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Miller Fisher Syndrome- a Case Report and Review of Literature

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Abstract:

Background and Objective:: Miller Fisher syndrome (MFS) is a variant of Guillan Barre syndrome characterized by ophthalmoplegia, ataxia and areflexia. Although self-limiting disease course is expected, disease modifying treatment options for MFS are no different than for GBS and include intravenous immune globulin (IVIG) and plasmapheresis. Here, we report a case of MFS presented with bilateral ptosis, ophthalmoplegia, ataxia with quadriparesis and normal NCS. Patient - Methods: A 14- year-old young boy was admitted to our hospital with the complaints of double vision, vertigo, difficulty in walking, imbalance. He had no diarrhea or upper respiratory tract infection prior to this illness. On neurological examination, he had limited ability to move his eyes up and out, had bilateral ptosis, ataxia. The muscle strength was mildly impaired. The plantar reflexes were flexor and the deep tendon reflexes were absent. Results: The blood laboratory, CT and brain MRI were normal. In the first sample of CSF, there was no change. Subsequent sample after 14 days revealed high protein with albuminocytological dissociation. The NCS and EMG were normal. Anti GQ 1b antibody was negative. He showed marked improvement with conservative management. Conclusion: MFS is a rare disease that must be diagnosed with the clinical findings and in the following days the diagnosis can be supported by the laboratory findings.

Key words: *Ataxia, Cerebrospinal fluid , Miller Fisher Syndrome, Ophthalmoplegia etc.*

Abbreviations: *CSF (Cerebrospinal Fluid), EMG (Electromyography), GBS (Guillain Barre Syndrome), IVIg (Intravenous Immunoglobulin), MFS (Miller Fisher Syndrome), NCS (Nerve Conduction Study).*

Introduction:

Miller Fisher Syndrome (MFS) is an acquired disease of nervous system which is considered as a rare variant of Guillain-Barré Syndrome (GBS). It is also called Fisher's syndrome, was first recognized by James Collier in 1932 as a separate clinical triad of ophthalmoplegia, ataxia, and areflexia. Later, MFS was named after Charles Miller Fisher who reported it in 1956 as a limited variant of Guillain- Barré syndrome (GBS) [1]. Miller Fisher Syndrome (MFS) is a geographically variable variant of GBS observed in about 1% - 5% of all GBS cases in Western countries, yet up to 19% and 25% in Taiwan and Japan, respectively [2]. There is an estab-lished male predominance at a ratio of 2:1 and a mean age of onset of 43.6 years, although cases of MFS have been reported in all age ranges [3]. Despite its rarity, MFS has played an important role in under-standing the pathogenesis of immune-mediated neuropathies, which is thought to involve molecular mimicry incited by an-tecedent infection [4, 5]. Chiba et al first reported the presence of anti-GQ1b antibodies in strong association with MFS in 1992 [6]. This serological marker, present in well over 90% of afflicted patients, has become an important diagnostic tool in MFS and has been implicated in other variants of GBS that involve ocular muscles [4, 5] . Although self-limiting disease course is expected, disease modifying treatment options for

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MFS are no different than for GBS and include intravenous immune globulin (IVIG) and plasmapheresis. Benefits of treatment are not as clear in MFS, but a rationale for treatment is to encourage faster resolution of symptoms and perhaps decreased likelihood of complications [7]. Here we are reporting a case of MFS having weakness of all four limbs, ptosis along with ataxia, areflexia, ophthalmoplegia conservatively managed. The patient gradually improved in symptoms including power, ataxia, ophthalmoplegia without intravenous immunoglobulin. After 2 weeks, the patient was discharged from hospital with marked recovery.

Case Report:1

A 14 year old young boy presented to the department Neurology, National Institute of Neurosciences and Hospital, Dhaka with sudden onset of both lower limb weakness followed by weakness of all four limbs, bilateral drooping of eyelids, more on the left and double vision for past 7 days. Drooping of eyelids is not of fatigable type and there was no diurnal variation. After two days of onset of symptoms, he developed unsteadiness of gait, while walking he had tendency to fall on either side and was able to walk only with support. His imbalance was not proportionate to weakness. There was no history of fever, headache, loose motions and upper respiratory tract infections in the past one month. There was no history of bladder and bowel incontinence. There was no recent history of trauma, drug abuse, alcohol addiction and vaccination.

