Article ▸ A Case Presentation of a Third-Nerve Palsy as a Characteristic of Miller Fisher Syndrome

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ABSTRACT

Background: A rare clinical variant of Guillain-Barre syndrome, known as Miller Fisher syndrome (MFS), is an immune-mediated neuropathy classically characterized by a triad consisting of ophthalmoplegia, ataxia, and areflexia.[1,2] Although MFS is thought to be a disease of immunological basis, other pathological entities may give rise to the syndrome as well. The diagnosis of MFS relies upon clinical signs, a combination of lab tests including antibody serum, cerebrospinal fluid, and electrophysiological findings. Understanding the clinical course of MFS and its ocular components can aid in the rehabilitation and co-management of these patients.

Case Report: A 79-year-old white male presented with a four day onset of double vision and an inability to walk unassisted. An examination revealed a pupil-sparing third-nerve palsy with a left eye ptosis. Due to the patient being in moderate pain throughout his entire body and presenting with an acute onset of symptoms, the patient was sent to the emergency room in the same hospital building. The patient was immediately admitted for evaluation and testing which revealed the diagnosis of MFS.

Conclusions: Although a complaint of diplopia can lead to an array of diagnoses, when accompanied by an acute inability to walk, MFS should be on the list of possible causes. Although mostly a self-limiting disease, there is the possibility of progressing to respiratory failure. Knowledge of the syndrome, its clinical course, and prognosis, along with an appropriate evaluation with current laboratory testing, will lead to the proper diagnosis, treatment, and management.

Keywords: areflexia, ataxia, diplopia, Miller Fisher Syndrome, neuropathy, ophthalmoplegia, third-nerve palsy

Introduction

Miller Fisher syndrome (MFS) is characterized clinically as a triad of ophthalmoplegia, ataxia, and areflexia. Not all three characteristics have to be present to make the diagnosis of MFS. In some reported cases, only one or two characteristics of the triad have been present in patients with diagnosed MFS.[1,2] Miller Fisher syndrome accounts for about 1-10% of patients with Guillain-Barre syndrome (GBS).[2,7,11,14] The incidence of GBS is about 1-2 per 100,000 per year, whereas MFS is much lower at about 0.09 per 100,000 per year depending on regional location.[1,2,11,20] Miller Fisher syndrome is more common among patients with GBS in Far East locations including Taiwan, Hong Kong, Japan, and Thailand.[1-3,14] There is a slight male predilection, with most studies agreeing upon males being about 1.5 times more likely to be affected by MFS than females.[1,5,6,14] Miller Fisher syndrome may occur at any age, but the median age of onset is in the fifth decade of life.[1,3,6,10] Some studies suggest an onset of MFS more in the spring than any other season.[3]

Case Report

A 79-year-old white male presented in April due to an acute onset of blurry, double vision associated with gait disturbance and bi-temporal headaches. He noticed his left eye turning out four days ago. He also noted a sudden inability to walk unassisted and the feeling of being extremely cold. He experienced a partial fall in the shower one week prior but did not experience any trauma from the fall. He denied dizziness or vertigo. Aside from the blurry vision, the patient confirmed feeling fatigued and generally "not feeling well." The patient had undergone multiple hip surgeries and had a removal of infected hip replacement hardware about six weeks prior to the onset of double vision. Best-corrected visual acuity the day of the initial consultation measured 20/30 in the right eye and 20/60 in the left eye complicated by a known diagnosis of age-related macular degeneration.

