# Miller Fisher Syndrome: A Case Report Highlighting Heterogeneity of Clinical Features and Focused Differential Diagnosis

Ilya V. Yepishin DO; Randall Z. Allison MSIV; David A. Kaminskas MD; Natalia M. Zagorski MD; and Kore K. Liow MD

## Abstract

*Miller Fisher Syndrome (MFS) is a rare variant of Guillain-Barré Syndrome (GBS) that has a geographically variable incidence. It is largely a clinical diagnosis based on the cardinal clinical features of ataxia, areflexia, and opthalmoplegia, however, other neurological signs and symptoms may also be present. Serological confirmation with the anti-GQ1b antibody is available and allows for greater diagnostic certainty in the face of confounding symptoms. A self-limiting course is typical of MFS. The following case report is that of a patient who presented with generalized weakness, somatic pain, inability to walk, and diplopia following an upper respiratory illness. The patient exhibited the classic triad of ataxia, areflexia, and opthalmoplegia characteristic of MFS, but also had less typical signs and symptoms making for a more challenging diagnostic workup. Our suspected diagnosis of MFS was serologically confirmed with positive anti-GQ1b antibody titer and the patient was successfully treated with Intravenous immune globulin (IVIG).*

## Introduction

The triad of ataxia, areflexia, and opthalmoplegia was first described by James Collier in 1932. It was subsequently reported as a variant of Guillain-Barré Syndrome (GBS) by Charles Miller Fisher in three clinical cases in 1956.[1] Fisher recognized both the uniqueness of this cluster of clinical signs and its relationship to what is now considered a heterogeneous group of immune-mediated neuropathies classified under Guillain-Barré Syndrome.[1-3] Aptly named, 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.[4] There is an established 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.[2,5] As in GBS, an antecedent infectious illness can be identified in the majority of MFS cases. *Campylobacter jejuni* and *Haemophilus influenza* have been the most commonly implicated pathogens; however, multiple others are also associated, including *Mycoplasma pneumonia,* and *cytomegalovirus*. Upper respiratory infection is the most commonly described prodromic entity, followed by gastrointestinal illness.[2,4]

Unlike the classic ascending weakness or paralysis that is characteristic of the more typical types of GBS, neurological deficits follow a top down pattern in MFS, starting with diplopia in the eyes; caused by external opthalmoplegia—the most common presenting symptoms.[4,5] In a clinical series of 50 consecutive cases of MFS in Japan it was discovered that 78% of cases presented initially with diplopia, 46% with ataxia, and 34% with both. Other abnormalities reported, albeit less frequently, were limb dysethesia; blepharoptosis; face, bulbar, and pupillary palsies; mild (grade 4) motor weakness; and mictruition disturbance.[4]

An acute onset is typical of MFS, beginning with neurologic symptoms approximately 8-10 days (range of 1-30) following the antecedent illness.[2-4] The disease then progresses until a clinical nadir is reached approximately 6 days (range of 2-21) after the initial neurologic symptoms.[4] The recovery period is marked by gradual improvement and often resolution of symptoms; although rarely, serious complications such as respiratory failure or cardiac arrhythmia (that are common in GBS, with 30% of cases requiring ventilator support) have been reported.[2] Ataxia and opthalmoplegia resolve within 1-3 months after onset and near complete recovery is expected within 6 months.[4] Areflexia may persist, but is not associated with functional disability.

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. 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.[6]

Despite its rarity, MFS has played an important role in understanding the pathogenesis of immune-mediated neuropathies, which is thought to involve molecular mimicry incited by antecedent infection.[6-8] Chiba, et al, first reported the presence of anti-GQ1b antibodies in strong association with MFS in 1992.[9] 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.[7,8] The following case presents key clinical features of MFS and offers a discussion of focused differential diagnoses, anti-GQ1b antibody test, prognosis, and available treatments. Familiarity with this rare syndrome will clue the clinician to consider MFS in patients presenting with areflexia, ataxia, and ophthalmic symptoms.