General physical examination was normal with stable vitals. On neurological examination higher cerebral functions were normal. Cranial nerve examination revealed bilateral external opthalmoplegia with ptosis, more on the left (Figure 1). There was no nystagmus, optic fundus was normal. On motor system examination, muscle tone decreased in both lower limbs, power is 4/5 in both lower limbs and normal in upper limbs. There was no muscular wasting / atrophy, involuntary movements were not present. In all four limbs deep tendon reflexes were absent, plantars were flexors bilaterally. Sensations like thermal, pain and touch including lower limbs Joint position sense and vibration sense were normal. Romberg's test was positive in open eyes. He had ataxic gait with grossly impaired tandem walking and tendency to fall on either side. Finger nose test and other cerebellar signs were normal.

His routine investigations are normal. CT and MRI of brain, thyroid function tests, S. Vit B-12, VDRL were normal. CSF Analysis was done for 2 times at 14 days interval. First time it showed 0 cells with normal protein and sugar. Subsequent CSF study showed 3 cells, all are lymphocytes, protein 80 mg%, albuminocytological dissociation present. Gm stain, AFB stain, ADA and Gene Xpert were negative. Anti GQ 1b antibody was negative. Nerve conduction study showed normal sensory and motor nerve action potential.

As the patient shown triad symptoms of MFS - ataxia, areflexia, ophthalmoplegia and weakness of lower limbs, clinically he was diagnosed to have Miller Fisher variant of GBS.. The patient was managed conservatively and he had shown gradual improvement in symptoms including power, ataxia, ophthalmoplegia without intravenous immunoglobulin (IVIg). We discharged and followed up the patient. After 30 days the patient was recovered completely (Figure 2).

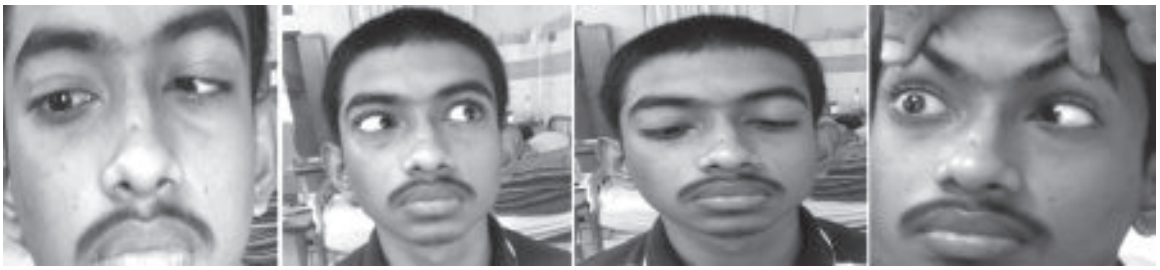

Fig.-1: *Bilateral ptosis with external ophthalmoplegia (lateral rectus, inferior oblique, superior rectus palsy).*

