

Received: 2026.07.08
Accepted: 2026.09.03
Available online: 2026.09.17
Published: 2026.XX.XX

e-ISSN 1941-5923
© Am J Case Rep, 2026; 27: e954763
DOI: 10.12659/AJCR.954763

An Approach to Acute Cranial Symptoms in Primary Care: Lesson From a Case of Miller Fisher Syndrome

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDEF 1 **Humaira Jasme**
EF 2,3 **Mimi Nashra Mohd Noh**
ADEF 1,3 **Aiza Nur Izdihar Zainal-Abidin** 

1 Department of Primary Care Medicine, Faculty of Medicine, Universiti Teknologi MARA Cawangan Selangor, Kampus Sungai Buloh, Sungai Buloh, Selangor, Malaysia
2 Department of Medicine, Hospital Al-Sultan Abdullah, Universiti Teknologi MARA Cawangan Selangor, Kampus Puncak Alam, Puncak Alam, Selangor, Malaysia
3 Hospital Al-Sultan Abdullah, Universiti Teknologi MARA Cawangan Selangor, Kampus Puncak Alam, Puncak Alam, Selangor, Malaysia

Corresponding Author: Aiza Nur Izdihar Zainal-Abidin, Department of Primary Care Medicine, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh Campus, Selangor, Malaysia
Financial support: None declared
Conflict of interest: None declared

Patient: Female, 38-year-old
Final Diagnosis: Miller Fisher syndrome
Symptoms: Diplopia • headache • perioral numbness
Clinical Procedure: Blood test • CT brain • lumbar puncture • nerve conduction study
Specialty: Family Medicine • Neurology
Objective: Challenging differential diagnosis
Background: Miller Fisher syndrome (MFS) is a rare variant of Guillain-Barré syndrome characterized by the classic triad of ophthalmoplegia, ataxia, and areflexia following a recent infection. Early recognition is particularly challenging due to the rarity of the condition and its tendency to mimic other common neurological and non-neurological disorders. We report a case highlighting the diagnostic and referral challenges encountered in the primary care setting.
Case Report: A 38-year-old woman with no significant comorbidity presented to a primary care clinic with acute diplopia, right eye pain, headache, and perioral numbness following an upper respiratory tract infection 2 weeks earlier. Initial neurological examination was unremarkable. She was referred to the ophthalmology and emergency departments to exclude ocular pathology and posterior circulation stroke. Laboratory investigation and computed tomography of the brain were unremarkable and she was managed as a case of migraine. Meanwhile, ophthalmological review subsequently demonstrated ophthalmoplegia and the following day she developed bulbar symptoms prompting urgent neurological consultation. Repeated neurological examination revealed the classic triad of MFS. She received plasma exchange therapy following her clinical deterioration. Her neurological symptoms gradually improved with complete recovery, with residual diplopia resolving 8 weeks after symptom onset.
Conclusions: MFS remains a predominantly clinical diagnosis with subtle and evolving features that may delay recognition in the primary care setting. This case underscores the crucial role of primary care physicians in maintaining a high index of suspicion, recognizing atypical presentation, and providing appropriate safety-netting and timely specialist referral to facilitate early diagnosis and improve clinical outcomes.
Keywords: Ataxia • Guillain-Barre Syndrome • Miller Fisher Syndrome • Ophthalmoplegia • Primary Health Care • Safety-net Providers
Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/954763>

 2515  1  1  22

Publisher's note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher



Introduction

Miller Fisher syndrome (MFS) is an uncommon immune-mediated peripheral neuropathy and a recognized subtype of Guillain-Barré syndrome (GBS), typically triggered by infection with various pathogens, including *Campylobacter jejuni*, *Haemophilus influenzae*, cytomegalovirus, Epstein-Barr virus, and human immunodeficiency virus (HIV). Although the precise pathophysiological mechanism remains incompletely elucidated, approximately half of cases occur following a recent infection, with nearly 2 out of 3 preceded by symptoms of upper respiratory tract infection or diarrhea [1]. Clinically, MFS is classically characterized by the triad of ophthalmoplegia, ataxia, and areflexia, with at least 2 of these features typically present at onset [2].