Clinical evaluation revealed a >45 prism diopter left exotropia with complete impairment of left eye adduction and a 30 prism diopter left hypotropia measured with cover test and Maddox rod. A partial impairment of infraduction and supraduction was noted on motility testing. Left eye abduction was intact. Right eye motility was normal and intact. Pupils were symmetric and equal with a sluggish direct and consensual pupillary response. There was no afferent pupillary defect noted in either eye, indicating a pupil-sparing third-nerve palsy. There was no facial asymmetry aside from the ptosis of the left eye. Facial sensation was intact to light touch and pin prick. He did have a mild vibratory deficit bilaterally from his toes to his hips. The patient demonstrated normal strength bilaterally throughout his body and did not present with a hearing disturbance. No oral or pharyngeal asymmetry was noted, and normal tongue extrusion and lateral movement with normal speech and comprehension was exhibited. Testing did reveal a positive Romberg test. He had wide-based, ataxic

gait with a tendency to fall on either side, but his stride and arm-swing movements were normal. The patient's wife and daughter accompanied him to the hospital and reported that he did not walk like this nor was he falling over while walking a week prior. They confirmed that his ataxic gait was new and not due to the hip replacement surgery. Deep tendon reflex testing showed a bilateral loss of the patellar reflex and severely reduced bilateral reflex of the Achilles tendon. Blood pressure measured 206/99 mmHg. Before performing any other procedures, the patient was sent to the urgent care department in the hospital and given intravenous hydralazine to lower his blood pressure. The patient reported not taking his blood pressure medication for the last two days.

A neurological consultation including neuroimaging was scheduled immediately. A magnetic resonance imaging (MRI) test and a magnetic resonance angiogram (MRA) along with a head computed tomography (CT) scan without contrast were ordered. The neuroimaging showed no evidence of acute intracranial pathology including mass, infarction, or hemorrhage. The only pathology that was seen was suggestive of an abnormal signal on the fluid attenuated inversion recovery (FLAIR) MRI at the level of the left side of the midbrain, suggesting but not diagnostic of small vessel hypertension-related brainstem stroke. A complete blood count and a basic metabolic panel were only significant for hyponatremia with a sodium level of 128 mEq/L (normal 135-145mEg/L). A bilateral lower extremity Doppler venous ultrasound ruled out a deep vein thrombosis.

Differential diagnosis of a pupil-sparing, cranial third-nerve palsy with ataxia includes mononeuropathy secondary to diabetes, hypertension, myasthenia gravis, aneurysmal bleed, intracranial bleed, vasculitis, multiple sclerosis, migraine, or infection.[1,4] As imaging was not diagnostic for a cause of the third-nerve palsy and did not explain his bilateral lower extremity ataxia and areflexia, further testing was ordered and included an erythrocyte sedimentation rate (ESR) and a hemoglobin A1c, acetylcholine antibodies, an electromyogram (EMG) using a concentric needle electrode, and a lumbar puncture. The lumbar puncture revealed an increase in protein in the cerebrospinal fluid (CSF) of 90.7 mg/dL (normal 15-45 mg/dL). No oligoclonal bands were identified in the CSF. Hemoglobin A1c was normal, and the patient did not have a history of diabetes. The myasthenia gravis panel was negative. The patient was tested for methicillin-resistant Staphylococcus aureus (MRSA), which was negative.

Electrodiagnostic evidence of segmental motor demyelination with patchy increased distal motor latencies, abnormal temporal dispersion, and conduction block, which is consistent with findings associated with acquired inflammatory demyelinating polyneuropathy, was revealed on the EMG. The bilateral tibial H-wave latencies were absent. Based on the patient's presenting signs and symptoms, a vibratory deficit of the bilateral lower extremities, bilateral lower-extremity ataxia, bilateral lower-extremity areflexia, EMG results, and increased protein in the CSF, a diagnosis of MFS was made even though serum testing did not reveal a high level of anti-GQ1b antibodies (results were <1:800). A possible brainstem stroke secondary to hypertension, which was suggested on the FLAIR MRI, was a coincidental finding but was ruled out as the cause of the ophthalmoplegia due to the bilateral lower-extremity ataxia and areflexia. A brainstem stroke secondary to hypertension would have led to a pupil-sparing third-nerve palsy with a contralateral weakness or sensory deficit of the face and/or body, which was not the case for this patient. This patient also did not have motor strength weakness, vertigo, and/or speech problems, nor did he present with a hearing disturbance, which can all be found in conjunction with a brainstem stroke. In addition to the hydralazine, the patient was given a five-day course of methylprednisolone and intravenous immunoglobulin (IVIg). After completion of the five-day dosing of intravenous medications, the patient participated in physical therapy rehabilitation and showed improved functional status. He is scheduled to continue physical therapy three times per week as an outpatient.