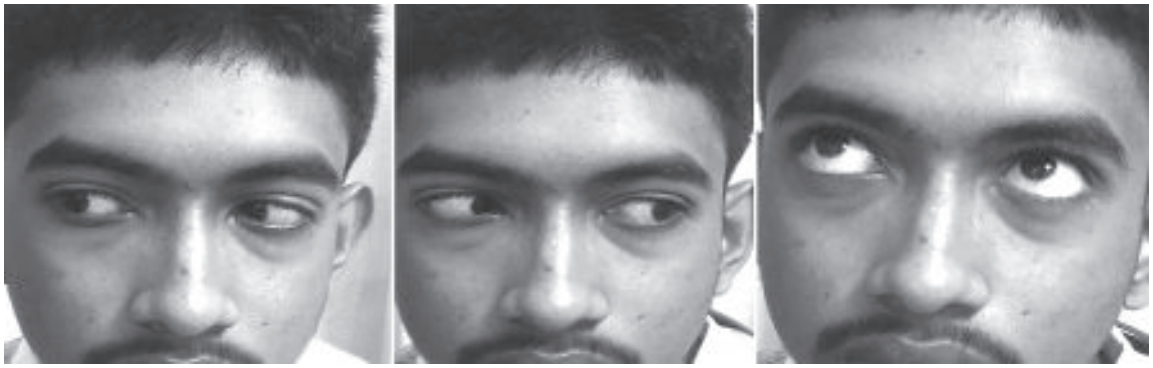

Fig.-2: *After recovery all EOM works with full range of motion (30 days after event).*

Discussion:

Miller-Fisher syndrome (MFS) is known for the characteristic triad of opthalmoplegia, ataxia, and areflexia without overt sensory deficits. It is considered a variant of GBS, which is also known as acute idiopathic neuritis. An increasing body of evidence sug-gests that a rather wide range of neurological features may be present and significant overlap exists in MFS and other forms of GBS. MFS accounts for one to five percent of all GBS cases in Western countries, but 19% and 25% in Taiwan and Japan, respectively [2]. MFS is twice as common in men as women 8. It affects people of all ages, with the median age of onset being in the fifth decade [8]. MFS presents commonly with diplopia (78%), ataxia (48%), and both (34%). The less frequent symptoms consist of limb dysesthesia; blepharoptosis; face, bulbar, and pupillary palsies; mild (grade 4) motor weakness; and micturition disturbance [2]. These clinical signs are preceded by signs of upper respiratory tract infection in 56–76% of the patients. The most common pathogens are Campylobacter jejuni and Haemophilus influenzae. However, Mycoplasma pneumoniae and cytomegalovirus are also found to be associated. MFS onset is typically acute, beginning with neurologic symptoms approximately 8–10 days (range of 1–30), following the antecedent illness [2,3]. The disease then progresses until a clinical nadir is reached approximately a week (range of 2–21) after the initial neurologic symptoms [2]. A diagnosis of MFS can be made with compatible clinical history taking, cardinal symptoms, normal findings on CT or MRI, and presence of albuminocytologic dissociation in the CSF of affected patients. Anti-GQ1b antibodies, which act against GQ1b (a ganglioside component of nerves), blocks acetylcholine release from the motor nerve terminals. It relates to the disease activity and can be used as a diagnostic marker in MFS [6]. It is not unique to MFS, but helps in serological confirmation to allow for more definite diagnostic certainty in the presence of confounding symptoms. Kusunoki et al found 5 patients with a variant form characterized by ataxia but no ophthalmoplegia in 149 patients who had the IgG anti-GQ1b antibody without profound weakness. These cases could fit with autoimmune ataxic neuropathy, having pathological lesions mainly in the dorsal root ganglion. GD1b antibody plays the key pathogenic role in autoimmune ataxic neuropathies. Because of the existence of cross-reactivity between GQ1b and GD1b, it is thought that the pathogenesis of this form is similar to that of MFS [9].

Numerous case reports and series of patients with MFS treated with immunotherapy [generally plasma exchange, intravenous immunoglobulin G (IVIG) or a combination including one of these] have been reported. Analysis of the largest MFS case series failed to show any beneficial effects in the group who had received plasmapheresis when compared with the group who received no immunotherapy [10]. Furthermore, in a recent randomized trial of patients with GBS, the addition of intravenous methylprednisolone with IVIG did not confer any additional effect on recovery from disability at 4 weeks, when compared with that of IVIG therapy alone [11]. MFS is generally regarded as a self-

limiting, benign condition. All of 28 untreated MFS patients in the largest published case series returned to normal activities 6 months after the neurological onset. The respective median (range) periods between neurological onset and the disappearance of ataxia and ophthalmoplegia were reported as 32 (8-271) and 88 (29-165) days. However, cases progressing to respiratory failure and requiring mechanical ventilation have also been described, particularly in children. Other serious complications reported include coma, ballism, cardiomyopathy from dysautonomia, lactic acidosis, and pain [3].

