involving a large number of patients. Common findings of pilot studies[12-14] include: 1. reduced amplitude of SNAPs in many patients, 2. reduced amplitude of facial compound muscle action potentials (CMAPs) when associated with facial nerve palsy, and 3. absence of soleus H-reflexes, all of which suggest peripheral abnormalities. In addition, one reported case showed absent or delayed H-reflexes, and the other showed abnormal silent periods and absent H-reflexes. The decrease in amplitude of SNAPs was not severe enough to account for prominent ataxia, and in some patients routine sensory nerve conduction studies are completely normal. Accordingly, only the absence of H-reflexes was a constant finding in a previous series of cases of MFS. Selective involvement of group Ia muscle spindle afferents has been proposed as the mechanism for ataxia and areflexia, and this could account for the occasionally normal SNAPs, which consist of group II afferent components[15].

Our patient had absent SNAPs and significantly reduced conduction velocity. Motor conduction velocity was at the lower limit of the normal values (Table I). Thus, unlike GBS, the sensory nerves were more severely affected than motor nerves in the limbs and motor involvement was more prominent in the cranial nerves. Electrophysiologic tests were normal at the third month of follow-up and these results correlated with the clinical findings.

The differential diagnosis of MFS includes neurologic, toxic, infectious and postinfectious diseases. BBE and MFS share some of the

common clinical characteristics, such as ophthalmoplegia, ataxia and areflexia or hyporeflexia. Serum samples of patients with BBE and ophthalmoparesis have increased titers of anti-GQ1b antibody. However, BBE should be a diagnosis reserved for patients showing coma, brisk reflexes or long tract sensory disturbance in addition to the MFS triad[7]. Although GBS carries many similarities with MFS, such as antecedent infection, areflexia, cerebrospinal fluid findings, and conduction delay on EMG, paresthesias and significant limb and respiratory muscle weakness are rarely observed in MFS[5].

As a result, although the electrophysiologic tests are not specific for MFS, they are important to diagnose the disease and to determine the prognosis. MFS is a rare disorder and has a better clinical course compared to GBS. The diagnosis of MFS depends on differential diagnosis from many serious disorders. At this point, it is important to distinguish this syndrome from another by clinical features and use of any practical test methods. Thus, the detection of anti- GQ1b IgG antibodies in the serum is a simple test and it is helpful in the diagnosis of MFS.

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