Miller-Fisher Syndrome.

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Background: *The Guillain-Barré syndrome (GBS) is an acute idiopathic polyneuritis, it has several variants. Miller-Fisher syndrome (MFS) is an uncommon variant of GBS and is characterized by a triad of acute ophthalmoplegia, ataxia, and areflexia. The difference between common variants of GBS and MFS is that GBS exhibits limb weakness, whereas in MFS the limb weakness is absent.*

Case Report: *We present a 60-year-old male complaining of bilateral progressive ptosis and gait ataxia. Eye examinations revealed bilateral ptosis and complete total ophthalmoplegia. Neurological examinations revealed normal deep tendon reflexes and no motor or sensory deficits. MRI brain and orbit demonstrated normal cavernous sinuses and brainstem. Lumbar puncture revealed albuminocytological dissociation. The diagnosis was confirmed by a serum test showing anti-GQ1b antibody seropositivity.*

Conclusion: *MFS is uncommon and may be frequently misdiagnosed as brainstem stroke or myasthenia gravis. Neurological examinations are of clinical importance. MFS must be considered in the differential diagnosis in patients presenting with bilateral total ophthalmoplegia and ataxia or areflexia.*

Conflict of interest: *none.*

Keywords: *Guillain-Barré syndrome, Miller-Fisher syndrome, ophthalmoplegia, anti-GQ1b*

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Introduction

Miller-Fisher syndrome (MFS) is an uncommon variant of Guillain-Barré syndrome (GBS) and is characterized by a triad of acute ophthalmoplegia, ataxia, and areflexia without limb weakness.[1,2] The new diagnostic criteria of GBS is based on clinical features.[3] Diagnosis of MFS requires at least two features from the clinical triad and albuminocytological dissociation and antibodies to gangliosides. Absence of certain features indicates incomplete MFS such as patients presenting with acute ophthalmoplegia in the absence of ataxia. About 5 % of classic GBS cases may have cranial nerve-innervated muscles involved and present with ophthalmoplegia. The presence of ophthalmoplegia may indicate overlap with MFS, while some MFS cases may progress to GBS with ophthalmoplegia. The following case report is that of a patient who presented with complete bilateral ophthalmoplegia and ptosis. Initial differential diagnoses included myasthenia gravis (MG), brainstem ischemia, diabetic cranial polyneuropathy, chronic progressive external ophthalmoplegia (CPEO) and possible occult tumor. Investigations did not support any of the differentials and MFS was considered.

Case Report

A 60-year-old healthy male presented with throbbing headache and gait disturbance. He did not have nausea or vomiting, weakness, numbness, or abnormal hearing. He went to the public health center and found that he had a high blood pressure. Subsequently, he was referred to secondary care and received anti-hypertensive drugs. Two weeks later, he developed bilateral ptosis without complaining of diplopia. His vision was unaffected, but his wife noticed that he could not roll his eyes as normal and the drooping of his eyelids has worsened, so he went back to the hospital. The physician conducted a computerized tomography (CT) scan of the brain but did not find any abnormality, hence the patient was referred to our hospital. Past history revealed heavy alcohol drinking and smoking for more than 30 years. Initial best corrected visual acuities were 20/70 OD and 20/100 OS. External eye examinations revealed bilateral asymmetrical ptosis (Figure 1). The intraocular pressure was normal in both eyes. Slit-lamp examination revealed dense nuclear cataracts in both eyes. The pupils were 5 mm in size and sluggishly reactive to light in both eyes, afferent pupillary defect was negative. The ocular motility was completely limited in all direction of gazes in both eyes (Figure 2). The vestibule-ocular reflex (VOR) was impaired. Fundus examinations revealed only epiretinal membrane in the left eye with normal bilateral optic discs. Neurological examinations revealed no decrease of sensation, motor weakness, and other cranial nerve involvement. Deep tendon reflexes were normal and cerebellar signs were absent.

