Steroid-Responsive Miller-Fisher Variant of Guillain-Barré Syndrome in a 25-year Old Male: A Case Report

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Abstract

Introduction: Miller Fisher syndrome (MFS) is a variant of Guillain-Barré syndrome (GBS) characterized by an immune-mediated polyneuropathy. Diagnosis is largely clinical and spontaneous recovery is observed in most cases. Treatment options such as IVIg, plasmapheresis, and steroids have been studied as options to shorten the disease course, but with inconclusive results.

Case: A 25-year-old male complained of sudden onset diplopia, gait instability and hand parasthesia. Diagnosis of MFS was done clinically; chest CT scan, nerve conduction studies, and MRI of brain and orbits were unremarkable. Anti-GQ1b determination was not performed. Low dose oral corticosteroid was initiated with gradual recovery of symptoms noted over two weeks and full recovery in two months.

Discussion: Miller Fisher syndrome (MFS) is a rare entity and the least common of the GBS variants. Its incidence as a proportion of GBS accounts for one to five percent in Western countries. Most patients have evidence of an upper respiratory tract infection one to three weeks before symptom onset. MFS is largely considered to be a self-limiting condition, but case series have shown that patients return to normal activities approximately six months after neurological onset. The patient in this report was treated with low dose steroids, with gradual taper over two months. Significant improvement of symptoms was noted over two months, which is shorter than the six months recovery in literature.

Conclusion: Worldwide incidence of MFS can be underestimated as it is often overlooked during the initial work-up of the disease. The risks of treatment, therefore, should be weighed against the likelihood of spontaneous recovery. Although use of steroids in this case report have noticeably caused a shorter course of the disease, prospective studies are suggested to look into the role of low dose oral corticosteroids in shortening the onset-to-recovery course of this illness.

Keywords: miller-fisher syndrome; miller fisher variant; guillain-barré syndrome; diplopia; steroids

Introduction

Guillain-Barré syndrome (GBS) is a type of neuromuscular paralysis that has several variants. Miller-Fisher Syndrome (MFS) is an uncommon variant of GBS, observed in only one to five percent of all cases of GBS in western countries.[1,2] It is characterized by a triad of areflexia, ataxia and ophthalmoplegia, although variants may occur within the syndrome as it may present with just two, or even one of the clinical findings.[3] Majority of the cases of MFS has been treated with IV immunoglobulin (IVIg) and plasmapheresis, however, steroid use has been limited to single reports. A case of a steroid responsive Miller-Fisher variant presenting with diplopia and gait instability is reported here.

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Case Presentation

A 25-year-old male with no known comorbidities was assessed in an outpatient setting due to complaints of sudden onset diplopia and gait instability that started the morning of consult. Patient likewise noted mild paresthesia on both hands. Significant past medical history included being treated for an upper respiratory tract infection one week prior, which had been resolving on the day of consult. There were no complaints of headache, eye pain, blurring of vison, tremors, aural symptoms, muscle weakness or vertigo. Patient likewise had no prior history of gastrointestinal symptoms or recent immunizations.

On examination, the patient was cooperative and oriented with stable vital signs. On neurologic examination, orientation to time, place and person was intact, speech and language was normal, with no aphasia or apraxia noted.

Visual acuity was 20/20 both eyes and visual fields were intact by confrontation tests. On cranial nerve examination, eye adduction was limited with paresis of upward gaze on both eyes. Ptosis of the left eye was noted. Pupillary response was equally brisk and reactive to light. The rest of the cranial nerves were normal. Nystagmus was absent and optic fundus was normal. Motor and sensory system examinations were unremarkable. Romberg test was negative. Finger-to-nose test was mildly impaired, without dysdiadochokinesia. Deep tendon reflexes were +2 on all four limbs. Patient walked with a wobbly gait with eyes open and with eyes closed. The rest of the physical exam was unremarkable.

Patient was evaluated by a neuro-ophthalmologist and a neurologist. Among the differentials considered was ocular myasthenia gravis and a possible structural brain lesion such as posterior communicating artery aneurysm. Ice test was done with an equivocal result. Laboratory work-up revealed an unremarkable complete blood count and erythrocyte sedimentation rate. Chest CT scan revealed minimal fibrosis of the lateral segment of the right lower lobe, with no evidence of mediastinal mass or lymphadenopathy.