Ophthalmoplegia in MFS is believed to be due to the targeted effect of anti-GQ1b antibodies at the neuromuscular junctions of the cranial nerve supplying the extraocular muscle, leading to impaired ocular motor function. While anti-GQ1b antibodies are detected in approximately 70-90% of patients with MFS, an estimated 10-30% remain seronegative [2-4]. More than half of patients present with the complete triad, typically following an upper respiratory tract infection approximately 1 week before symptom onset, while a smaller proportion report preceding gastrointestinal infections [5]. Nevertheless, up to 30% of cases may present with atypical manifestations such as headache, delayed-onset facial palsy, divergence insufficiency in the absence of external ophthalmoplegia, or impaired taste sensation [6].

Although the tertiary management of MFS is well established, guidance addressing the diagnostic challenges encountered in primary care during the early phase of the disease remains limited. This case report provides a practical perspective by illustrating the potential value of continuity of care, serial clinical evaluation, safety-netting strategies, and timely specialist referral in facilitating the recognition of MFS despite an initial normal neurological examination. This case-based observation is intended to highlight clinical considerations rather than establish definitive diagnostic or management guidance.

Case Report

The patient, a 38-year-old woman with no significant past medical history, presented to a primary care clinic with a sudden onset of diplopia with progressive worsening of right eye pain, headache, and perioral numbness upon awakening on the day of presentation. She sought medical attention approximately 4 hours after symptom onset. On further history, she reported a 3-day history of right eye discomfort and redness prior to presentation, for which she had been self-medicating with ocular lubricants with minimal symptomatic relief. The

headache was localized to the occipital region, radiating to the neck, and was associated with dizziness described as unsteadiness on ambulation. The pain was described as non-specific headache. She also reported numbness involving the perioral region including jaw and tongue. Notably, she had recovered from an upper respiratory tract infection 2 weeks prior. She denied any current fever, cough, rhinorrhea, gastrointestinal symptoms, or constitutional complaints. There was no history of limb weakness, dysphagia, or dysarthria.

On examination, she was alert, oriented, and hemodynamically stable, with normal body temperature. She was able to ambulate independently with a normal gait. There was no facial asymmetry nor slurring of speech. Cranial nerve examination showed no obvious ophthalmoplegia and pupillary responses were normal. Motor examination revealed normal tone and full strength in all 4 limbs. Deep tendon reflexes were present and there were bilateral plantar flexor responses. Sensory examination was intact, and cerebellar signs were negative. Visual acuity was normal. In view of her ocular symptoms, an urgent referral to ophthalmology was made to exclude acute angle-closure glaucoma. A computed tomography (CT) scan of the brain was arranged and she was referred to the emergency department for further evaluation to exclude central causes such as transient ischemic attack or stroke.

Ophthalmological evaluation demonstrated impaired extraocular movement with a mild limitation of the lateral rectus muscle function. There was saccadic nystagmus noted on left lateral gaze. Alternating esotropia was observed with right eye fixation preference. These findings were suggestive of early ophthalmoplegia. The patient was subsequently scheduled for a follow-up ophthalmology assessment the following day. In the interim, during evaluation in the emergency department, she was managed as a case of migraine. Brain CT reported no significant abnormality. She received a stat dose of paracetamol with additional doses as required. Subsequently, she was observed overnight in the emergency department.

At her follow-up ophthalmology review the following day (fourth day of illness) her condition had worsened, and she was unable to complete further eye examination. She developed worsening headache and new onset of numbness over face and hands along with generalized body weakness. She also experienced an episode of choking while drinking water in the ophthalmology clinic. In view of her clinical deterioration and emerging bulbar symptoms, she was referred back to the emergency department for further neurological assessment and consultation. She was subsequently reviewed by the neurology team. Further neurological examination revealed generalized areflexia with preserved muscle tone and normal muscle strength in all extremities. Sensory examination demonstrated reduced sensation in a glove-and-stocking distribution. Cerebellar assessment

Table 1. Blood investigations.