At a four-week follow up appointment with the neuro-ophthalmologist, left eye adduction was still impaired, with the eye adducting to the midline. The infra- and supraductions were slightly improved. Cover and Krimsky tests revealed a 30 prism diopter left exotropia. The vertical deviation was not quantified, but a hypotropia was still present. The patient was given basic version eye movement exercises to be completed three times per day. The patient did not notice the double vision most of the time, and it is probable that the ptosis of the left eye covering the visual axis was blocking the image or that the patient was suppressing the left eye. The patient was given an eye patch to use for mobility activities including walking if he were to notice any double vision.

At a 12-week follow up appointment, the patient's ptosis of the left eye had completely resolved, infraduction and supraduction returned to normal, and adduction of the left eye was much improved with a small amount of residual exophoria and convergence insufficiency. Maddox rod and cover tests revealed minimal exophoria at distance and 14 prism diopters of exophoria at near. The patient was instructed to continue the version eye movement exercises. Pencil push-up exercises would have been added to the management regimen, but Worth 4 dot testing showed that the patient was suppressing the left eye. He was to return in eight weeks but was lost to follow-up.

Discussion

Diplopia is a common presenting concern in MFS, which occurs because of the acute ophthalmoplegia.[1,3-6,10] Other ocular findings associated with MFS are ptosis, pupillary abnormalities such as light-near dissociation and sluggish constriction to light, anisocoria, lid retraction, and upper lid

jerks.[1,3] Facial nerve involvement has been found in about 30-46% of patients, which can result in orbicularis oculi weakness and lead to dry eye syndrome.[1,3,6] Another less common finding in MFS is cardiovascular autonomic dysfunction; data is mixed depending on how the results are reported. Bedside clinical findings are much higher than quantitative autonomic function examinations and, according to Lyu et al., are inadequate for assessing abnormalities in autonomic dysfunction. Three months after the onset of MFS, most abnormal autonomic dysfunctions are improved.[17] There have been reports of respiratory failure with MFS, particularly in children.[3]

The cause of reduced deep tendon reflexes in MFS is secondary to peripheral nerve dysfunction as documented by electrophysiological studies.[1] The exact etiology of MFS is now better understood and is thought to be immunological in origin. The pathogenesis of MFS has been investigated extensively, and the most common finding is elevated serum anti-GQ1b antibodies. Studies show that about 83-90% of patients diagnosed with MFS have these elevated antibodies.[5,6,14,22] These particular antibody titers are not normally found in other neuroimmunological diseases and have been found to be very important in the diagnosis of MFS and other anti-GQ1b antibody syndromes.[1,3,5,6,9-14,16,20] It is important to note that these titers are not found in other pathologies most likely to be differential diagnoses of MFS such as myasthenia gravis and multiple sclerosis.[16] Myasthenia gravis with MFS is very rare, but there have been cases reported in the literature.[18]

Other anti-GQ1b antibody syndromes include GBS with ophthalmoplegia, Bickerstaff brainstem encephalitis (BBE), acute ophthalmoparesis (ophthalmoplegia following an antecedent illness without the ataxia or areflexia), pharyngeal-cervical-brachial weakness, and, of course, overlap of these diseases.[10,14,16] There are similarities between MFS and BBE including ophthalmoplegia, ataxia, areflexia, increased protein in the CSF, elevated anti-GQ1b antibodies, and the characteristic of developing the syndrome after an antecedent infection. The main difference between MFS and BBE is impaired consciousness, which is necessary to make the diagnosis of BBE, and this characteristic is not found in patients diagnosed with MFS.[1,10,14]

