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Review Article

**AUTONOMIC NERVOUS SYSTEM INVOLVEMENT IN
PATIENTS WITH THE MILLER-FISHER VARIANT OF
GUILLAIN-BARRÉ SYNDROME: A REVIEW**Sundal Aziz¹, Usman Ghani², Hamza Asif³¹ Department of Medicine, Khyber Medical University, Peshawar, Pakistan[\(sundalkhan7@gmail.com\)](mailto:sundalkhan7@gmail.com)² Northwest General Hospital and Research Centre, Peshawar, Pakistan[\(ghaniusman13@yahoo.com\)](mailto:ghaniusman13@yahoo.com)³ Department of Medicine, Khyber Teaching Hospital, Peshawar, Pakistan[\(hamza9169@gmail.com\)](mailto:hamza9169@gmail.com)**Abstract:**

Background: The Miller-Fisher variant of Guillain-Barré syndrome (MFS-GBS) is a rare subtype of the autoimmune neuropathic disorder that is characterized by a unique clinical triad of ophthalmoplegia, ataxia, and areflexia. While the peripheral nervous system is primarily affected, there is growing evidence of autonomic nervous system (ANS) involvement in MFS-GBS.

Objective: This review aims to examine the frequency of ANS involvement in patients with MFS-GBS, exploring its clinical manifestations, underlying pathophysiology, and implications for diagnosis and management.

Methods: A comprehensive literature search was performed in electronic databases, including PubMed, Embase, and Google Scholar, using the keywords "Miller-Fisher variant," "Guillain-Barré syndrome," "autonomic dysfunction," "dysautonomia" and "autonomic nervous system." Articles published in English from inception to September 2022 were considered. Studies reporting on the frequency and clinical manifestations of ANS involvement in MFS-GBS were included. Relevant studies were identified and included in this review.

Result: The findings suggest that ANS dysfunction is uncommon in MFS-GBS, with various autonomic symptoms reported, including cardiovascular, gastrointestinal, and sudomotor dysfunctions. Early recognition and appropriate management of ANS involvement are essential for optimizing patient outcomes.

Conclusion: Further research is needed to better understand the mechanisms underlying ANS dysfunction in MFS-GBS and to develop targeted therapeutic interventions.

Keywords: Miller-Fisher variant, Guillain-Barré syndrome, autonomic nervous system, cardiovascular dysfunction, gastrointestinal dysfunction, sudomotor dysfunction

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INTRODUCTION:

Guillain-Barré syndrome (GBS) is an immune-mediated polyradiculoneuropathy characterized by rapidly progressive symmetric limb weakness, areflexia, and sensory impairments¹. GBS often results in the serious and common consequence of autonomic neuropathy. Studies on the long-term function of the autonomic system have shown that the autonomic dysfunction in GBS is temporary and may progressively get better². As signs of autonomic dysfunction, GBS patients may have cardiac arrhythmias, blood pressure changes, sweating problems, gastrointestinal disorders, and sphincter disturbances³. Previous studies found that tachycardia, bradycardia, hypotension, hypertension, and fluctuating blood pressure were among the clinically evident cardiovascular autonomic abnormalities that were present in 27–79% of GBS patients². According to studies, two-thirds of GBS patients experience signs of autonomic nerve damage⁴. GBS is brought on by lymphocyte infiltration in the autonomic nervous system's ganglion, hypothalamus, and brainstem, which kills intramural ganglion cells, inflames the ganglion, causes edema, and results in the lysis of nerve cells⁵. In addition, some reports indicate the presence of ganglioside autoantibodies, such as anti-GM1 antibodies⁶, which can result in excitation disorders of the sympathetic and parasympathetic nervous systems and hyper- or hypofunction of that systems⁷. The Miller-Fisher variant of GBS (MFS-GBS) is a distinct clinical subtype that comprises approximately 5-10% of all GBS cases. MFS-GBS presents with a unique triad of symptoms, including ophthalmoplegia, ataxia, and areflexia⁸. Lyu, Tang, Hsu, et al conducted a study on Nine patients with Fisher syndrome (FS) who underwent longitudinal quantitative cardiovascular autonomic function assessments. The Valsalva ratio and RR interval fluctuation were used to assess the parasympathetic autonomic function during deep breathing and rest. Blood pressure responses to sustained handgrip and vigorous standing were used to assess sympathetic autonomic function. Throughout the course of their disease, none of the individuals with FS had any clinical indications of autonomic dysfunction. However, up to 83% of FS patients had abnormalities in autonomic function. As a result, when compared to a quantitative autonomic function examination, bedside clinical symptoms of autonomic dysfunctions are insufficient for the assessment of autonomic abnormalities. The majority of autonomic function tests tended to improve after 4-12 weeks⁹. Although both sympathetic and parasympathetic processes were active at the worst of FS, parasympathetic fibers were more susceptible. In a rare instance, a patient with SARS-CoV-2 infection who acutely presented with