Differential Diagnosis of Opthalmoplegia, Ataxia, and Areflexia [12]

Opthalmople-gia caused by MFS is often rapid in onset compared to a more gradual course in chronic diseases such as myotonic dystrophy, thyroid eye disease, and myasthenia gravis. More than 50% of patients with MG present with ptosis and/or diplopia. The weakness of the ocular muscles may switch from one eye to another and improve or worsen over the course of a day, unlike MFS which progressively worsens until the nadir of symptoms has been reached before any recovery is seen. Ataxia can be seen in many conditions, often affecting the cerebellum, the spinocerebellar tracts, or the proprioception channels in peripheral nerves and dorsal columns. Cerebellar ischemia occurs due to compromise of the posterior circulation and often presents with non-specific symptoms of unsteady gait, dizziness, headache, eye movement dysfunction, as well as nausea and vomiting. Though both MFS and vascular compromise are acute events, ataxic patients with MFS typically lack lateralization of ataxia which helps to differentiate MFS from the majority of cerebel-lar lesions. Toxins and medications also have the capability of inducing acute onset ataxia. Sodium channel modulators such as phenytoin and chemotherapeutic agents such as fluorouracil can precipitate ataxic episodes. Arguably the most frequent cause of ataxia, alcohol consumption, mostly affects the lower extremities and is also associated with poor fine motor control of the hands, slurred speech, and impaired vision. The natural history of MFS is progression of weakness in a “head down” fashion, whereas the initial symptom would not be weakness and ataxia in the lower extremities. Often alcohol consumption can be determined through the patient’s history or urine toxicol-ogy screen. Areflexia is indicative of a lower motor neuron deficit, which would not be seen in many of the conditions affecting the central nervous system. Paradoxically, patients with spinal shock—seen in transection or compression of the spinal cord—are areflexic or hyporeflexic in the subacute stage of the disease, which then progresses to hypereflexia as the pathology evolves. Peripheral neuropathy, seen most often in diabetics and malnourished individuals, can lead to areflexia in severe cases. Anterior horn cell destruction, seen in polio and amyotrophic lateral sclerosis (ALS), will leave patients areflexic as well. Like MFS, spinal shock is an acute condition, while ALS typically has a gradual onset. Temporary paralysis and areflexia similar to that of MFS and Guillain-Barre can also be due to poliovirus infection, with functional recovery occurring 4-6 weeks after paralysis. Our case describes a patient who presented with quadriaresis, diplopia and ataxia. On examination he was dysdi-adochokinetic, dysmetric, and severely ataxic, with prominent opthalmoplegia. Our top differential for this clinical scenario included Brainstem encephalitis, Brainstem stroke, MG, and Miller Fisher variant of GBS. A clinical triad of ataxia, areflexia, ophthalmoplegia and high protein count in his CSF with albuminocytological dissociation were consistent with MFS variant of GBS, as was the favorable response with conservative management and his gradual recovery to improved function.

Conclusion:

Although uncommon, MFS is an important diagnosis to make since the presenting symptoms of ataxia and ophthalmoplegia may confuse the clinician and suggest an upper motor neuron sign or central cause. The presence of additional neurological symptoms may make clinical evaluation more challenging. Therefore, high clinical suspicion is needed to diagnose Miller Fisher Variant of Guillain-Barré Syndrome because all symptoms may not appear at the same time. It is necessary to rule out other clinical conditions with rapid onset of

ophthalmoplegia and ataxia, such as brainstem stroke, Wernicke's encephalopathy, Bickerstaff brainstem encephalitis and also other acute painful ophthalmoplegias such as bilateral cavernous sinus thrombosis, Tolosa-Hunt syndrome and superior orbital fissure syndrome before the clinical diagnosis of MFS in Primary health care setups.

Conflicts of interests: None

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