The GQ1b antigen is highly expressed in the muscle spindles of the oculomotor, trochlear, and abducens nerves.[14] The pathogenesis of MFS is found to be due to the anti-GQ1b antibodies binding to this antigen in the paranodal regions of these cranial nerves and peripheral nerves. Consequentially, this activates complement, culminating in the formation of the lytic membrane attack complex (MAC:C56-9), causing structural derangement of the muscle spindles in the neuromuscular junction and therefore blocking nerve conduction. This causes paralysis that sequentially induces the characteristic triad seen in Miller Fisher syndrome.[14,16,19,23] Due to reports of Bell's palsy and orbicularis oculi weakness in some cases of MFS, this pathogenesis may also take place in the muscle spindles

of the facial nerve, as it is found to be involved in 45.7% of patients in one study.[3]

With the pathogenesis of MFS in mind and the findings of antecedent illnesses, researchers have investigated the possibility of molecular mimicry of infectious pathogens due to the structural similarities of the GQ1b gangliosides on the cranial and peripheral nerves and the lipo-oligosaccharide epitopes of the pathogens.[2,3,11,12,14,16,20] The most common pathogens reported are Campylobacter jejuni and Haemophilus influenzae.[1-6] Other pathogens that have been reported less commonly include Mycoplasma pneumonia,[7] Pasteurella multocida,[21] Epstein-Barr virus, cytomegalovirus, Helicobacter pylori, Influenza A, and a possible case of MFS developing after a flu vaccination.[7,10-12,19-21]

Given that MFS is a rare, self-limiting disease, there is limited research, and no randomized controlled studies have been performed to find any benefits of the standard treatments currently being used as therapy. A retrospective chart review of 50 patients performed by Mori et al. revealed that plasmapheresis did not influence the recovery of ataxia or ophthalmoplegia in patients with MFS.[15] Another retrospective analysis done by Mori et al. of 92 patients with MFS failed to prove that treatment with intravenous immunoglobulin (IVIg) changed patient outcome. The one benefit found from this study was that IVIg marginally accelerated the time between the onset of ophthalmoplegia and ataxia and the start of improvement of these findings.[25] MFS patients with overlapping diseases like GBS and BBE will most likely benefit from IVIg.[25]

Most studies agree upon a recovery time from MFS within two to three months of onset with a complete recovery at six months. Ataxia is usually the first of the deficits to improve, followed by the ocular component, and lastly the depressed tendon reflexes, or areflexia.[1,3,6,14] The study of 50 patients with MFS by Mori et al. found that areflexia remained the longest, indicating that tendon reflex recovery took longer to recover than the other deficits.[6] Miller Fisher syndrome is mainly monophasic, but cases of recurrences have been documented in the literature, and these later episodes may have different presentations.[1,3,14]

Newer therapies being studied are the complement inhibitor antibodies used to block the immune-mediated motor neuropathy seen in the pathogenesis of MFS. In two separate studies done on mice, one used the humanized monoclonal antibody eculizumab, and the other study used the complement C5-inhibiting recombinant protein rEV576. Both studies showed protection against complement-mediated damage in MFS-affected mice, showing reason for future clinical studies.[23,24]

The importance of the anti-GQ1b antibody in diagnosis is evident by the pathogenesis and the studies backing this finding, but electrophysiological findings can be very important as well. Studies have shown that the absence of F waves on neurophysiological studies has been a consistent finding in MFS.[2,7,8] The patient in this case report did not have

elevated anti-GQ1b antibodies at the time of presentation but was still diagnosed with MFS due to the EMG results, the high protein in the CSF, and the characteristic triad of signs and symptoms. The patient did have hip surgery to remove infected hip replacement hardware six weeks prior to the onset of symptoms, which could have been the precursor infection to MFS, even though no infectious cause was cultured at the time of the presentation. The patient continues to improve and is making progress with the help of physical therapy.

Conclusion

A third-nerve palsy presenting with bilateral ataxia and areflexia should lead the practitioner down a different path of diagnosis, i.e. a diagnosis other than a stroke. Remember that the ophthalmoplegia, ataxia, and areflexia should completely resolve within six months from onset and that the course of MFS is mostly self-limiting and has a very good prognosis. Knowing the signs and symptoms of a less common neurological disease such as MFS will aid the optometrist in an efficient consultation and appropriate management.

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