autonomic dysfunction was described by Biswas et al. The patient was ultimately determined to be a case of post-COVID-19 MFS with dysautonomia and anti-ganglioside antibody positivity, and the patient was treated with intravenous immunoglobulin with excellent results. Bulbar palsy and dysautonomia were identified in a retrospective cohort of 11 adult Miller-Fisher syndrome patients as potential indicators of a generally poor prognosis¹⁰. Two examples of MFS with cholinergic hypersensitivity and light-near dissociation were described by Keane¹¹. According to the author, the pupillary observations were produced by abnormal reinnervation of the iris sphincter muscles, which had been denervated as a result of a postganglionic parasympathetic lesion by the fibers to the ciliary muscles.^{11,12,13}

Autonomic Nervous System Involvement in MFS

The frequency of ANS involvement varies among different studies. This variability may be due to differences in patient populations, diagnostic criteria, and assessment methods. The frequency of autonomic nervous system involvement in Miller-Fisher syndrome can vary, and specific numbers may not be readily available¹⁴. Miller-Fisher syndrome is considered a rare variant of Guillain-Barré syndrome, and autonomic dysfunction is generally less common in MFS compared to other subtypes of GBS. However, some of the common clinical manifestations of ANS involvement are discussed here.

**Clinical Manifestations of ANS Involvement
Cardiovascular Dysfunction**

Cardiovascular autonomic dysfunction is an observed feature of ANS involvement in MFS-GBS. Patients may present with a wide spectrum of cardiovascular abnormalities, including tachycardia, bradycardia, orthostatic hypotension, and arrhythmias. These manifestations can lead to hemodynamic instability and require close monitoring and management.

Miller Fisher syndrome with reversible cardiomyopathy brought on by dysfunction of the autonomic nervous system is described by Oomura et al in their paper. Due to the fleeting nature of this cardiac condition and the lack of significant abnormalities in usual laboratory results, it is frequently overlooked. But a thorough cardiac examination that includes an ECG left ventriculography, and MIBG scintigraphy may help identify additional Miller Fisher syndrome cases that manifest this cardiac problem¹⁵. Placing a permanent pacemaker is one of the treatments for people with Guillain-Barre syndrome (GBS) or its variation Miller-Fisher syndrome (MFS) who have severe autonomic dysfunction. In a case of MFS with severe

bradycardia and asystole, Kordouni et al. describes the use of a transvenous, active fixation right ventricular lead as a "bridge" to permanent pacing in addition to an external permanent (temporary-permanent) pacemaker¹⁶. Cardiovascular problems are uncommon, yet there has previously been research between MFS and autonomic dysfunction. In a case report, Shiraiwa et al. describe sinus arrest due to autonomic dysfunction in a patient with MFS¹⁷.

