International Journal of Research in Medical Sciences
Kumar GP et al. Int J Res Med Sci. 2025 Mar;13(3):1295-1298
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20250703

Case Report

Beyond anti-GQ1b: unravelling atypical Miller Fisher syndrome

Gyan Prakash Kumar*, Shubhanshu Chandra Prasad, Anurag

Department of Medicine, Patna Medical College and Hospital, Patna, Bihar, India

Received: 12 January 2025
Accepted: 07 February 2025

***Correspondence:**
Dr. Gyan Prakash Kumar,
E-mail: kumargprakash530@gmail.com

ABSTRACT

Anti-GQ1b negative Miller Fisher syndrome (MFS) is an uncommon variant of the classic MFS, a condition that is typically characterized by a triad of ataxia, ophthalmoplegia and areflexia, often accompanied by the presence of anti-GQ1b antibodies. In patients with anti-GQ1b negative MFS, these characteristic clinical features are observed despite the absence of the hallmark antibodies, posing a diagnostic challenge. The pathophysiology underlying this variant remains poorly understood, though alternative immune mechanisms, such as the involvement of other ganglioside antibodies or T-cell mediated autoimmunity, are suspected. The absence of anti-GQ1b antibodies necessitates reliance on clinical presentation, neurophysiological evaluations, and the exclusion of other potential causes for diagnosis. Treatment strategies remain similar to those for the antibody-positive form, typically involving immunotherapies such as intravenous immunoglobulin (IVIG) or plasmapheresis. Recognizing anti-GQ1b negative MFS is essential for timely and effective management, as early intervention can improve patient outcomes despite the absence of the usual antibody marker. Further research is needed to elucidate the underlying immune mechanisms and refine diagnostic and therapeutic approaches for this rare variant of MFS.Here we are presenting case report of a 53 year old female presented with diplopia, unilateral ptosis, tingling sensation in all limbs and ataxia. The patient exhibited the classic triad of ataxia, areflexia and opthalmoplegia characteristic of MFS but negative anti-GQ1b antibody titre and the patient was successfully treated with IVIG.

Keywords: Miller Fisher syndrome, Ataxia, Ophthalmoplegia, Areflexia, Autoimmunity

INTRODUCTION

Miller Fisher syndrome (MFS) is characterised by triad of ataxia, areflexia and opthalmoplegia and was first described by James Collier in 1932. It was subsequently reported as a variant of GBS (Guillain-Barré Syndrome) 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 GBS.[1-3] Incomplete forms of MFS exist, including acute ataxic neuropathy without ophthalmoplegia and acute ophthalmoplegia without ataxia.[4,5] Anti-GQ1b is an antiganglioside antibody that is self-reactive to the GQ1b ganglioside component of a nerve and is present in about 85-90% of all patients with MFS.[6,7] In addition, the GQ1b antibody is strongly associated with oculomotor nerves lesion and hence can also be found in patients with prominent oculomotor weakness and GBS. The initial diagnosis of GBS is based on its clinical presentation. Lumbar puncture and cerebral spinal fluid (CSF) analysis of patients with GBS often reveals albumin-cytological dissociation. This describes an increase in CSF protein while cell count remains normal, that is, <5 cells/mm^3, and is initially present in about 50-66% of GBS patients following their first week of symptoms, and in ≥75% of patients in their third week.[4-9] Here we are presenting a rare case report of a 53 year old female presented with diplopia, unilateral ptosis, tingling sensation in all limbs and ataxia. The patient exhibited the classic triad of ataxia, areflexia and opthalmoplegia characteristic of MFS but negative anti-GQ1b antibody titre.

CASE REPORT

A 53-year-old female presented with complaints of diplopia, unilateral ptosis, tingling sensation in both hands spreading to whole body and inability to walk since 4 days. Patient was asymptomatic 4 days ago when she noticed double vision of each object and after 3-4 hours, she felt inability to open her left eye, then 3-4 hours later, she started experiencing of tingling sensation in both hands spreading to both upper limbs and lower limbs in next 3-4 hours and she also developed ataxia. She also gave history of cough and cold 15 days ago. She has history of hypothyroidism for last 11 years, Hypertension for last 5 years and type 2 DM (recently diagnosed), for which she was on regular medication and There was no history of recent vaccination, fever, loose stool and trauma.

