Recognizing Miller Fisher Syndrome

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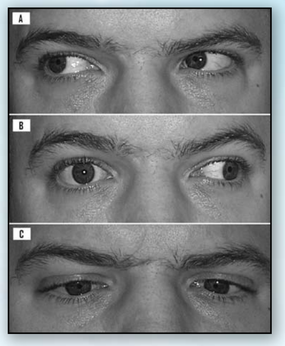
Abstract

- In a case of Miller Fisher Syndrome (MFS) with an atypical presentation of internuclear opthalmoplegia (INO), a convergence deficit was present without discernable pathology on brain MRI to suggest central nervous system lesions
- This unusual presentation may indicate that severe peripheral nerve conduction defects may manifest as pseudo-internuclear opthalmoplegia rather than true INO (Image 1)
- This case suggests that CNS involvement and INO may be overdiagnosed in atypical cases of MFS

Image 1: True INO



Introduction

- Guillain-Barré syndrome (GBS), once considered a single disorder, is now recognized as a spectrum of distinguished variants. Miller Fisher syndrome (MFS) comprises 1 - 5% of GBS cases in the US and 25% of cases in Japan
- Pathophysiology involves antigenic mimicry typically following exposure to infectious agents, resulting in an autoimmune response targeting peripheral nerve myelin (GM1,GD1 ganglosides of spinal nerves & GQ1b gangliosides of cranial nerves)
- Median age at onset is 40 (range 13 – 78 years). A consistent male predominance of 2:1 is typically noted
- Median onset of neurologic symptoms after infection is 8 days (range 1- 30 days)
- There are many variations for the pattern in which conduction defects present (Table 1)
  - Typically, initial symptoms include diplopia and ataxia, which progress to opthalmoplegia and areflexia by week 1 of clinical presentation
  - By week 2 and 3, 60% and 92% respectively will reach a nadir in symptoms, and by definition all symptoms must peak at week 4 followed by a plateau period before improvement
  - Clinical manifestations are often self limited and complete resolution of less severe cases occurs over weeks to months
- CSF analysis reveals normal pressure and cell counts with an albuminocytologic dissociation after 48 hrs of symptom onset
- Nerve conduction studies and electromyography often demonstrate evolving multifocal demyelination, i.e., slowed conduction velocity, motor conduction blockade, prolonged distal latencies
- MRI is sensitive but not specific, often showing nerve root enhancement
  - Cauda equina nerve roots are affected in 83% of patients with GBS and MFS
- IgG antibodies to GQ1b has sensitivity and specificity of 90% in diagnosing MFS and Bickerstaff's brainstem encephalopathy (BBE), a rare variant of GBS
- Plasmapheresis is the definitive therapy in severe cases of MFS compromise and decreasing vital capacity.
  - Treatment of choice for patients who progress to a prolonged course of illness, longer than 4-8 weeks, or those with cardiopulmonary compromise and decreasing vital capacity

Table 1. Frequencies of Presenting Symptoms

Symptoms	% of Cases
Opthalmoplegia, Ataxia, Areflexia	100
Diplopia	80
Headache	45
Ptosis	27.3
Nausea and Vomiting	25
Lower Limb Weakness	20
Upper Limb Weakness	16
General Weakness	8
Micturition Disturbance	3
Babinski Reflex	<1
Decreased Vibratory Sensation	<1
Internuclear Opthalmoplegia	<1

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Case

- A 53 year old male presented with a new onset of diplopia and headache after having URI symptoms two weeks prior
- On day 2 of presentation, exam revealed bilateral internuclear opthalmoplegia (INO), with nystagmus and mild skew deviation of the abducting eye
- Pupils became unreactive and dilated, with a convergence dysfunction as ataxia developed on day 3 with a worsening unsteady gate. Initial head CT and MRI of the brain were nonspecific.
- By day four, the patient had developed complete areflexia of upper and lower extremities
- An LP showed elevated CSF protein
- A nerve conduction study revealed symmetrically diminished sensory and motor nerve peaks of both upper and lower extremities, compatible with the clinical suspicion of MFS
- The patient also tested positive for antibodies against GQ1b, a component of ganglioside in nerve tissue
- Treatment with plasmapheresis was undertaken and the patient progressively improved on physical exams.

Discussion

Central nervous system involvement in Miller Fisher Syndrome is often debated with inconsistent supportive findings throughout published literature. Multiple case studies have reported possible brainstem and spinal cord involvement based solely on symptomology and physical exams without evidence of cerebral CT or MRI changes.[1,2]

One case study found posterior column lesions on MRI 5 months after immunotherapy and complete symptom resolution.[3] Few patients have been evaluated using transcranial magnetic stimulation to suggest conduction delay in MFS[4] whereas cerebral glucose nuclear scans showed generalized hypermetabolism without describing focal lesions.[5]

Postmortem examinations of MFS patients failed to reveal central demyelination, often finding incidental histopathologic abnormalities of the CNS in the background of diffuse peripheral nerve root lesions. Such CNS findings were thought to be infiltrative postmortem changes rather than true demyelination.[6,7]

Ito, et al. analyzed 581 patients with either Bickerstaff's brainstem encephalitis or Miller Fisher syndrome. Their findings suggest that GBS, MFS, and BBE all form a continuous spectrum with overlapping characteristics and variable CNS and PNS involvement. BBE was however noted more frequently on MRI and postmortem exams than MFS. No MRI lesions were noted in the CNS of this study's MFS patients who displayed INO and other CNS findings like Babinski sign.[7]

Out of 50 confirmed MFS patients evaluated by Mori, et al., one was reported to have internuclear opthalmoplegia on exam. This was speculated as being a CNS lesion, however, there was no further workup.[8]

Internuclear ophthalmoplegia is characterized by impaired adduction of the affected eye, and abduction nystagmus of the contralateral eye. It is a specific finding in Multiple sclerosis. Unilateral and bilateral internuclear opthalmoplegia have been described in cases of Miller Fisher syndrome. Pseudo-internuclear opthalmoplegia is associated with Myesthenia gravis and indicative of severe peripheral neuromuscular blockade. It is believed that the CNS causes hypermetria in an attempt to overcompensate for the peripheral weakness, leading to oscillations and saccadic eye movements mimicking INO. This has been described in several cases of GBS and MFS.[9, 10]

Given the absence of lesions on MRI and the convergence deficits noted in our subject, it is possible to conclude that our patient displayed Pseudo-INO, which may be confused with internuclear opthalmoplegia.

Conclusion

- Given the scarcity of evidence to support CNS involvement, it is difficult to definitively conclude whether MFS is exclusively a peripheral or central nervous system process. There is however adequate support to suggest that GBS, MFS, and BBE are all components of the same spectrum. Overlapping characteristics of BBE and MFS may very well create confounding results and raise the question as to whether MFS is accurately being diagnosed.1[1] Without tangible evidence of internuclear opthaloplegia in MFS, this atypical presentation can be regarded as CNS overcompensation for severe peripheral nerve weakness.