Nerve conduction velocity studies of the upper and lower limbs were normal, and repetitive nerve stimulation studies of the left spinal accessory and the left facial nerve were unremarkable. A brain MRI with gadolinium, contrast revealed no demonstrable abnormalities intrinsic to the orbits, medulla, pons or midbrain. There were no parasellar or cavernous sinus abnormality, with no evidence of aneurysm or arteriovenous malformations, ruling out a structural brain lesion as a cause of the diplopia.

A test dose of pyridostigmine 60 mg/tab one tab TID was given for three doses. The pyridostigmine trial was then discontinued because there was no improvement of symptoms. Ocular myasthenia gravis was ruled out due to failure of response to trial of pyridostigmine, an equivocal ice test, and normal nerve conduction velocity results.

A lumbar tap was initially considered in the work-up but was not done due to the invasiveness of the test and a probable non-diagnostic cerebrospinal fluid (CSF) findings since the documentation of an elevated CSF protein depends on when in the course of the disease the specimen was collected - information that is not consistently reported and available in varied reports/journals.

On the following basis: 1.) background of a prior upper respiratory tract infection, 2.) ophthalmoplegia and gait instability on presentation 3.) having ruled out the common causes of diplopia, the patient was clinically diagnosed with Miller-Fisher variant of GBS. Determination of anti-GQ1b antibodies would have been a useful marker in the diagnosis but was not done due to unavailability of the test in the local setting. Patient was given the option for intravenous

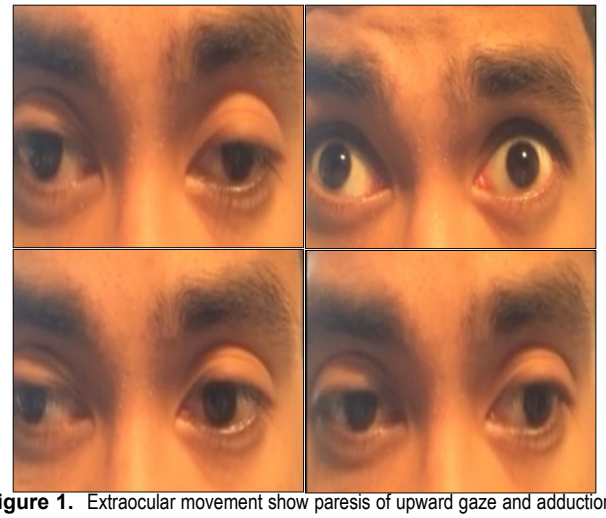

Figure 1. Extraocular movement show paresis of upward gaze and adduction, both eyes

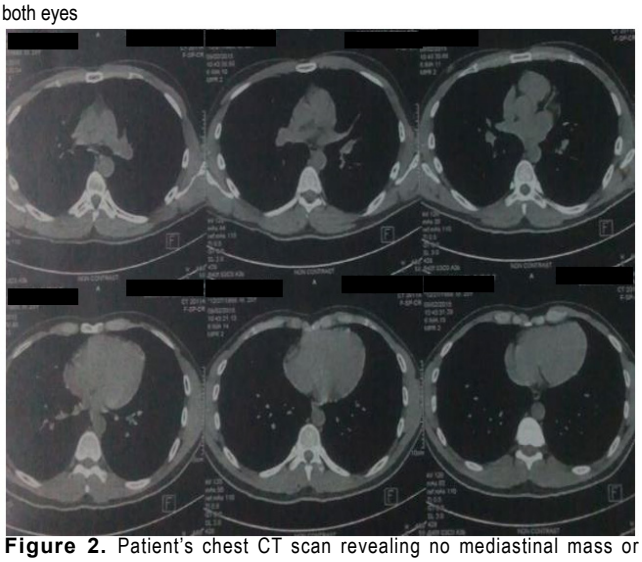

Figure 2. Patient's chest CT scan revealing no mediastinal mass or lymphadenopathy

