

Anti-GQ1b-negative Miller Fisher syndrome presented with one-sided horizontal gaze palsy

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SUMMARY: Akıncı G, Öztura İ, Hız-Kurul S. Anti-GQ1b-negative Miller Fisher syndrome presented with one-sided horizontal gaze palsy. Turk J Pediatr: 210; 52: 317-320.

Miller Fisher syndrome classically presents with ophthalmoplegia, ataxia and areflexia. The syndrome may present rarely with atypical clinical features. Whether the central or peripheral nervous system is primarily involved remains controversial. Miller Fisher syndrome usually follows an infection, the most likely being *Campylobacter jejuni*. *Mycoplasma pneumoniae* has been reported rarely as the antecedent infectious agent in some patients.

Herein, we report a 13-year-old girl with positive mycoplasma immunoglobulin (Ig)M and IgG serology who presented with one-sided horizontal gaze palsy, ataxia, areflexia, and bulbar palsy. Her cranial magnetic resonance imaging was normal and blood serum was negative for anti-GQ1b IgG antibodies.

Key words: Miller Fisher syndrome, horizontal gaze palsy, mycoplasma, bulbar palsy.

Miller Fisher syndrome consists of ophthalmoplegia, ataxia and areflexia¹. It may present rarely with atypical clinical features, such as bulbar involvement or limb weakness or without one of the three components.

Immunoglobulin G (IgG) anti-GQ1b antibody is present in 90% of the Miller Fisher syndrome patients, and it is thought to be related with ophthalmoplegia². However, the diagnosis of Miller Fisher syndrome can be done by clinical features in the absence of positive anti-GQ1b antibody. A preceding infection has been identified in about 70% of patients with Miller Fisher syndrome, as it is in Guillain-Barré syndrome². *Mycoplasma pneumoniae* has been reported rarely as the antecedent infectious agent in some patients with Miller Fisher syndrome³⁻⁵.

Herein, we report a case of Miller Fisher syndrome who presented with one-sided horizontal gaze palsy and bulbar palsy. The presence of one-sided horizontal gaze palsy and bulbar palsy is unusual for Miller Fisher syndrome. Our case was also conspicuous because of her negative GQ1-b antibody and positive *Mycoplasma pneumoniae* serology.

Case Report

A 13-year-old girl presented to the emergency department with difficulty in walking, ataxia, dysarthria, and dysphagia. She had an upper respiratory infection that had begun 10 days earlier with the onset of sore throat and fever. She had no history of exposure to any medications or toxic substances, tick bite, recent immunization, or head trauma. She was fully immunized.

She looked alert and fully conscious on admission. Her vitals were: axillary body temperature: 36.5°C, heart rate: 78 beats per minute and blood pressure: 100/65 mmHg. On the examination, it was noted that her eyes were deviate towards the right side in the neutral position, and she had left-sided horizontal gaze palsy (Fig. 1). Ptosis was absent. Pupils were reactive to light with equal size, and there was no papilledema. Slurred speech was present; she had a nasal voice with absent pharyngeal reflex. There was no weakness. She was not able to walk unsupported and she had dysmetria. Deep tendon reflexes were diminished in the upper limbs and absent in both legs, and plantar

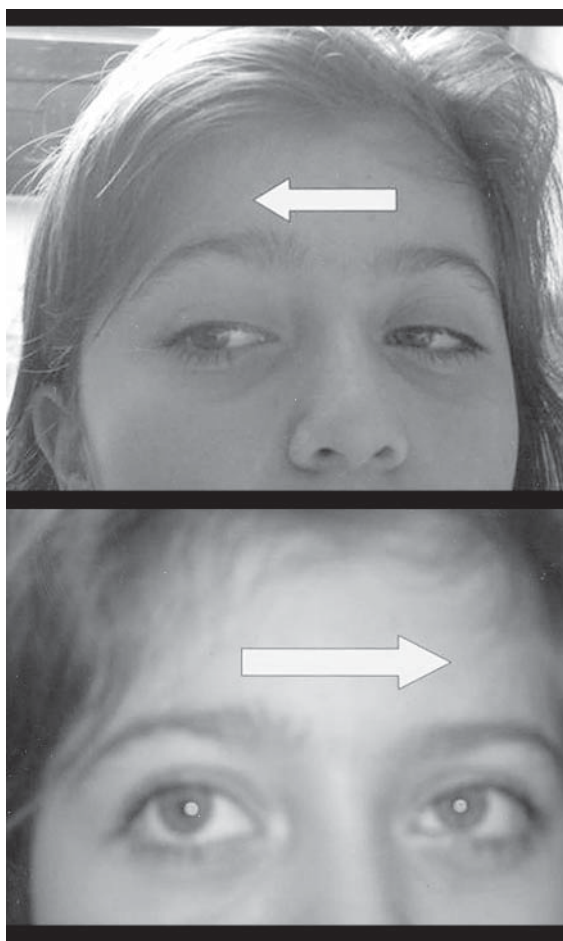


Fig. 1. Right gaze is normal (left), but on attempted left gaze, the eyes do not move beyond midline (right).

