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CASE REPORT

A Unique Pediatric Case of Miller Fisher Syndrome

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Abstract

This case report introduces a 6-year-old male with a rare presentation of Miller Fisher syndrome (MFS), an autoimmune-mediated peripheral neuropathy. The patient exhibited acute-onset right facial weakness, asymmetric bilateral upper and lower extremity abnormalities, areflexia, and ataxia. He reported diplopia exacerbated by lateral gaze, gastrointestinal upset, and a constellation of other systemic symptoms. Examination revealed bilateral abduction limitations as well as right-sided cranial nerve palsy with associated exposure keratopathy. This case report discusses the clinical presentation, diagnosis, and management of MFS, emphasizing the importance of considering this rare variant of Guillain-Barré Syndrome (GBS) in pediatric patients with acute neurological and ophthalmic symptoms.

Keywords

Miller Fisher syndrome, Guillain-Barré syndrome, GQ1b, Cranial nerve palsy, Ataxia, Areflexia

Abbreviations

MFS: Miller Fisher Syndrome; GBS: Guillain-Barré Syndrome; ESR: Erythrocyte Sedimentation Rate; CRP: C-reactive protein; ANA: Antinuclear Antibody; MRI: Magnetic Resonance Imaging; CSF: Cerebrospinal Fluid; EOM: Extraocular Muscles; NMJ: Presynaptic Neuromuscular Junctions; IVIG: Intravenous Immunoglobulin; TNF: Tumor Necrosis Factor; COVID: Coronavirus; CNS: Central Nervous System; PNS: Peripheral nervous system; EMG: Electromyography

Introduction

Miller Fisher syndrome is a rare autoimmune disorder that primarily targets the peripheral nervous system. Although considered a variant of Guillain-Barré Syndrome (GBS), MFS presents with a characteristic triad: Ophthalmoplegia, ataxia, and areflexia [1-12]. These characteristic features distinguish it from the more familiar presentation of GBS, which typically involves ascending muscle weakness or paralysis [1].

Ophthalmoplegia is a hallmark sign for MFS. Internal ophthalmoplegia is common, and pupillary constriction may range from sluggish to absent [6]. Generally, the external ophthalmoplegia observed in MFS is bilateral and symmetrical, but rare unilateral cases have also been reported [4]. The related ocular motor deficit(s) can be consistent with isolated or combined involvement of cranial nerves III, IV, and VI [5]. Facial nerve pathology, which occurs in approximately 30% of patients, results in orbicularis oculi weakness and, consequently, lagophthalmos [4]. The most common presenting symptom is diplopia (65%) [1]. Other common symptoms of MFS include gait disturbance (32%), limb weakness (25%), and dysesthesias (14%) [1]. Less common signs and symptoms include altered consciousness, ptosis, bulbar dysfunction, dysphagia, photophobia, dizziness, blurry vision, headache, facial weakness, and micturition abnormalities [1].

MFS is quite rare, occurring in 0.09 per 100,000 people annually [5,13]. The condition affects all age groups; however, adults are more commonly affected [5]. Studies have reported a mean age of 43 years, with a range of 13 to 78.5. Males are twice as likely to develop the disease [11]. MFS occurs more often in the winter and spring seasons, likely due to the increase in associated infections [5]. The global incidence of GBS is 1 to 2 per 100,000. Interestingly, MFS is estimated to be 1 to 7% of GBS cases in the West, but as high as 15 to 25% in Asia [8]. The primary mechanism of MFS involves autoimmune-mediated peripheral neuropathy after

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exposure to a pathogen capable of molecular mimicry [1]. The diagnosis of MFS is primarily clinical after exclusion of alternative etiologies and is confirmed later by additional laboratory testing [14]. Understanding the unique clinical presentation of MFS, especially in pediatric patients, is crucial for timely diagnosis and intervention. This case report elucidates the clinical presentation, diagnosis, and management of MFS, highlighting the significance of considering MFS in the differential diagnosis for acute-onset neurological and ophthalmic symptoms.

Case Description

A 6-year-old Hispanic male presented with acute onset of right facial droop, bilateral upper and lower extremity weakness (more prominently right-sided), areflexia, and ataxia. The patient endorsed diplopia exacerbated by lateral gaze and frequent eye rubbing. He denied blurry vision, photophobia, fever, and respiratory symptoms. Review of systems was positive for GI symptoms, musculoskeletal pain, fatigue, urgency, and balance problems. Past medical history was significant for a recent episode of oral herpes, which had been appropriately treated with acyclovir.

The patient's visual acuity was 20/20 OU. His pupils were briskly reactive and equal. The patient had -1 abduction restriction in the right eye and -3 abduction restriction in the left. Intraocular pressure and confrontational fields were unremarkable. Examination revealed complete right-sided cranial nerve seven palsy with associated lagophthalmos and mild exposure keratopathy. Optic nerves appeared normal, without signs of swelling.