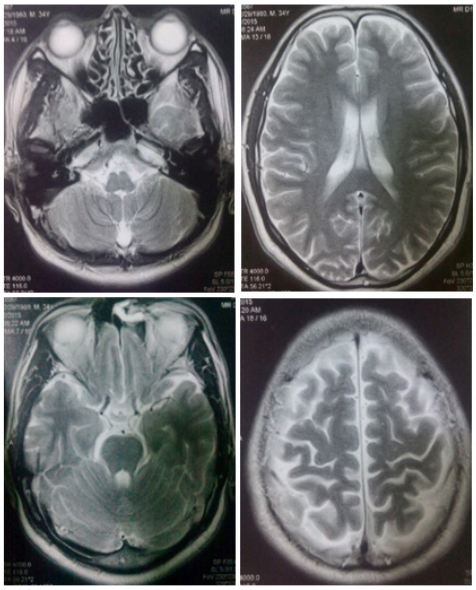

Figure 3. MRI of the brain and orbits with MRA of intracranial vessels show no structural abnormalities

immunoglobulin (IVIg) but refused such treatment, thus oral corticosteroid was initiated on the fifth day of illness with prednisone 20 mg/tab one tab PO OD. An eye patch was put in place for the diplopia.

Approximately two weeks into the treatment, gradual improvement of gait instability was noted with disappearance of the wobbling gait. The ptosis improved three weeks into the treatment; in two months, diplopia improved with resolving ophthalmoplegia and unnoticeable ptosis. Oral prednisone was given for two months with gradual tapering of dose.

Discussion

Miller Fisher syndrome in itself is a rare entity and the least common of the GBS variants. The worldwide incidence of GBS is one to two per 100,000 per year IV, however the incidence of MFS as a percentage of GBS varies depending on geography. MFS has been reported to be much more common in Asia, comprising 18%–19% of cases of GBS studied in Taiwan [5,6] and 25% of GBS in Japan.[2] To date, no available data of its incidence is available in the Philippines. A retrospective study of 466 patients with MFS reported a median age of onset of 44 years with a bi-modal age distribution peaking between 30 and 39 years and 50 and 59 years.[7] Miller Fisher syndrome occurs more in men than women with ratio of 2:1.3.2 The patient in this case is a 25-year-old male, and although the median age is at 44 years old, but reports have documented MFS in individuals as young as 13 years old.[2]

Most patients have evidence of infection one to three weeks before the development of ophthalmoplegia or ataxia. The disease peaks at a median of one week, and improvement often starts at a median of two weeks. Prodromal upper respiratory symptoms are experienced more commonly than gastrointestinal symptoms.[2,7]

The pathogenesis of MFS is triggered by an antecedent illness which leads to molecular mimicry between the GQ1b ganglioside on cranial and peripheral nerves, and molecularly similar lipo-oligosaccharides on the surface of the infectious agent. The clinical course of MFS is self-limiting and is similar to an acute phase primary immune response, with a median time from the infection onset to development of neurological symptoms of approximately 10 days.[7] Once molecular mimicry is established, an inflammatory autoimmune response occurs, leading to the characteristic neurological findings.

The initial symptom in MFS is typically diplopia (65%), followed by gait disturbance (32%).[2] Less common presenting symptoms are mild limb weakness, photophobia, blurred vision, headache, and facial weakness. Hence, on initial presentation, MFS may be mistaken for a brainstem stroke. Other entities to consider in the differential diagnosis are encephalitis, meningitis, optic neuritis, myasthenia gravis and other neuromuscular junction disorders.[2,3]

The diagnosis of MFS is descriptive and clinical, depending on the presentation of the triad. A useful marker in the diagnosis of MFS is a positive anti-GQ1b antibody test. This is because the GQ1b ganglioside complex has been identified as the glycolipid that is most often involved in cases of MFS. However, although anti-GQ1b antibody is present in the serum of more than 85% of patients with MFS early in the course of illness, it is not specific to MFS.[8]

Lumbar taps often show elevation of CSF protein with minimal or no cellular reaction or albuminocytologic dissociation. This finding, however is not specific and may be absent at the time of initial symptoms, becoming prominent over the next weeks. However, it is difficult to compare CSF findings among these variants because the finding of elevated CSF protein depends on when in the course of the disease the specimen is collected, information that is not consistently reported.[9]