## Case Report

A 50-year-old part-Hawaiian man presented to the emergency department (ED) with a principal complaint of generalized weakness. An emergency medical response unit had been summoned to the patient's home; upon arrival he was found lying on the couch, weak, and unable to ambulate. Recent history revealed that he had been to the ED earlier that day and was able to ambulate with some difficulty at that time. He had also been to another ED twice in the preceding three days. During those

visits he had complained of myalgias, weakness, and malaise. Further history revealed that the patient had been feeling ill with a tactile fever, sore throat, cough, and a runny nose three days prior to the onset of the presenting symptoms. The patient had not received a current influenza vaccination; however, he tested negative for rapid influenza A and B. Therefore, based on clinical evaluations, he was diagnosed with a viral syndrome and treated with analgesics and intravenous fluids.

A neurological consultation was conducted in the ED. The patient's additional complaints included diplopia that had started three days prior followed by a discomforting stiffness in his back, numbness in his mouth, and loss of taste. He then developed weakness in his arms, followed by his legs, and generalized achiness with movement. By the time of the evaluation he had progressed to generalized weakness and an inability to walk.

The patient's past medical, surgical, and family histories were largely non-contributory. He was residing in a group home and was a recovering methamphetamine and marijuana user with last use being 2-3 years prior to presentation. He worked in a restaurant kitchen.

Upon physical examination his vital signs were in the normal range. The patient was observed to be in a moderate level of discomfort, preferring to keep his eyes closed and occasionally moaning. Despite this, he was fully alert and oriented with an intact memory and no loss of his ability to communicate other than a delay in and mild slurring of his speech. Neurological examination revealed marked opthalmoplegia with severe abduction palsy, prominent nystagmus on lateral gaze, and bilateral ptosis. His facial muscles were symmetrical without evidence of seventh cranial nerve deficit. There was marked pronator drift with the patient's arms bowing up and down in a pendulous fashion. He displayed significant dysmetria on finger-to-nose and alternating movements testing; this was less pronounced on heel-to-shin testing. A global areflexia was present, and muscle strengths testing revealed fairly symmetrical mild weakness of all extremities, at the grade of 4 out of 5. His sensory examination was normal. The patient was not able to walk.

Laboratory testing revealed normal complete blood count, comprehensive metabolic panel, thyroid stimulating hormone, and cardiac markers. Urine toxicology screens (collected on two separate ED visits) were negative for common substances of abuse. There was no elevation in erythrocyte sedimentation rate, C-reactive protein, or creatine kinase; HIV and RPR serologies were negative. Of note, laboratory investigations for some of the more commonly implicated pathogens in MFS (*Campylobacter jejuni* ,*Haemophilus influenza*, *Mycoplasma pneumonia,* or *cytomegalovirus* ) were not undertaken. A lumbar puncture was performed and revealed cytoalbuminologic dissociation in the CSF with normal cell counts and a mildly elevated protein count of 61.2 mg/dL.

Imaging studies were obtained of the patient's chest and brain. The chest radiograph showed no evidence of acute or chronic disease processes. Contrast enhanced brain magnetic resonance imaging did reveal an incidental ectopic posterior pituitary gland that sat overlaying the anterior pituitary gland. It also revealed mildly thickened mucosal tissue in the left maxillary sinus indicating sinus disease; otherwise, the study appeared normal without areas of contrast enhancement or parenchymal abnormalities.