Blood tests revealed white blood cell counts within normal limits as well as mildly elevated platelets, monocytes, and creatine kinase. Kidney and liver function tests, urine analysis, drug screen, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and immunoglobulin levels (IgG, IgM, and IgA), did not reveal any significant abnormalities. Lyme screening was negative. Notably, the patient's stool tested positive for campylobacter, and respiratory PCR identified rhinovirus/enterovirus. Moreover, an antinuclear antibody (ANA) test was also positive.

The imaging workup included a magnetic resonance imaging (MRI) of the head which revealed intense symmetric enhancement along the third branches of the fifth cranial nerves, extending into the infratemporal fossa, as well as portions of the seventh nerves. There was no evidence of periventricular plaques or ventriculomegaly. Additionally, an MRI of the cervical, thoracic, and lumbar spine showed intense enhancement along the ventral nerve roots of the cauda equina.

A lumbar puncture was performed, but opening pressure could not be ascertained. However, the primary assessment did not indicate elevated intracranial pressure. Cerebrospinal fluid (CSF) culture revealed no growth, and the encephalitis panel returned negative results. Although the CSF analysis did not reveal albuminocytologic dissociation, the CSF was positive for oligoclonal bands and ganglioside GQ1b titer came back 1:800.

Based on the clinical findings and the extensive workup, the patient received a diagnosis of Miller Fisher syndrome (MFS), a rare autoimmune-mediated peripheral neuropathy. The Neurology team recommended a course of intravenous immunoglobulin (IVIG) therapy for five days. However, after receiving the initial IVIG dose, the patient developed severe myalgias, which did not respond to reduced doses. Consequently, the treatment plan was adjusted, transitioning the patient to a 500 mg dosage of intravenous methylprednisolone. Furthermore, frequent lubricating ointment was recommended during the daytime as well as eyelid taping at night to treat the patient's exposure keratopathy. After three days of steroid treatment, the patient reported significant improvements in pain and mobility.

At the patient's two-week ophthalmology follow up, there was no significant improvement in EOM. In fact, the patient had a new -2 superonasal restriction in the left eye. He also presented with a moderate esotropia at distance and near. The right-sided ptosis had improved to a MRD of 3 mm. Stereoacuity testing revealed 3000 seconds of arc, and the patients color vision via Ishihara test was unremarkable. Optical coherence tomography of the nerves did not show any degree of thinning. The patient's related signs and symptoms related finally resolved after approximately 14 weeks.

Discussion

Miller Fisher syndrome is a rare variant of Guillain-Barré Syndrome characterized by the unique triad of ophthalmoplegia, ataxia, and areflexia [9-12]. While MFS can present with a diverse range of symptoms, including diplopia and ophthalmoplegia, prompt diagnosis and appropriate management are crucial [1]. In this case, the patient was initially treated with IVIG, which resulted in severe myalgias. The patient's symptoms improved significantly with the administration of methylprednisolone, lubricating eye ointment, and eyelid taping. Clinicians should remain vigilant and monitor for complications, including chronic pain and, in rare cases, respiratory failure. This case underscores the importance of recognizing MFS, particularly in pediatric patients, and considering it as a differential diagnosis for acute-onset neurological and ophthalmic symptoms.

Many triggers of MFS have been identified. The most common causes are Campylobacter jejuni (21%) and Haemophilus influenzae (8%) [1]. A large majority of cases develop after recent upper respiratory infections [6]. Other infectious etiologies include Aspergillus, Coxiella burnetti, Epstein-Barr virus, Helicobacter pylori, group

A streptococcus, Pasteurella multocida, varicella zoster, and coronavirus (COVID) [1]. Autoimmune and neoplastic causes include thyroid disease, myasthenia gravis, Still's disease, systemic lupus erythematous, Burkitt lymphoma, Hodgkin's disease, chronic lymphocytic lymphoma, leptomeningeal signet cell carcinomatosis, and lung cancer [1]. Medication and vaccination etiologies include tacrolimus, tumor necrosis factor (TNF) alpha inhibitors, Stavudine, influenza vaccine, and Pneumovax [1]. The patient in our case study had many associated risk factors: Stool analysis positive for ***C. jejuni***, respiratory PCR identifying rhinovirus/enterovirus, and anti-nuclear antibody seropositivity.

The pathogenesis of MFS involves an autoimmune response through molecular mimicry, in which the immune system targets peripheral nerves, leading to the characteristic neurological deficits seen in MFS [1]. One distinctive aspect of MFS is the presence of anti-GQ1b antibodies in a large majority of affected individuals [10,11]. These antibodies target the ganglioside GQ1b, which is abundant in the plasma membranes of the cranial nerves supplying the extraocular muscles (EOM) and the presynaptic neuromuscular junctions (NMJ) [4]. Anti-GQ1b antibodies block acetylcholine release from the motor nerve terminals [5].