Investigations	Result	Normal reference range
Full blood count	White blood cell count: $11.0 \times 10^9/L$	$4.0-10.0 \times 10^9/L$
	Red blood cell count: $4.9 \times 10^{12}/L$	$3.8-4.8 \times 10^{12}/L$
	Hemoglobin (Hb): 11.6 g/dL	12.0-15.0 g/dL
	Hematocrit: 35.9%	13.6-46.0%
	Mean cell volume: 73.6 fL	83.0-101.0 fL
	Mean cell hemoglobin: 23.7 pg	27.0-32.0 pg
	Platelets: $507 \times 10^9/L$	$150-410 \times 10^9/L$
C- reactive protein	7.7 mg/L	< 5 mg/L
Renal profile	Urea: 3.10 mmol/L	2.76-8.07 mmol/L
	Creatinine: 60 $\mu\text{mol}/L$	44-80 $\mu\text{mol}/L$
	Sodium: 139 mmol/L	136-145 mmol/L
	Potassium: 4.0 mmol/L	3.5-5.1 mmol/L
Serum electrolytes	Calcium: 2.23 mmol/L/ adjusted	2.15-2.50 mmol/L
	Calcium 2.24 mmol/L	0.81-1.45 mmol/L
	Phosphate: 0.93 mmol/L	0.66-1.07 mmol/L
	Magnesium: 0.88 mmol/L	0.65-1.05 mmol/L
Liver function test	Total protein: 74.3 g/L	64.0-83.0 g/L
	Albumin: 39.6 g/L	35.0-52.0 g/L
	Alanine transaminase: 15.8 U/L	0.0-35.0 U/L
	Alkaline phosphatase: 68 U/L	35.0-104.0 U/L
	Gamma-glutamyl transferase: 34.0 U/L	< 40 U/L
Thyroid function test	Free T4: 14.49 pmol/L	7.86-14.41 pmol/L
	Thyroid stimulating hormone: 1.75 mIU/L	0.38-5.33 mIU/L
HbA1c	5.1%	
Serum vitamin B12	256.0 pmol/L	133-675 pmol/L
Serum folate	17.9 nmol/L	7.0-45.1 nmol/L
Hepatitis B/C, HIV	Non-reactive	
Anti-ganglioside antibodies	All negative	

HIV, human immunodeficiency virus.

was positive with impaired tandem gait consistent with ataxia. Meningeal signs were not specifically assessed or documented during the neurological examinations, as the patient did not exhibit clinical features strongly suggestive of meningeal irritation. Instead, the neurological assessment was primarily focused on localizing the evolving neurological deficits. Given the presence of the classical triad of ophthalmoplegia, areflexia, and ataxia, a clinical diagnosis of probable MFS was made. The patient was subsequently admitted for further evaluation and close neurological monitoring.

A series of investigations was performed to support the clinical suspicion of MFS. However, the findings were inconclusive. Repeated attempts at lumbar puncture were unsuccessful, precluding cerebrospinal fluid analysis. Nerve conduction study did not demonstrate any abnormalities. In addition, anti-ganglioside antibody testing, including serum anti-GQ1b antibodies yielded negative results. Further laboratory evaluations (Table 1), including full blood count, renal profile, serum electrolytes, blood glucose, liver function test, and thyroid function test were all within normal limits. Inflammatory and infective

markers did not suggest any recent infectious process. Serum folate and vitamin B12 levels were likewise normal. Brain and spinal magnetic resonance imaging (MRI) were not performed during the admission, as the clinical findings were considered sufficient to support the diagnosis of MFS.

During her inpatient stay, she was managed conservatively under close neurological observation. No disease-specific treatment, including corticosteroids, antibiotics, or intravenous immunoglobulin, was initiated. On the third day of admission (seventh day of illness), her neurological condition deteriorated, with worsening lower limb weakness that necessitated ambulation with a walking frame. In view of her clinical deterioration, plasma exchange therapy was initiated and she completed 3 cycles of treatment. Concurrent supportive care was provided and an inpatient rehabilitation program focusing on lower limb strengthening was commenced. Subsequently, her condition gradually improved and she was discharged on the seventh day of hospitalization.