responses were flexor. Pain and light touch sensations were normal. White blood cell count and C-reactive protein levels were normal; erythrocyte sedimentation rate was 38 mm/hour. Cerebrospinal fluid (CSF) examination was normal. Magnetic resonance imaging (MRI) showed no abnormality in the orbits, brain or brainstem.

Nerve conduction, F-wave and H-reflex studies were carried out on day 6 of onset. The follow-up study was performed on day 35. Motor nerve conduction studies were performed on the left median, ulnar, peroneal, tibial, and right tibial nerves using conventional procedures. Antidromic sensory nerve conduction studies were performed in the left median, ulnar and sural nerves. All the nerve conduction parameters were within the normal range. F-

waves were elicited after distal stimulation at the wrist and 20 consecutive responses were recorded. Median and ulnar F waves were present with normal frequency and latency. H-reflex studies were performed on the right and left soleus muscle and revealed absence of H-reflexes. On day 35, H-reflexes were obtained with normal amplitude and latency. Blink reflexes were obtained by stimulating the left supraorbital nerve and recording from the orbicularis oris muscle with surface electrodes. R1 and R2 responses were elicited with normal latency.

Serum *M. pneumoniae* IgM (titer > 1:10) and IgG (titer > 1:10) were positive. Further investigations for any other infective causes were negative, including CSF, blood and urine cultures, stool culture for *Campylobacter jejuni*, and serology for Epstein-Barr virus, cytomegalovirus, herpes simplex virus, rubella, toxoplasma, chlamydia and group A streptococcus. Serology for anti-GQ1b antibodies was negative.

Atypical Miller Fisher syndrome was diagnosed. She was admitted to a monitored setting and received intravenous immunoglobulin (IVIG), 400 mg/kg daily for five days. Two weeks later, left-sided horizontal gaze palsy began to improve, and her ataxia, dysarthria and dysphagia completely resolved. After four weeks, she had no abnormality regarding left horizontal gaze, and her deep tendon reflexes were normoactive.

Discussion

Miller Fisher syndrome is an acute demyelinating disorder that is considered a cranial nerve variant of Guillain-Barré syndrome. It has been proposed that Miller Fisher syndrome, Guillain-Barré syndrome, and Bickerstaff brainstem encephalitis may be forms of a continuous spectrum⁶. Bickerstaff brainstem encephalitis differs from Miller Fisher syndrome in that the former also includes disturbance of consciousness and/or hyperreflexia. Although it remains controversial as to whether the central or peripheral nervous system is primarily involved in Miller Fisher syndrome, most authors are proponents of the peripheral hypothesis^{7,8}. In contrast, Al-Din et al.⁹, the first proponents of a central origin, revealed that Miller Fisher syndrome is a variant of brainstem encephalitis.

Our patient was diagnosed with Miller Fisher syndrome, as she had ataxia, areflexia and ophthalmoplegia. We excluded Bickerstaff brainstem encephalitis, because she never developed impaired consciousness. Although albuminocytological dissociation in CSF is often present, protein concentration was increased in only 25% of Miller Fisher syndrome patients during the first week, while it was increased in 71% during the second and 84% during the third week¹⁰. Normal CSF findings in our patient might be associated with obtaining the sample during the early period of the symptoms. As was the case in our patient, nerve conduction studies in Miller Fisher syndrome are usually normal or only slightly abnormal². Ito et al.¹¹ suggested that the most frequent abnormality in nerve conduction and H-reflex studies was the absence of soleus H-reflexes, in 75% of four Bickerstaff brainstem encephalitis and 74% of 28 Miller Fisher syndrome patients, whereas routine motor and sensory nerve conduction study results were normal for both groups.