The patient was admitted to the telemetry unit for additional evaluation and treatment. His condition continued to worsen during the initial days of his hospitalization with more pronounced opthalmoplegia, persistent weakness, and somatic discomfort. On the second hospital day the patient developed urinary retention requiring straight catheterization; this was indicative of dysautonomia in the presenting clinical scenario. Treatments for the likely conditions were initiated promptly. Because of the ataxia, areflexia, and history (albeit remote) of substance abuse, there was a concern for Wernicke's encephalopathy, and the patient was started on intravenous thiamine (500mg every 8 hours). One would expect a rapid response to treatment in this case; however, this was not observed. The other two main competing diagnoses at this time were an atypical presentation of Myasthenia Gravis (MG) or MFS. Tests were ordered to look for antibodies that would support or refute each of these diagnoses; meanwhile, decisions to start further treatment trials were made based on the patient's worsening symptoms. Continuing with the thiamine infusions, the patient was additionally given a cholinesterase inhibitor, Pyridostigmine, orally (60mg every 8 hours) to treat for possible MG; however, after three doses the patient did not show any clinical improvement. Lacking the expected clinical response in a case of MG, the Pyridostigmine was discontinued. The patient was subsequently treated with intravenous immune globulin (IVIG) for five days to treat for possible MFS. Serum antibody test results eventually refuted MG as a diagnosis, but were positive for GQ1b IgG—confirming the diagnosis of MFS.

While treatment with IVIG was initiated early in the patient's hospital course, the initial worsening of his condition prompted further workup looking for paraneoplastic maladies that may occasionally be the presenting symptoms of advanced cancer. A panel of paraneoplastic antibodies was negative, and a computed tomography scan of visceral organs failed to show suspicious lesions. The nadir of the patient's symptoms was reached by the sixth hospital day. Physical, occupational, and speech therapy specialists were working daily with the patient and he began to exhibit steady improvement. He was able to ambulate with assistance by the eighth hospital day, and on the ninth day he was discharged from the acute hospital to an inpatient rehabilitation facility.

Outpatient follow-up one month from the hospitalization revealed that the patient was doing very well with a nearly 80% improvement in his symptoms. He was ambulating with a cane and reported resolution of somatic discomfort. His ocular symptoms, which were the first symptoms to come on, had been the slowest to resolve.

## Discussion

Miller-Fisher syndrome 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 suggests that a rather wide range of neurological features may be present and significant overlap exists in MFS and other forms of GBS. MFS seems to more notably affect the peripheral nervous system, yet evidence of central elements has also been reported. It is interesting to note that our patient exhibited many of the atypical abnormalities through the course of illness. Although the defining features of ataxia, opthalmoplegia, and areflexia are generally required for the diagnosed as MFS, other symptoms and signs may be present and confound a clinician's diagnostic decision making.

The GQ1b ganglioside complex is most often associated with MFS, positive in over 90% of patients with MFS and is not present in unaffected individuals.[3] The GQ1b autoantibodies, which target the epitopes that are abundant on cranial nerves III, IV, and VI are thought to give rise to the characteristic opthalmoplegia of MFS. This antibody, however, is not unique to MFS and has been characterized in other conditions resulting in what some experts have designated as an "anti-GQ1b antibody syndrome" known for both central and peripheral nervous system deficits. Though not intended to be used as a clinical diagnosis, this syndrome is useful for recognizing the symptom cluster and perhaps providing rationale for using established treatments for GBS in other conditions.[8]

## Differential Diagnosis of Opthalmoplegia, Ataxia, and Areflexia

Other disease processes are known to cause opthalmoplegia, ataxia, and areflexia, though often not in concert. Opthalmoplegia 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.[10,11]

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.[12] As other authors have pointed out, presentation of MFS can be confused with an ischemic event.[13,14] 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 cerebellar lesions.[12] Toxins and medications also have the capability of inducing acute onset ataxia.[15] 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 though the patient's history or urine toxicology 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.[8]

Our case describes a patient who presented with diplopia and ataxia following an upper respiratory illness. He also had confounding symptoms of myalgias, dysesthesias, weakness, and bulbar muscle dysfunction. On examination he was dysdiadochokinetic, dysmetric, and severely ataxic, with prominent opthalmoplegia. Autonomic dysfunction was also expressed in the form of transient urinary retention. Our top differential for this clinical scenario included Wernickie's encephalopathy, MG, and Miller Fisher variant of GBS. A high protein count in his CSF and anti-GQ1b antibodies were consistent with MFS, as was the favorable response with five days of IVIG treatment and his gradual recovery to improved function.