At the 2-week post-discharge review in the neurology clinic, the patient was clinically well with complete resolution of her neurological deficits. However, she reported persistent mild diplopia. Ongoing follow-up with the ophthalmology team was arranged for further assessment and monitoring. At subsequent ophthalmology review, her diplopia had completely resolved, approximately 2 months after symptom onset.

Discussion

MFS is an uncommon immune-mediated neuropathy and a well-recognized variant of GBS, classically characterized by the triad of ophthalmoplegia, areflexia, and ataxia. As part of the GBS spectrum of disorders, MFS typically follows a progressive clinical course, with neurological deficits evolving over several days [7]. This dynamic progression, coupled with its rarity, makes early recognition particularly challenging in primary care settings, where patients often present in the early stage with subtle signs before the complete triad becomes clinically apparent. Early symptoms may not be specific and may fluctuate over the time, leading clinicians to consider other common diagnoses such as migraine, viral illness, ocular pathology, posterior circulation stroke, myasthenia gravis, or microvascular cranial nerve palsy [8-11]. Previous reports have also highlighted the potential for MFS to mimic acute ischemic stroke, particularly posterior circulation infarct due to overlapping symptoms including dizziness, headache, diplopia, and gait instability [9,10]. Furthermore, incomplete presentations of MFS are well-recognized, with some patients lacking 1 or more components of the classic triad, particularly areflexia or ataxia during the early phase of illness [12-14].

At the initial presentation, migraine was considered because of the accompanying headache and eye pain in the absence

of objective neurological deficits. Given that diplopia and ophthalmoplegia were predominant presenting features, the patient was also evaluated by the ophthalmology team to exclude ocular pathologies, including acute angle-closure glaucoma, isolated cranial nerve III, IV, and VI palsies, and ocular myasthenia gravis. Posterior circulation stroke remained an important differential diagnosis owing to the acute onset of diplopia and dizziness. However, CT brain imaging demonstrated no significant abnormalities and the progressive evolution of symptoms over several days was less characteristic of an acute cerebrovascular event.

This case provides a primary care perspective on the diagnostic evolution of MFS, illustrating the challenges of recognizing the condition before the objective neurological deficits become clinically apparent. The patient initially presented with diplopia, eye pain, headache, and perioral numbness without ataxia or areflexia and her neurological examination was largely unremarkable. This reflects the progressive and evolving nature of MFS, in which the classic triad may evolve over several days, rendering a single clinical assessment insufficient to establish the diagnosis [12-14]. Accordingly, this case reinforces the importance of serial reassessment and safety-netting, particularly in patients presenting with acute cranial nerve symptoms, atypical sensory disturbances and a recent antecedent infection.

In this case, the diagnosis of MFS was established primarily on clinical grounds, as routine laboratory investigation and neuroimaging did not reveal any significant findings. This finding is consistent with previous reports indicating that neuroimaging is typically unremarkable in MFS and that up to 15% of cases may be seronegative for anti-ganglioside GQ1b antibodies despite having the disease [15]. Although cerebrospinal fluid analysis and MRI were unavailable, and ancillary investigations including nerve conductive studies and anti-GQ1b antibody testing were non-contributory, the diagnosis was considered clinically probable. The patient fulfilled the level 3 clinical diagnostic criteria for classic MFS as proposed by Wakerley et al, on the evolution of the characteristic triad of ophthalmoplegia, ataxia and areflexia following a preceding upper respiratory tract infection [16,17]. Nevertheless, the absence of cerebrospinal fluid analysis and neuroimaging limited supportive evidence and the exclusion of alternative diagnoses, highlighting the importance of serial clinical assessment, careful clinical judgement, and recognition of evolving neurological signs in establishing the diagnosis. At the initial assessment, the patient was diagnosed with migraine following inconclusive investigations, illustrating the diagnostic challenges associated with early stages of MFS.