Figure 1: primary gaze showed bilateral asymmetrical ptosis.

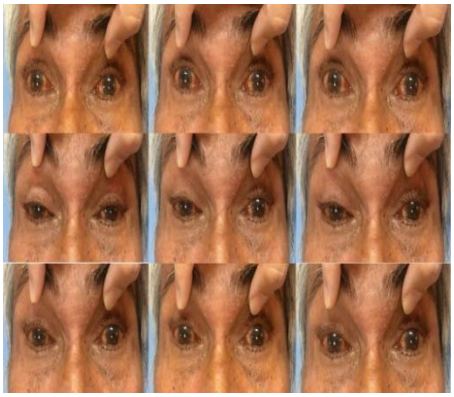
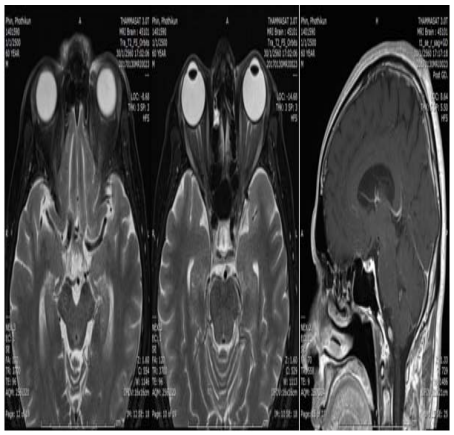


Figure 2: nine diagnostic gazes show complete limitation in all directions of gazes in both eyes

Laboratory investigations revealed normal complete blood count, fasting blood sugar, syphilis serology, and serum inflammatory markers. Contrast enhanced brain and orbit MRI revealed non-specific white matter change at bilateral fronto-parietal lobe, with no evidence of brainstem infarction or demyelination. Bilateral cavernous sinus and posterior orbits were normal (Figure 3).



Due to negative neuroimaging, we re-considered the differential diagnosis for a non-localized lesion involving polyneuropathy as the following etiologies; infection such as meningitis, inflammation such as GBS, metabolic such as drug toxicity or Wernicke encephalopathy from thiamine deficiency, these can present with acute progressive bilateral ophthalmoplegia with gait ataxia. Further history revealed that the patient did not have recent fever, respiratory tract infection, or viral prodrome. The patient admitted to cessation of smoking and drinking 6 years ago. He has a normal diet and did not have signs of malnutrition. His regular medications only consisted of anti-hypertensive drugs.

The patient was consulted by a neurologist and underwent lumbar puncture procedure. The cerebrospinal fluid (CSF) analysis revealed normal opening CSF pressure, normal CSF sugar with a mildly elevated CSF protein of 57.4 mg/dL and white blood cell counts of 6 cells per high-power field. Elevated CSF protein without pleocytosis suggested "cytoalbuminologic dissociation" which caused a suspicion of MFS. Additional investigation of serum anti-GQ1b antibody titer was performed. Nerve conduction velocity (NCV) and electromyography (EMG) were performed and the results were normal. The neurologist recommended conservative treatment because the clinical course of this patient reached the nadir phase, which was followed by a plateau. He was discharged from the hospital without any treatment. During the second week follow-up at the eye clinic, the patient had some improvement of bilateral ptosis and ocular motility, his eye could move about 10% (Figure 4). Gait ataxia was normalized. After the diagnosis was confirmed by antiGQ1b seropositivity, the patient was planned for observation because MFS has a good prognosis. Most patients with MFS will have their symptoms gradually improve within 4-8 weeks.

