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CLINICAL VIGNETTE

Miller Fisher Syndrome, a Guillain-Barre Variant

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Introduction

Miller Fisher Syndrome (MFS) is a clinical variant of Guillain-Barre syndrome (GBS), an acute, immune-mediated monophasic illness that is usually triggered by a preceding viral or bacterial infection. MFS is characterized by ophthalmoplegia, ataxia, and areflexia. It is commonly associated with lower cranial nerve involvement but tends to spare limb motor weakness.¹ We present a 54-year-old male who presented with facial paralysis, ophthalmoplegia, areflexia, and ataxia, and was diagnosed with Miller Fisher Syndrome.

Case Report

A 54-year-old male with no prior medical history presented to the emergency room with dysarthria and facial paralysis. Symptoms began after he developed a sore on his tongue and hard palate. After about three days, the patient developed headache, neck stiffness, visual changes, as well as phonophobia. Two days later, he noticed tongue-biting during meals and facial and lip numbness. This progressed to diplopia and worsening facial paralysis with inability to furrow his eyebrows and forehead, as well as difficulty moving his mouth, resulting in slurred speech. He reported disequilibrium and gait instability. On presentation, the patient was afebrile, pulse was 79, blood pressure was 154/82 and room air SpO₂ of 97%. He was sexually polygamous homosexual male with last sexual intercourse four days prior with a partner who had recently tested positive for an unknown sexually transmitted disease. The patient was admitted to the hospital for further evaluation, Neurology was consulted, and he underwent lumbar puncture with CSF cell count of 4, protein 52, and glucose of 90. Laboratory findings were notable for WBC of 12.8 with 87.5% neutrophils and 8.2% lymphocytes. Comprehensive metabolic panel was unremarkable and HIV screen was non-reactive. Physical exam was notable for bilateral lower motor neuron facial nerve palsy. He was unable to close his eyes, smile, or raise his brows. There was decreased sensation along V1-V3 bilaterally. Tongue was midline. No reflexes were elicited on biceps, triceps, patellar, or achilles tendons. Toes were down-going and gait was intact. Brain MRI with and without gadolinium revealed no acute intracranial pathology. His respiratory status was intact with tidal volume of 2.9L and negative inspiratory force (NIF) of -60.

The patient was diagnosed with Miller Fisher Syndrome, which was precipitated by a preceding herpes simplex infection transmitted via oral intercourse with a partner with likely genital HSV. He underwent plasmapheresis for five consecutive days

and started on valacyclovir. His symptoms gradually improved over the following weeks. He was seen in follow up two months after the hospital admission and was back to his prior baseline with no residual deficits.

Discussion

Guillain-Barre syndrome (GBS) is a category of acute immune-mediated polyneuropathies. The most common form is acute inflammatory demyelinating polyneuropathy (AIDP). Demyelinating neuropathies occur when Schwann cells are unable to appropriately conduct nerve impulses along axons. This can occur due to exposure to toxins, genetics, or can be immune-mediated.¹ In GBS antibodies to peripheral nerve myelin are detected in the serum. Declining titers of antibodies correlate with clinical improvement.² GBS occurs in 1-2/100,000 people,¹ usually in the setting of preceding bacterial or viral illness. It is characterized by onset of acroparesthesias, followed by weakness in a symmetric, ascending pattern, usually initially involving the distal legs and then progressing to the arms, though some present with initial arm weakness. This progresses to hyporeflexia, and facial nerve involvement. Severe cases may lead to severe flaccid quadriplegia, respiratory failure, and dysautonomia.^{2,3} Miller Fisher syndrome (MFS) is a rare subset of GBS that was reported by Charles Miller Fisher in 1956⁴ and has a worldwide prevalence of 1 in 1,000,000.^{1,4} The incidence is higher in Asian countries, where it can comprise 15-20% of GBS cases.⁵ Mean age of onset is 43.6 years, and it affects males double the rate in females.⁶ GBS/MFS is considered to be an immune response to a preceding infection. Pathogens include *Campylobacter jejuni* (reported in as many as 30% of GBS cases⁷), cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, as well as upper respiratory pathogens, including *Haemophilus influenzae*.^{1,5} However, in most cases, the culprit pathogen is unknown. In recent years, there have been reports of MFS following SARS-CoV2 (COVID-19) infection.⁵ A study demonstrated an increase of GBS in patients following COVID-19 infection. A systematic review reported 9 MFS variants in 99 cases of COVID-19 related cases of GBS.⁵ One patient developed MFS following BNT162b2 mRNA COVID-19 vaccination with symptom onset 7 days after vaccination was administered.⁸