However, the presence of atypical neurological features, particularly the combination of acute diplopia and perioral numbness

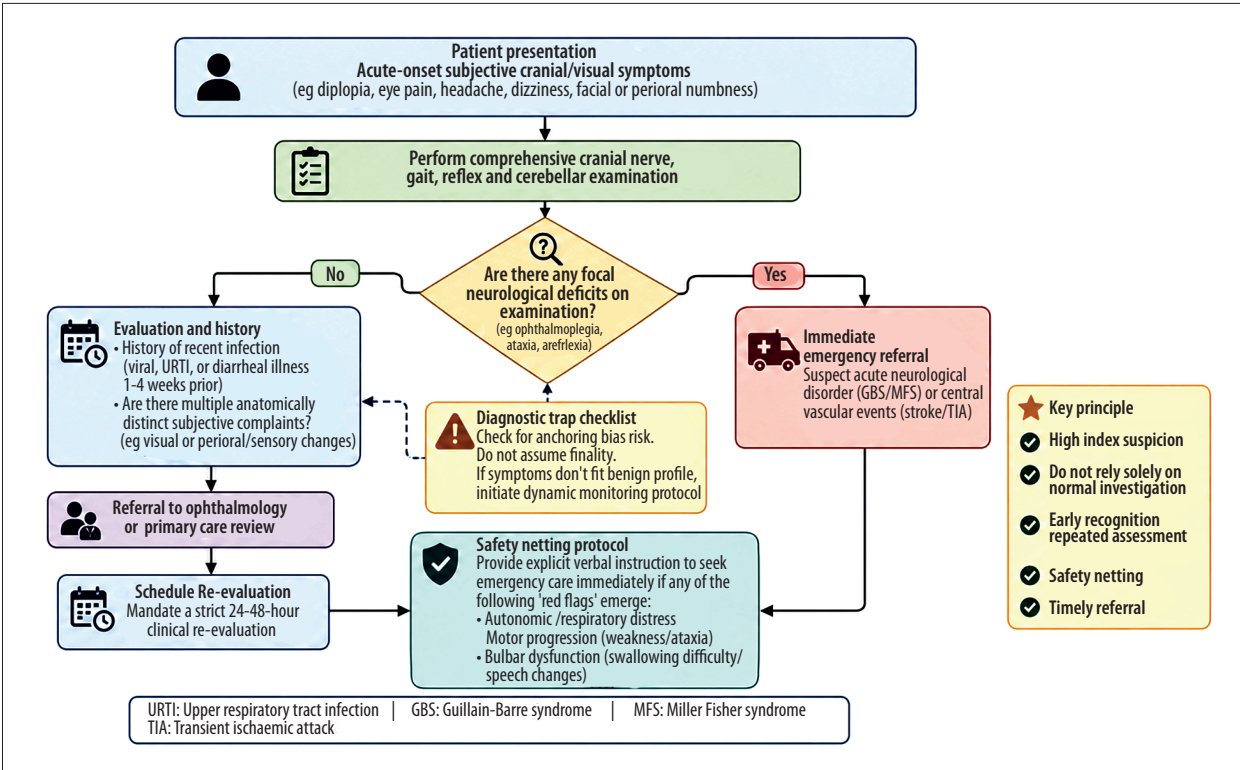


Figure 1. Proposed primary care diagnostic and safety-netting pathway for acute cranial neuropathies.

should prompt clinicians to consider alternative diagnoses when the clinical picture does not align with a benign condition. This case underscores an important lesson in primary care: that clinicians cannot rely solely on diagnostic testing to confirm their clinical suspicion, particularly in patients presenting with rare neurological disorders. Rather, careful clinical assessment, pattern recognition, and vigilance for evolving symptoms remain essential.

The added value of this case lies in highlighting the importance of primary care clinicians in identifying patients who require early escalation of care despite initially reassuring findings. The coexistence of acute diplopia, sensory symptoms, and a recent history of upper respiratory tract infection should raise suspicion for an evolving immune-mediated neuropathy, even in the absence of objective neurological deficits on the initial examination. Hence, it justifies the need for multidisciplinary collaboration, safety-netting, and repeat assessment even when the first neurological examination is unrevealing.