On examination at presentation, she was conscious and oriented. Respiratory, cardiovascular and per abdominal examination were unremarkable. Nervous system examination revealed normal higher mental function, neck was soft and spine was in mid line with no deformity and tenderness, on cranial nerve examination revealed 3rd, 4th and 6th cranial nerve affected, pupil was dilated and fixed in both sides and ptosis present only in left eye, on motor examination revealed normal nutrition, tone and power (4+/5) but bilateral absent deep tendon reflexes, ataxic gait and sensory system examination was unremarkable.

On the basis of ophthalmoplegia, ataxia and areflexia, the patient was diagnosed as MFS and patient was admitted in ICU. Routine investigations (complete blood count, renal function test, liver function test, electrolytes, thyroid profile etc.) were all normal. MRI brain, CSF and nerve conduction study were also within normal limits. Her paraneoplastic profile and Anti Gq1b antibody report was negative.

Based on the above clinical findings, IVIG (2 gm/kg) given for 5 days and her ophthalmopleia disappeared on day 4 of IVIG therapy and ataxia also started improving and at time of discharge, her ophthalmoplegia completely disappeared and she was able to walk on her own support with mild ataxia. After 1 month of follow up, her ataxia completely disappeared and she is currently in good health state.

DISCUSSION

MFS is a rare, acquired neurological disorder that is considered a variant of Guillain-Barré syndrome (GBS). It is characterized by a distinct set of neurological symptoms, including ophthalmoplegia (paralysis or weakness of the eye muscles), ataxia (lack of coordination or balance), and areflexia (absence of reflexes). MFS is primarily caused by an autoimmune response, where the body's immune system attacks its own peripheral nervous system, particularly the nerves that control eye movements and balance.

Epidemiology

MFS is uncommon, accounting for approximately 1-5% of all GBS cases. It is typically seen in adults, although it can affect children as well. The disorder has a slight male predominance. It most frequently occurs after an infection, often a respiratory or gastrointestinal infection. The syndrome is more common in individuals of Asian descent, though it occurs worldwide.

Pathophysiology

The underlying cause of MFS is believed to be an immune-mediated attack on the peripheral nervous system, particularly the Schwann cells that insulate nerve fibers. This leads to demyelination of the affected nerves, disrupting normal transmission of electrical signals and causing the characteristic neurological symptoms.

Autoantibodies: In many cases, MFS is associated with antibodies against gangliosides, especially GQ1b, a ganglioside found on the surface of nerve cells. These antibodies are believed to contribute to the immune-mediated damage of the peripheral nerves.

Molecular mimicry: The condition often follows an infection, with bacterial or viral pathogens having molecular structures that resemble those of gangliosides, thereby triggering an autoimmune response.

Clinical features

MFS has a classic triad of symptoms:

Ophthalmoplegia (eye muscle weakness): This is often the first symptom, causing double vision or difficulty moving the eyes. Patients may experience ptosis (drooping eyelids) or trouble focusing on objects.

Ataxia: This refers to a loss of coordination, often manifesting as difficulty walking, maintaining balance, or performing fine motor tasks.

Areflexia: The absence of deep tendon reflexes, such as the knee jerk or ankle reflex, which is a hallmark of MFS.

While these are the defining features of MFS, other symptoms can include:

Facial weakness: Mild facial paralysis or weakness may occur in some patients.

Sensory disturbances: Numbness or tingling, though less common, can sometimes accompany the motor symptoms.

Respiratory involvement: Severe cases may involve difficulty breathing, though this is less common compared to classic GBS.

The onset of symptoms is often acute, with progression over a few days. Unlike GBS, which typically involves ascending paralysis starting from the lower limbs, MFS often presents with cranial nerve involvement first.