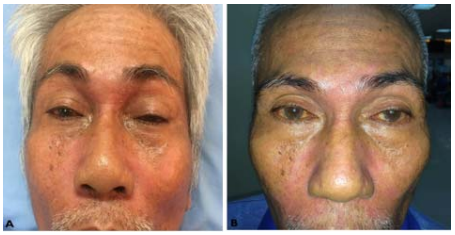


Figure 4: showed some improvement of bilateral ptosis (figure 4A on the initial visit compared to figure 4B on the follow-up visit)

The Guillain-Barré syndrome (GBS) is a group of acute autoimmune peripheral polyneuropathy affecting all limbs with or without cranial neuropathy.[4] The most common variant of GBS was acute inflammatory demyelinating polyneuropathy (AIDP). A pathogenesis of AIDP, the immune-mediated attack is directed at the peripheral nerves, resulting in demyelination or axonopathy.[5] Incidence of GBS ranges from 0.6 to 4.0 per 100,000 people in wordwide.[6] GBS affects males slightly more than females of all ages with a mean age of onset of 40 years.

GBS is characterized by weakness in lower limbs spreading to the upper limbs, sensory loss, disruption of bowel and bladder function, or difficulty breathing. Patients with GBS usually has rapid progressive weakness to a nadir phase within two to four weeks after onset.[7] About 50%-70% of GBS cases exhibit antecedent infectious symptoms one to two weeks prior to the onset.[8] Common organisms associated with MFS includes Campylobacter jejuni, Haemophilus influenza, cytomegalovirus, Epstein Barr virus, and Mycoplasma pneumonia.[9] The lipopolysaccharide capsule of the organism shares epitopes with myelin gangliosides resulting in cross-reacting antibodies against peripheral nerve myelin.10 About 90% of GBS cases are associated with raised protein levels in cerebrospinal fluid (CSF), but no increased cell content, also termed albuminocytological dissociation.[11]

Bilateral total ophthalmoplegia is a rare condition. To determine the cause of paralysis of all extraocular muscles, the localized lesion may be categorized as the following: (1) supranuclear lesion (2) nuclear or brainstem lesion and (3) infranuclear lesion. Supranuclear lesions that involve the neural pathways that carry commands from the cerebral cortex to the ocular motor nuclei in the brainstem or lesion that involve pathways between the gaze centers and the ocular motor nuclei can present with bilateral total ophthalmoplegia. Nuclear lesions that involve the ocular motor nuclei of third, fourth, and sixth nerve in the brainstem can present with bilateral total ophthalmoplegia. Infranuclear lesion that involve the third, fourth, and sixth nerves which are located nearly in the lateral wall of cavernous sinus, bilateral cavernous sinus lesions or unilateral lesions that cross midline can present with bilateral total ophthalmoplegia. Neuromuscular junction lesion such as severe MG can present with bilateral total ophthalmoplegia. Extraocular muscles (EOMs) lesions that involve multiple EOMs can present with bilateral total ophthalmoplegia. Ocular MG can mimic isolated or multiple cranial nerve palsies, gaze palsies, internuclear ophthalmoplegia, and even a brainstem stroke. [12]

Initial differential diagnoses included ocular MG, brainstem ischemia, diabetic cranial polyneuropathy, CPEO and possible occult tumor. The present case had impaired VOR, thus the supranuclear lesion can be ruled out. The serum fasting blood sugar was normal. The ice-pack test and the sleep test do not demonstrate a positive response. Edrophonium test and

Neostigmine test could not be done in our hospital. We do not measure the level of serum anti-acetycholine receptor antibodies due to the resource limitations. Due to the absence of the characteristic variable ptosis and variable involvement of EOMs, we did not suspect ocular MG in this case. CPEO is a disorder of mitochondrial myopathies, which typically present with bilateral, progressive ptosis and external ophthalmoplegia.[13] Most patients do not complain of diplopia because of the slow symmetrical onset of ophthalmoplegia. A review of old photos in the present case did not establish the characteristic chronic slow progressive course over a period of years. We do not perform the diagnostic skeletal muscle biopsy as it is an invasive procedure and no clinical suspicion of a muscle disease.

