

# An atypical presentation of Miller Fisher Syndrome

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## Abstract

Miller Fisher Syndrome (MFS) is a variant of Guillain-Barré syndrome classically characterized by ophthalmoplegia, ataxia and areflexia. MFS is believed to be an autoimmune-mediated peripheral nerve disorder, often precipitated by a respiratory or gastrointestinal infection. MFS is associated with the presence of GQ1b antibodies. Early diagnosis and prompt immunotherapy have been shown to decrease permanent disability in patients with MFS. As the neurologic symptoms, signs and natural history of the disease are not fully understood, MFS can be a challenging diagnosis. Here we report an atypical presentation of MFS in a patient with subtle ataxia, profound ophthalmoplegia and facial diplegia, but with normal reflexes in the context of markedly elevated GQ1b antibodies.

## Keywords

Guillain-Barré syndrome; Miller Fisher Syndrome; GBS; MFS; Anti-GQ1b; neurology; neuro-immunology

## Abbreviations

MFS: Miller Fisher Syndrome; GBS: Guillain-Barré syndrome; IVIg: intravenous immunoglobulin; GAD65: glutamic acid decarboxylase 65

## Introduction

Miller Fisher Syndrome (MFS) is a rare variant of Guillain-Barré syndrome (GBS) which was first described in 1956 [1]. Clinically, MFS is characterized by the triad of ophthalmoplegia, ataxia and areflexia [1]. Similar to other forms of GBS, MFS is believed to be autoimmune-mediated, often triggered by a preceding respiratory or gastrointestinal infection one week prior to the onset of neurological symptoms [2]. Serologically, MFS is characterized by elevated GQ1b antibodies, which are present in >90% of patients [3]. Dense concentrations of GQ1b ganglioside are found in the oculomotor, trochlear and abducens nerves which may account for the pathophysiology of ophthalmoplegia in MFS [4]. We report a case of a 55-year-old man who presented with ataxia, near-total external ophthalmoplegia, but persistently normal reflexes with elevated GQ1b antibody titers. With this case report we demonstrate that serologically-confirmed MFS can present without all of the classically described triad symptoms.

## Case Presentation

A 55-year-old right handed man presented to our neurology clinic with nine days of progressive diplopia, gait instability and ptosis. The patient reported that he had a severe five-day diarrheal illness

three weeks prior to the onset of his neurologic symptoms. He reported that nine days ago he developed progressive unsteadiness on his feet over the course of one day requiring him to hold onto walls for support. Later that day he noticed drooping of both eyelids. The following day he developed diplopia and subsequently presented to an outside hospital for evaluation. The patient was admitted and told that his visual symptoms were secondary to bilateral extraocular muscle palsies of unclear etiology. He was discharged home after three days with instructions to follow up with an ophthalmologist. The patient presented to his ophthalmology appointment five days from symptoms onset and was immediately referred to our neurology clinic for evaluation.

On examination in clinic, the patient was alert and in no acute distress with intact cognition. Fundoscopic examination revealed no evidence of optic nerve pathology. His visual fields were full and his pupils were 4 mm bilaterally and briskly reactive to light. Examination of his extraocular movements revealed near-complete external ophthalmoplegia in all directions. The patient had bilateral ptosis (left greater than right) without fatigability. He also displayed facial diplegia (left greater than right) with forehead involvement. Facial sensation to light touch and pinprick were normal. Hearing, palatal elevation and tongue protrusion were normal.

Motor examination revealed normal bulk and tone throughout. Strength testing revealed 4/5 neck flexion, but otherwise the patient had full strength throughout. The patient displayed slight ataxia on finger-to-nose and heel-to-shin bilaterally. Sensation for light touch, position and pinprick was normal throughout. Deep tendon reflexes were symmetric and 2+ throughout, with downgoing toes bilaterally. Gait was slightly wide-based and ataxic, with inability to tandem gait.

The patient was admitted to our institution for further evaluation and management. Lumbar puncture revealed normal cell counts, protein and glucose levels, without evidence of infection or inflammation. 3T MRI brain with and without contrast revealed no evidence of structural brainstem or cranial nerve pathology. Electromyography and nerve conduction studies on date of admission revealed no evidence of neuromuscular junction disorder, demyelinating or axonal polyneuropathy. Further laboratory evaluation revealed no evidence of acetylcholine receptor antibodies, thyroid dysfunction or evidence of infection. The patient received a five-day course of intravenous immunoglobulin (IVIg) for presumed atypical presentation of MFS. During his admission, he demonstrated slight improvement in his ophthalmoplegia and ataxia. His facial weakness progressed to involve both sides of his face symmetrically and reached a nadir on hospital day three. He was discharged home after six days of hospitalization, with no appreciable deficit on reflex testing.

On follow up examination one week after discharge, the patient continued to show improvement in his ophthalmoplegia and facial weakness, with resolution of his ptosis and ataxia. His reflexes on follow up visit continued to be normal. Ultimately, serum studies revealed a high titer for ganglioside GQ1b antibodies (1:400, reference value < 1:100) and glutamic acid decarboxylase 65 (GAD65) antibodies (0.16 nmol/L, reference value ≤0.02). At follow up visit three months after discharge, the patient had near complete resolution of his ophthalmoplegia and no other neurologic deficits.

## Discussion

MFS and other variants of GBS prove to be challenging cases to diagnose. GBS and its variants

encompass a group of peripheral nerve disorders, each distinguished by their unique distribution of nerve involvement and underlying pathophysiology [5]. The reported incidence of GBS in western countries ranges from 0.89 to 1.89 cases per 100,000 person-years [6]. MFS has been estimated to account for 1-5% of these cases of GBS [2]. The symptoms of MFS typically peak at 1 week and improvement often starts at 2 weeks [2]. The onset of MFS frequently involves diplopia (78%), ataxia (46%) or both (34%) on the same day [2]. Interestingly, facial palsy has been estimated to occur in 32% of patients and worsens in 38% of these patients while their other neurological symptoms improve [2]. In a review of 194 patients with 1 or more clinical features of MFS and serum GQ1b antibodies present, 7 of these patients had ataxia and ophthalmoplegia with normal reflexes [7]. In this study, these patients were considered “unclassified” by the diagnostic clinical criteria for MFS, Bickerstaff's brainstem encephalitis or overlapping variants of these syndromes [7]. Similar to these previously unclassified cases, our present patient supports the notion that some individuals with MFS may not present with the classical triad of symptoms used to define MFS. Additionally, 34% of patients with MFS do not have cerebrospinal fluid albuminocytological dissociation, classically considered the hallmark of GBS [7] and notably absent in our patient.

A review of recent literature reveals other atypical presentations of serologically-confirmed MFS. Gupta and Liu describe a patient presenting with isolated ophthalmoplegia and anisocoria without ataxia or areflexia in the setting of elevated GQ1b and GAD antibodies [8]. Mori et al describe a patient with acute ataxia and areflexia, but no ophthalmoplegia, associated with GQ1b antibodies [9]. These cases along with our current one support the hypothesis that these conditions represent a spectrum of disorders, in which some or all of the clinical triad symptoms are present.

A common misconception is that patients with GBS have a good prognosis [5]. Approximately 18% of patients remain severely disabled and 5% die despite immunotherapy [10]. Early treatment with plasma exchange or IVIg significantly reduces disability, but has not been shown to reduce mortality [10]. Our present case highlights the need for high clinical suspicion in diagnosing and treating patients with MFS and other variants of GBS.

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