Our patient was diagnosed and treated for MFS based on clinical suspicion, and the elevated anti-GQ1b antibody level returned one week after the patient had been discharged home. The diagnosis of MFS is primarily clinical after exclusion of alternative etiologies and is confirmed later by additional laboratory testing. While not necessary to make a diagnosis of MFS, testing for anti-GQ1b antibodies assists with narrowing down the differential. Serological testing for the anti-GQ1b antibody is positive in 80-95% of patients with MFS and is not present in the general population [11]. These antibodies can be detected one week after the onset of symptoms [13]. Research has shown anti-GQ1b testing to be superior to CSF studies in the first three weeks when suspecting MFS [13]. If clinical suspicion for MFS remains high although GQ1b autoantibodies are not identified, a ganglioside panel should be ordered. Other anti-glycoside antibodies, such as antiGT1a, anti-LM1, anti-GD3, anti-GM1, anti-GM2, anti-GD1a, anti-GD1b, and anti-GalNacAc have also been implicated in the disease, and each specific type of antibody is correlated with different symptom presentation [5]. The anti-GQ1b antibody syndromes include MFS, GBS, Bickerstaff brainstem encephalitis, and acute ophthalmoparesis without ataxia [2,14]. These diagnoses should be considered when managing patients with presentations that could be consistent with MFS, especially if the clinical picture is atypical or incomplete.

Neuroimaging is typically unremarkable in MFS. Rarely, nonspecific MRI abnormalities appear in 1% of patients, including abnormalities in the cerebellum, middle cerebellar peduncle, midbrain, posterior columns, and nerve roots [11]. Such radiologic findings have suggested both central nervous system (CNS) and peripheral nervous system (PNS) involvement. However, the main purpose of neuroimaging is to exclude other potential etiologies. Our patient's imaging revealed involvement of bilateral cranial nerves V3 and VII as well as ventral nerve roots of the cauda equina.

CSF studies in MFS reveal albuminocytological dissociation in a large majority of cases [13]. A key study found that 64.4% of MFS patients have increases in CSF protein [15]. Research has also shown that CSF protein levels may correlate with the course of disease [4,16]. However, it is important to note that albuminocytologic dissociation in the CSF appears later in the disease course [4]. This likely explains why our patient's labs did not show this finding. Another interesting aspect for our case was CSF oligoclonal band positivity. Previous literature has suggested that oligoclonal IgG is transient and correlates significantly with the development of blood-CSF barrier damage, cranial neuritis, and disease severity [17]. Electromyography (EMG) and nerve conduction studies, which can be useful in diagnosing other subtypes of GBS, are often normal in MFS [8].

Generally, MFS is a self-resolving disease with an excellent prognosis in most cases [10]. The mean recovery time is about 10 weeks, although one-third may have residual neurological deficits [15]. Supportive care may be sufficient for mild cases, especially if respiratory function is spared. For moderate to severe cases, the treatment of choice for MFS is IVIG, or plasmapheresis in drug-resistant cases. Nearly all cases of ophthalmoplegia resolve by 6 months [5,10]. The mortality rate is approximately four percent, with a three percent chance of recurrence [1]. Minor complications may include fatigue (75%) and chronic pain (33%) [8]. Severe complications are rare but have been described, including respiratory failure requiring mechanical ventilation, ballismus, coma, cardiomyopathy from dysautonomia, lactic acidosis [1,4].

Medical therapies have yet to be proven effective, and researchers have not conducted randomized trials to investigate the efficacy of different treatment modalities. Retrospective research has found that IVIG does not have a significant impact on outcomes, though it does minimally hasten the onset of recovery from ophthalmoplegia (12.0 days after symptom onset compared to 13.5 days) [18]. However, IVIG introduces many risks, including anaphylaxis, cerebral infarction, and encephalopathy [8]. IgA levels should be checked prior to administration to reduce the risk of anaphylaxis [8]. Although plasmapheresis has shown some success in case reports, retrospective studies have not supported this [19]. Furthermore, corticosteroids alleviate neuropathic/radicular pain but have no impact on the recovery or outcome. Interestingly, eculizumab, a

monoclonal antibody that inhibits complement function, has been shown to minimize neuromuscular junction disruption from anti-GQ1b antibody in mice models, which may be promising for patients diagnosed with MFS [11]. However, this pharmacologic drug has yet to be studied on humans with MFS and further research is necessary.

Conclusion

Miller Fisher syndrome is a unique autoimmune-mediated peripheral neuropathy characterized by a distinct triad of ophthalmoplegia, ataxia, and areflexia [1,17]. It presents as a rare variant of Guillain-Barré Syndrome and is frequently triggered by infections. MFS has a favorable prognosis, with most patients experiencing complete recovery within several weeks to months. While IVIG is the treatment of choice for moderate to severe cases, it is essential to monitor for potential complications. This case report underscores the importance of recognizing MFS, particularly in pediatric patients, and considering it as a differential diagnosis for acute-onset neurological and ophthalmic symptoms.

Patient Consent

Written consent to publish this case has not been obtained. This report does not contain any personal identifying information.

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Conflicts of interest

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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