Although MFS is generally self-limiting and carries a more favorable prognosis compared with other GBS variants, with recovery typically occurring within 8-12 weeks, clinical deterioration may occur over several days, as demonstrated in this case [18]. Poor prognostic indicators include rapid progression, bulbar involvement, respiratory compromise, or overlap with classic GBS. Other GBS variants such as the pharyngeal-cervical-brachial

variant and Bickerstaff brainstem encephalitis should be considered in the differential diagnosis as they may present with facial, neck, and shoulder weakness accompanied by dysphagia, and can be associated with more severe clinical outcomes [19,20]. Close monitoring during the acute phase is also critical, particularly for respiratory function and autonomic instability. Early initiation of immunotherapy including intravenous immunoglobulin or plasma exchange is indicated in cases with significant progression, functional impairments, or overlap with GBS or its variants, and is associated with favorable outcome [7,21]. Although the effectiveness of these therapies is well established in specialist practice, this case demonstrates the contribution of primary care in recognizing clinical deterioration and facilitating timely referral to specialists before serious complications develop, thereby improving clinical outcome. Following plasma exchange therapy, the patient demonstrated gradual improvement with complete resolution of neurological deficits apart from mild residual diplopia, which resolved 2 months after symptoms onset, consistent with the typically favorable recovery trajectory of MFS [15,22].

Conclusions

MFS remains a predominantly clinical diagnosis that may initially present with subtle and evolving neurological features, particularly in the primary care setting. This case illustrates the

diagnostic uncertainty encountered when a patient presents with subtle symptoms and an unremarkable neurological examination. Rather than relying solely on the initial assessment and inconclusive investigations, clinicians should maintain a high index of suspicion in patients presenting with cranial neuropathies, especially in the context of a recent infection. Early recognition of atypical features, including cranial nerve symptoms and sensory disturbances, is essential as these may precede the development of the classic triad of MFS. Furthermore, distinguishing MFS from other causes, such as posterior circulation stroke, remains challenging and may require urgent investigation to exclude potentially life-threatening conditions. Importantly, this case does not advocate the initiation of disease-specific treatment based solely on clinical presentation. Rather, it emphasizes the importance of serial neurological reassessment, appropriate safety-netting, prompt recognition of evolving neurological deficits and red flag features, and timely specialist consultation or referral to facilitate early diagnosis and appropriate management, thereby improving clinical outcomes. In light of the diagnostic challenges illustrated by this case, we propose a triage flowchart for patients presenting with acute cranial nerve symptoms to assist primary care clinicians in identifying those who require urgent neurological evaluation and ensuring that appropriate safety-netting measures are implemented (Figure 1).

Acknowledgements

The authors wish to express their sincere gratitude to the patient for consenting to publication of this care report.

References:

- Kuwabara S. Guillain-Barré syndrome: Epidemiology, pathophysiology and management. *Drugs*. 2004;64(6):597-610
- Rocha Cabrero F, Morrison EH. Miller Fisher syndrome. StatPearls. Treasure Island (FL): StatPearls Publishing. Copyright© 2025, StatPearls Publishing LLC;2025
- Ueno T, Kon T, Kurihara AI, Tomiyama M. Unilateral oculomotor nerve palsy following campylobacter infection: A mild form of Miller Fisher syndrome without ataxia. *Intern Med*. 2017;56(21):2929-32
- Koga M, Gilbert M, Takahashi M, et al. GQ1b-seronegative Fisher syndrome: Clinical features and new serological markers. *J Neurol*. 2012;259(7):1366-74
- Yu H, Ding M, Cao Q, et al. Clinical features and differences of Miller Fisher syndrome in southern China: Retrospective analysis of 72 patients in 13 provinces of southern China. *J Clin Neurol*. 2023;19(6):589-96
- Jung JH, Oh EH, Shin JH, et al. Atypical clinical manifestations of Miller Fisher syndrome. *Neurol Sci*. 2019;40(1):67-73
- Bhatti KS, Maheshwary A, Sun CE. Guillain-Barre syndrome. StatPearls. Treasure Island (FL): StatPearls Publishing. Copyright© 2026, StatPearls Publishing LLC;2026
- Anthony SA, Thurtell MJ, Leigh RJ. Miller Fisher syndrome mimicking ocular myasthenia gravis. *Optom Vis Sci*. 2012;89(12):e118-23
- Edlow JA, Newman-Toker DE, Savitz SI. Diagnosis and initial management of cerebellar infarction. *Lancet Neurol*. 2008;7(10):951-64
- Yepishin IV, Allison RZ, Kaminskas DA, et al. Miller Fisher syndrome: A case report highlighting heterogeneity of clinical features and focused differential diagnosis. *Hawaii J Med Public Health*. 2016;75(7):196-99
- Robince C, Modi K, Park P, Norris T. Keys to an early diagnosis of Miller Fisher syndrome: A case of Miller Fisher syndrome masquerading as myasthenia gravis. *Cureus*. 2025;17(5):e84834
- Shoraka AR, Fang X, Hamouda D, et al. Ataxia and ophthalmoplegia: An atypical case of Miller Fisher syndrome (MFS) with anti-GAD antibody. *Int J Neurosci*. 2022;132(10):994-98
- Huang J, Lin L, Huang X, Yan X. Miller-Fisher syndrome presenting with headache and ophthalmoparesis: A case report and literature review. *Front Med (Lausanne)*. 2025;12:1575696
- Yuki N, Kokubun N, Kuwabara S, et al. Guillain-Barré syndrome associated with normal or exaggerated tendon reflexes. *J Neurol*. 2012;259(6):1181-90
- Noioso CM, Bevilacqua L, Acerra GM, et al. Miller Fisher syndrome: An updated narrative review. *Front Neurol*. 2023;14:1250774
- Wakerley BR, Uncini A, Yuki N, et al. Guillain-Barré and Miller Fisher syndromes—New diagnostic classification. *Nature Rev Neurol*. 2014;10(9):537-44
- Fokke C, van den Berg B, Drenth J, et al. Diagnosis of Guillain-Barré syndrome and validation of Brighton criteria. *Brain*. 2014;137(1):33-43
- San-Juan OD, Martínez-Herrera JF, Moreno García J, et al. Miller Fisher syndrome: 10 years' experience in a third-level center. *Europ Neurol*. 2009;62(3):149-54
- Nagashima T, Koga M, Odaka M, et al. Continuous spectrum of pharyngeal-cervical-brachial variant of Guillain-Barré syndrome. *Arch Neurol*. 2007;64(10):1519-23
- Odaka M, Yuki N, Yamada M, et al. Bickerstaff's brainstem encephalitis: Clinical features of 62 cases and a subgroup associated with Guillain-Barré syndrome. *Brain*. 2003;126(10):2279-90
- Mori M, Kuwabara S, Fukutake T, et al. Clinical features and prognosis of Miller Fisher syndrome. *Neurology*. 2001;56(8):1104-6
- Akoto A, Sain E. An atypical case of Miller Fisher syndrome. *Cureus*. 2024;16(11):e74212

Institution Where Work Was Done

Hospital Al-Sultan Abdullah, Selangor, Malaysia.

Informed Consent

Informed consent was obtained from the patient for publication of this case report.

AI Assistance Disclosure

The authors utilized ChatGPT (OpenAI), a large language model, to support language refinement, including improvement in grammar, clarity and overall readability of the report. ChatGPT was also used to reproduce the final version of Figure 1 based on the authors' original concept, design, and content. The AI tool was used exclusively for editorial assistance and did not contribute to the generation of clinical content, interpretation of findings, or scientific conclusions. All clinical information, case details, analysis, and discussion were independently developed by the authors. The authors critically reviewed, revised, and validated all AI-assisted text and assume full responsibility for accuracy and originality of the final report.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.