In a study done by Nishimoto et al. comparison of the prevalence of CSF protein elevation with that of serum anti-GQ1b antibodies was done and the study demonstrated that in the first week after onset of symptoms, anti-GQ1b antibodies were almost always present, whereas elevated CSF protein was found in only 25% of patients.[10] It was concluded that CSF findings are not as sensitive as the anti-GQ1b antibody assay in diagnosing MFS in the early stage of the disorder. In addition, anti-GQ1b antibody titers have been shown to decline with clinical recovery.[8,9]

Although no randomized, controlled clinical trials of treatment for MFS have been performed,[11] a retrospective analysis of 92 patients showed that treatment with intravenous immune globulin (IVIg) had no effect on overall outcome, presumably because patients with MFS typically show good spontaneous recovery.[12] Plasmapheresis has also been used in patients with MFS but without definite clinical benefit.[13] The use of steroids has not been extensively studied for MFS but there have been reports addressing its value in the treatment of GBS. Despite the lack of randomized clinical studies, currently, immunomodulating therapy with IVIg is the favored treatment modality.[2,9,11]

Review of literature showed that corticosteroids are of no benefit in GBS treatment. Data for treatment modalities in MFS are largely taken from trials for GBS. The use of intravenous methylprednisolone was evaluated in GBS in three studies.[14,15,16] In the GBS steroid trial group, a multicentre randomized double blind trial was conducted looking into the benefit of a high dose steroid regiment in GBS. One hundred twenty four patients received methylprednisolone

500 mg daily for five days within 15 days of onset and 118 patients received placebo and about half the patients in both groups received plasma exchange. There was no difference between the two groups in the degree of improvement at four weeks or in secondary outcome measures, thus the conclusion that high dose steroid in early in GBS is ineffective.[14] In the second study, a smaller Dutch open-label pilot study suggested that 25 patients receiving intravenous methylprednisolone and IVIg did better than 74 patients from the earlier Dutch study who received IVIg alone.[15] This then paved way for the third study, a randomized controlled study by the Dutch group. Patients unable to walk independently, treated within.[14] days after onset of weakness with IVIg were randomized to receive either intravenous methylprednisolone (500 mg per day) or placebo for five days within 48 hours of administration of first dose of IVIg.[16] There was no statistically significant difference in improvement from baseline in GBS disability at four weeks after randomization. Overall, data from these three studies suggested that corticosteroids is not a recommended therapy for GBS. Steroid use has been limited in Miller Fischer syndrome but single reports have suggested efficacy in recurrent cases of MFS, with clinical remission documented for secondary and tertiary recurrences of the disease entity. [17,18]

Miller Fisher syndrome (MFS) is largely considered to be a self-limiting condition. All of 28 untreated MFS patients in the largest published case series returned to normal activities six months after the neurological onset.[2] The respective median (range) periods between neurological onset and the disappearance of ataxia and ophthalmoplegia were reported as 32 (8-271) and 88 (29-165) days.[2]

The patient in this report was treated with low dose steroids, with a gradual taper of dose over two months. Significant improvement of symptoms were noted with full recovery documented over two months, which is shorter than the documented norm of six months from neurological onset. Likewise time to disappearance of ataxia was at 14 days and ophthalmoplegia at 60 days.

Conclusion

High clinical suspicion is needed to diagnose Miller Fisher variant of Guillain-Barré syndrome because all clinical findings in the triad may not be present simultaneously, as in the case presented. Therefore, the incidence rate of this condition has probably been underestimated since it may be overlooked in the initial diagnostic process when symptoms are so mild that they may spontaneously resolve. MFS was considered in the patient due to a sudden onset external ophthalmoplegia, in the setting of a prior infection, for which appropriate work-up revealed unremarkable results. Diagnosis of the condition was clinical due to the unavailability of anti-GQ1b testing in the local setting, and the probability that patient may not manifest serologic evidence of the antibody.

As spontaneous resolution is the rule, the risks of treatment in patients with MFS must be balanced with the high likelihood of spontaneous recovery. However, current modalities suggested to shorten the course have been immunomodulation such as IVIg and plasmapheresis. To date, use of steroids have been limited to case reports on recurrent MFS and not on new onset MFS, as manifested by the patient. Further studies are suggested to look into the role of low dose oral corticosteroids in shortening the onset-to-recovery course of this uncommon disease.

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