MFS primarily affects CN III, IV, and VI and is associated with the triad of ophthalmoplegia (both internal and external), ataxia, and areflexia. MFS is caused by anti-GQ1b antibodies against

the neuromuscular junction between the cranial nerves and ocular muscles in CN III, IV, and VI.^{4,7} A clinical suspicion for GBS/MFS warrants a lumbar puncture. Cerebrospinal fluid analysis reveals an albuminocytologic dissociation, which is the combination of normal CSF cell count and elevated CSF protein count. This is seen in 80-90% of patients at peak disease, three weeks after symptom onset. However, specifically in MFS patients (and other variants of GBS with heavy ocular involvement), anti-GQ1b antibodies are found in the CSF.^{1,7} Brain imaging in MFS patients is usually normal. Electrodiagnostic studies usually reveal normal motor and sensory conduction.

MFS and GBS are treated mainly with supportive care and respiratory support, if needed. GBS is treated with immunotherapy (IVIG) vs plasmapheresis vs combination therapy in severe, refractory cases. Prognosis of MFS is usually good with 95% recovery, and immunotherapy/plasmapheresis is reserved for patients with severe cases that involve swallowing and respiratory difficulties and is most effective when given within two weeks of illness onset.^{1,2} Corticosteroids have no role in the treatment of GBS/MFS. In multiple randomized trials of patients receiving IVIG with IV methylprednisolone vs placebo, there was no statistically significant difference between the two groups² and corticosteroids are not recommended treatment of GBS/MFS. Symptom resolution varies with average recovery from ataxia within 35 days, ophthalmoplegia within 93 days, and areflexia with variable recovery.⁵ According to Noioso, et.al, patients were symptom free after an average of six months with no residual functional limitations.⁵

Conditions that mimic MFS with features of ataxia and ophthalmoplegia include brainstem (Bickerstaff) encephalitis, which also involves acute encephalopathy and hyperreflexia. Brain stem stroke, Wernicke's encephalopathy, myasthenia gravis, Lambert Eaton syndrome, and botulism are other conditions with overlapping clinical features of MFS.^{1,7}

Conclusion

MFS is a variant of GBS and occurs in 1 per 1,000,000, with a higher prevalence in younger males and Asians. It is often preceded by a viral or bacterial infection, the most commonly associated organism being *Campylobacter jejuni*. It is described as the triad of ataxia, ophthalmoplegia, and areflexia. Diagnosis is made with CSF analysis showing albuminocytologic dissociation as well as antibodies to anti-GQ1b. Radiologic studies are often grossly unremarkable, and electrodiagnostic studies usually reveal normal motor and sensory conduction. Treatment is centered around symptomatic management and IVIG/plasmapheresis in more extreme cases of GBS/MFS. Corticosteroids have no treatment role. This 54-year-old male with likely primary HSV infection transmitted via oral-genital contact was followed by onset of the triad of ataxia, ophthalmoplegia, and areflexia. CSF studies revealed albuminocytologic dissociation, however, anti-GQ1b Ab did not result due to laboratory error. This patient was treated with plasmapheresis and antiviral therapy. He achieved complete

resolution of his symptoms within two months with no residual deficits.

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