Gastrointestinal Dysfunction

Patients with MFS-GBS very seldom experience gastrointestinal dysmotility. Anti-GM1 antibodies are one type of ganglioside autoantibody that can cause excitation problems of the sympathetic and parasympathetic nervous systems, as well as hyper- or hypofunction of both systems. Targeting the sensitive autonomic parasympathetic and sympathetic nerves that supply the GI tract might cause intestinal obstruction. Paralytic intestinal obstruction was probably the initial sign of MFS because Liu et al. indicated that the nerves innervating the gut were the first afflicted nerves in a case he documented¹⁸.

Sudomotor Dysfunction

Sudomotor dysfunction, characterized by abnormal sweating patterns in MFS is not reported much in the literature. However, Poudel et al in there study reported impaired skin sympathetic and cardiovascular autonomic function, which suggests autonomic nerve fiber involvement in MFS. Patients may present with either excessive sweating (hyperhidrosis) or reduced sweating (hypo hidrosis/anhidrosis)¹³.

Pathophysiology of ANS Involvement

The exact pathophysiological mechanisms underlying ANS involvement in MFS-GBS remain incompletely understood. It is hypothesized that the immune-mediated attack on peripheral nerves and ganglia may lead to inflammation and demyelination of autonomic fibers, resulting in autonomic dysfunction. Molecular mimicry and cross-reactivity of antibodies against gangliosides, particularly GD1b, have been proposed as potential triggers for autonomic involvement. The postganglionic sudomotor axon can be objectively evaluated by the quantitative sudomotor axon reflex test (QSART), which can assess autonomic dysfunction. Kuzumoto et al. performed QSART in 15 GBS or MFS patients to examine the relationship between antiganglioside antibodies and autonomic dysfunction, and they compared the severity of QSART with the findings of the antiganglioside antibody assay, which revealed a relationship between postganglionic sudomotor dysfunction and anti-GQ1b antibodies¹⁹.

DISCUSSION:

The autonomic nervous system (ANS) involvement in patients with the Miller-Fisher variant of Guillain-Barré syndrome (MFS-GBS) is an important aspect to consider in understanding the clinical manifestations, underlying pathophysiology, and implications for diagnosis and management of this rare subtype of the disease.

The findings of this review indicate that ANS dysfunction is uncommon in MFS-GBS. Various autonomic symptoms have been reported, including cardiovascular, gastrointestinal, and sudomotor dysfunctions. Cardiovascular dysfunction is a notable feature, with patients presenting with tachycardia, bradycardia, orthostatic hypotension, and arrhythmias. These abnormalities can lead to hemodynamic instability and require close monitoring and management. The presence of reversible cardiomyopathy in some cases further highlights the importance of comprehensive cardiac evaluation in MFS-GBS patients²⁰.

Gastrointestinal dysfunction is observed less frequently in MFS-GBS²¹. However, there have been reports of paralytic intestinal obstruction as an initial sign of MFS, suggesting the involvement of autonomic nerves that innervate the gut. This highlights the need for clinicians to consider gastrointestinal manifestations in MFS-GBS patients and assess for possible dysmotility²².

Sudomotor dysfunction, characterized by abnormal sweating patterns, is not extensively documented in the literature.

Early recognition and appropriate management of ANS involvement in MFS-GBS are crucial for optimizing patient outcomes. Clinicians should have a high index of suspicion for autonomic dysfunction in MFS-GBS patients and perform comprehensive assessments to identify and monitor autonomic symptoms. This may include cardiovascular monitoring, gastrointestinal evaluation, and assessment of sudomotor function. Treatment strategies should focus on supportive care and symptomatic management, with a multidisciplinary approach involving neurologists, cardiologists, and other relevant specialists.

Further research is warranted to better understand the mechanisms underlying ANS dysfunction in MFS-GBS. This includes studies investigating the role of specific antibodies, the inflammatory process, and the impact on autonomic nerve fibers. Additionally, the development of targeted therapeutic interventions for

managing autonomic symptoms in MFS-GBS patients is needed.

CONCLUSION:

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