The clinical manifestations of brainstem stroke depend on the location of the ischemic event. The superior colliculus is involved in the control of eye movements, and the pretectum is involved in the pupillary light reflex, vertical gaze, vertical saccades, and the convergence pathway. The paramedian pontine reticular formation is involved in the horizontal gaze center. The nuclei of the oculomotor nerve (III) and trochlear nerve (IV) are located in rostral and caudal midbrain, respectively. The nuclei of the trigeminal nerve (V), abducens nerve (VI), and facial nerve (VII) are found in the pons. Brainstem strokes can present with oculomotor cranial nerve palsies, ptosis and pupils abnormalities. The patient with bilateral total ophthalmoplegia from brainstem stroke should present with associated brainstem signs such as vertigo, dysarthria, dysphagia, ataxia, motor and sensory deficits. These neurological abnormalities can often be detected via through history taking and complete physical examination. We performed neuroimaging to exclude the brainstem and cavernous sinus lesions. Because of negative neuroimaging, we re-considered the differential diagnosis for non-localized lesions such as GBS which is a group of acute autoimmune idiopathic polyneuritis and can present with ophthalmoplegia. MFS is an uncommon variant of GBS and is characterized by a triad of acute ophthalmoplegia, ataxia, and areflexia. The difference between common variants of GBS and MFS is that GBS presents with limb weakness, where it is absent in MFS. In the present case, the patient presented with two features from the clinical triad with no limb weakness in addition to albuminocytological dissociation. Some MFS cases may present with antecedent infectious symptoms in upper respiratory tract or gastrointestinal tract few weeks prior to the onset, but the present case did not have such infection.

Although electrophysiological studies are not required in the diagnosis, the results can support the diagnosis. Electrophysiological studies in MFS indicate that MFS is axonal form of neuropathy with no specific pattern such as abnormal facial nerve conduction.[14] The axonal forms of neuropathy are associated with antibodies to gangliosides. The gangliosides are complex glycosphingolipids mostly in neuronal membrane especially the GQ1b ganglioside which is highly enriched in ocular motor cranial nerves, ciliary ganglia, muscle spindles and the reticular formation.[15] Anti-GQ1b antibodies are immunoglobulin G (IgG1 antibodies) which has been found in 90% of cases of MFS. Anti-GQ1b antibody has high specificity for MFS, but these antibodies also found in others variant of GBS such as Bickerstaff brainstem encephalitis

(BBE).[16] These antibodies explain the clinical features of total ophthalmoplegia and cerebellar-like ataxia in MFS, and hypersomnolence in BBE. In the present case, there was normal NCV and EMG testing, but was supported by characteristic antibodies.

GBS has a monophasic course, patients usually exhibit intervals of rapid progressive weakness to a nadir phase within two to four weeks after onset, followed by a clinical plateau. If the patients with GBS are present within the first week of onset, they should be closely observed for progression of the disease. Patients who are at risk of developing progressing limb weakness and respiratory failure should receive immunotherapy such as plasma exchange or intravenous immunoglobulin G (IVIg).[17] Corticosteroid therapy is ineffective for treating GBS.[18] There are no randomized controlled trials of the effect of immunotherapy in MFS. A retrospective study showed that IVIg had no effect on the outcome, presumably because MFS is a self-limited disease and has a good natural recovery.[19] The recovery time of ophthalmoplegia and ataxia was range 3-46 days and 3-41 days, respectively. Thus, conservative treatment is recommended except in severely affected patients or clinical overlapping GBS should probably receive immunotherapy. In the present case, the natural recovery was observed at four weeks after the onset of the disease and the patient should be follow-up for the full recovery within few months.

Conclusion

MFS is uncommon and may be frequently misdiagnosed as brainstem stroke or myasthenia gravis. Neurological examinations are of clinical importance. MFS must be considered in the differential diagnosis in patients presenting with bilateral total ophthalmoplegia and ataxia or areflexia. In the present case, the patient presented with clinical features suspect MFS and consultation with a neurologist is mandatory as the clinical may overlapping GBS with ophthalmoplegia which requires immunotherapy.

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