## Conclusion

Although uncommon, MFS is an important diagnosis to make since the presenting symptoms of ataxia and opthalmoplegia 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. A keen clinician with a meticulous neurologic examination will stumble upon the findings of areflexia thus localizing the predominant lesion to the peripheral nervous system. This should trigger an evaluation for demyelinating disorders and lead to confirmation of MFS as the diagnosis with the presence of GQ1b autoantibodies. MFS should be included in the differential diagnosis of anyone presenting with central findings of ataxia, areflexia, and opthalmoplegia.

## Conflict of Interest

None of the authors identify a conflict of interest.

Authors' Affiliations:
- Family Medicine Residency Program, John A. Burns School of Medicine, University of Hawai'i, Honolulu, HI (IVY)
- John A. Burns School of Medicine, University of Hawai'i, Honolulu, HI (RZA)
- Hawai'i Pacific Neuroscience, Honolulu, HI (DAK, KKL)
- Castle Medical Center, Kailua, HI (NMZ)

Correspondence to:
Ilya Yepishin DO; 736 Hawaii Street, Apt. A, Honolulu, HI 96817;
E-mail: yepishin@hawaii.edu

## References

1. Fisher, CM. An unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia and areflexia) [abstract]. *N Engl J Med*. 1956;255(2):57-65.
2. Lo YL. Clinical and immunological spectrum of the Miller Fisher syndrome. *Muscle Nerve.* 2007;36:615-627.
3. Berlit P, Rakicky J. The Miller Fisher Syndrome. Review of the Literature. *J Clin Neuroothalmol.* 1992;12(1):57-63.
4. Mori M, Kuwabara S, Fukutake T, Yuki N, Hattori T. Clinical features and prognosis of Miller Fisher Syndrome. *Neurology.* 2001;56(8):1104-1106.
5. Snyder LA, Rismondo V, Miller NR. The Fisher Variant of Guillain-Barre Syndrome (Fisher Syndrome). *J Neuro-Opthalmol.* 2009;29:312-324.
6. Overell JR, Willison HJ. Recent developments in Miller Fisher syndrome and related disorders. *Curr Opin Neurol.* 2005;18(5):562-566
7. Willison HJ, O'Hanlon GM. The Immunopathogenesis of Miller Fisher Syndrome. *J Neuroimmunol.* 1999; 100:3-12.
8. Odaka M, Yuki N, Hirata K. Anti-GQ1b IgG antibody syndrome: clinical and immunological range. *J Neurol Neurosurg Psychiatry.* 2001;70:50-55.
9. Chiba A, Kusunoki S, Shimizu T, Kanazawa I. Serum IgG antibody to ganglioside GQ1b is a possible marker of Miller Fisher syndrome [abstract]. *Ann Neurol.* 1992;31(6):677-679.
10. Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. *Muscle Nerve.* 2008;37(2):141-149.
11. Anthony SA, Thurtell MJ, Leigh RJ. Miller Fisher Syndrome Mimicking Ocular Myasthenia Gravis. *Optom Vis Sci*. 2012 89(12):e118-e123.
12. Eldow JA, Newman-Torker DE, Savitz SI. Diagnosis and initial management of cerebellar infarction. *Lancet Neurol.* 2008;7(70):951-64.
13. Kozminski MP. Miller Fisher Variant of Guillain-Barre Syndrome: A Report of Case. *J Am Osteopath Assoc.* 2008;108(2):51-52.
14. Das PP, Biswash S, Karim E, et al. Miller Fisher Variant of Guillain-Barre Syndrome: A Case Report & Clinical Review. *BSMMU J.* 2012;5(1):69-71.
15. Wakerley BR, Yuki N. Mimics and chameleons in Guillain-Berre and Miller Fisher syndromes [published online ahead of print August 25, 2014]. *Pract Neurol*. doi: 10.1136/practneurol-2014-000937.