Diagnosis

The diagnosis of MFS is primarily clinical, based on the characteristic signs and symptoms. However, several tests can aid in confirming the diagnosis:

Lumbar puncture: Cerebrospinal fluid (CSF) analysis typically reveals albuminocytologic dissociation, meaning a high protein concentration with a normal white blood cell count. This finding is not specific to MFS but is common in GBS.

Serological testing: Detection of antibodies against GQ1b (anti-ganglioside antibodies) is a key diagnostic tool. The presence of these antibodies in the blood is strongly suggestive of MFS but the absence of antibodies does not rule out the disease completely.

Electromyography and nerve conduction studies: These tests can show evidence of peripheral nerve involvement and help differentiate MFS from other conditions.

MRI: Imaging may help rule out other conditions but is typically normal in MFS, as the disease primarily involves peripheral nerves.

Differential diagnosis

Several conditions may mimic the symptoms of MFS:

GBS: GBS, especially the acute inflammatory demyelinating polyneuropathy (AIDP) form, can also present with ataxia and areflexia. However, GBS generally starts in the limbs and progresses more widely.

Brainstem or cerebellar disorders: Lesions affecting the brainstem or cerebellum can lead to ataxia and ophthalmoplegia but would be associated with other neurological findings on imaging.

Myasthenia Gravis: This condition can cause ptosis and ophthalmoplegia, but it typically involves fatigability and improves with rest, which is different from the persistent weakness seen in MFS.

Stroke: A stroke involving the brainstem can lead to eye movement abnormalities and ataxia, but it would typically present with a focal neurological deficit, such as facial weakness or hemiparesis.

Management and treatment

There is no specific antiviral or antibiotic treatment for MFS. However, there are a number of therapeutic approaches aimed at modulating the immune response and relieving symptoms:

IVIG: This is the first-line treatment for MFS. It involves the administration of pooled human antibodies and helps reduce the autoimmune response that is damaging the nerves. IVIG has been shown to improve clinical outcomes in many patients.

Plasma exchange (Plasmapheresis): In some cases, plasmapheresis may be used to remove the circulating antibodies or immune complexes that are contributing to the disease process. This is generally reserved for more severe cases.

Supportive care: This includes monitoring of vital functions, especially respiratory function, in severe cases. Physical therapy may be required for rehabilitation and to help with coordination and muscle strength recovery.

Corticosteroids: The use of corticosteroids in MFS is controversial. They are generally not recommended as they have not shown consistent benefit in improving outcomes and could potentially delay recovery.

Prognosis

The prognosis for MFS is generally good, especially compared to more severe forms of GBS. Most patients with MFS show significant improvement within a few weeks to months, with many recovering completely. However, recovery can vary, and some patients may experience residual mild symptoms such as imbalance or eye movement difficulties.

Recovery: The majority of patients (about 85-90%) recover fully or nearly fully, with most improvements seen within the first 6 months.

Long-term complications: In rare cases, MFS can result in persistent mild ataxia or ophthalmoplegia, though these are usually not debilitating.

CONCLUSION

Anti-GQ1b negative MFS is a rare variant of MFS that presents with the classic triad of ataxia, areflexia, and ophthalmoplegia, but without the presence of anti-GQ1b antibodies typically associated with the disorder. The negative anti-GQ1b result suggests that the pathophysiology of this variant may differ from classic MFS, possibly implicating other immune mechanisms or autoantibodies. Diagnosis of anti-GQ1b negative MFS requires careful clinical evaluation, including neurophysiological studies, and may involve excluding other conditions with similar presentations. While treatment approaches such as IVIG or plasmapheresis are often effective, further research is needed to better understand the underlying mechanisms and optimize

management for patients with this rare and atypical presentation.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Kumar GP, Prasad SC, Anurag. Beyond anti-GQ1b: unravelling atypical Miller Fisher syndrome. Int J Res Med Sci 2025;13:1295-8.