Our patient had left-sided horizontal gaze palsy and bulbar palsy, which are atypical features of Miller Fisher syndrome. Serum antiGQ1b antibody was negative. The ophthalmological features of Miller Fisher syndrome are of great clinical interest. Isolated abducens nerve palsy was thought to be a mild form of Miller Fisher syndrome². Other ophthalmological abnormalities determined for this syndrome have included divergence paralysis, lid retraction, upper lid jerks, internuclear ophthalmoplegia, convergence spasm, Parinaud's syndrome, defective vestibulo-ocular reflex, chronic ophthalmoplegia, areflexic mydriasis, convergence failure, and acute angle closure. One-sided horizontal gaze palsy, as seen in our patient, might be caused by a lesion of the pons, either ipsilateral paramedian pontine reticular formation (PPRF) or ipsilateral abducens nucleus¹². Since our patient could produce complete lateral motion of the eyes with oculocephalic maneuver, we thought that her ipsilateral abducens nucleus was intact and her ipsilateral PPRF was affected. Trauma, ischemia, infiltration, and compression may produce intrinsic brainstem damage, which results in acquired paralysis of horizontal gaze. In acute lesions of the PPRF, the eyes may deviate towards the unaffected side, as seen in

our patient. As bilateral horizontal gaze palsy has been reported in paraneoplastic brainstem encephalitis associated with neoplasm, the possibility of paraneoplastic syndrome should be considered in the differential diagnosis of horizontal gaze palsy. However, further laboratory and radiological investigations did not reveal any malignancy in our case.

There were signs of corticobulbar dysfunction in our patient. Her speech was slurred and she had a nasal voice with absent pharyngeal reflex. Corticobulbar dysfunction has been described rarely in Miller Fisher syndrome¹³⁻¹⁵. Unilateral horizontal gaze palsy, bulbar palsy and absence of antiGQ1b antibody in our case may be attributed to the triggering agent and the specific immune response. Another finding supporting autoimmune pathology in our case was the rapid improvement in her neurological signs after IVIG administration.

Miller Fisher syndrome is known to occur subsequent to a wide variety of infections, and antecedent respiratory symptoms occurred in 76% of the patients. Although several neurological complications after *M. pneumoniae* infection may develop, subsequent Miller Fisher syndrome development has been reported rarely³⁻⁵. The pathogenesis of damage in the central nervous system caused by *M. pneumoniae* remains unclear. Neurotoxicity, direct invasion of the central nervous system, and autoimmune mechanisms are the most common prevalent theories. In our patient, there was no brainstem lesion on cranial MRI. In the literature, however, cerebral infarction associated with *M. pneumoniae* has been described¹⁶. Previous reports have suggested that vasculopathy caused by the immunologic mechanism might be responsible for neurological involvement associated with *M. pneumoniae*.

Our patient developed neurological signs 10 days after the onset of the respiratory symptoms. She had normal physical examination and chest radiography in terms of mycoplasma infection on her admission. However, her serological tests revealed *M. pneumoniae* infection. Although culture and polymerase chain reaction are preferable to serology for definitive diagnosis, they are not widely available; thus, the serological tests remain the mainstay for the laboratory diagnosis. Serologic methods for detection of antibodies against

M. pneumoniae consist of complement fixation, indirect immunofluorescence and enzyme immunoassays. An indirect immunofluorescence test was used for the serologic diagnosis of the patient¹⁷. IgM antibodies increase shortly after the acute infection and persist for several months, to more than one year¹⁸. Therefore, the detection of the specific IgM in our patient does not indicate the time of infection, but only shows that the patient had been infected with *M. pneumoniae*.

We propose that *M. pneumoniae* might be the possible etiologic agent in our case. Because of its self-limiting clinical course, there are no randomized, double-blind, placebo-controlled trials about the treatment of Miller Fisher syndrome. A retrospective analysis of 92 consecutive Miller Fisher syndrome cases showed that IVIG somewhat lessened ophthalmoplegia and ataxia but had no significant effect on the outcome, presumably because of good natural recoveries¹⁰. Complete resolution of ataxia by one month and complete resolution of ophthalmoplegia by three months would be appropriate outcome measures based on the observational data available.

In conclusion, Miller Fisher syndrome may present with a wide range of clinical features, depending on the triggering agent and the specific immune response. Although important brainstem lesions, such as ischemia and infiltration, may first come to mind in a patient presenting with one-sided horizontal gaze palsy and bulbar palsy, the diagnosis of Miller Fisher syndrome should be considered in the presence of other clinical features of the disease.

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