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An unusual case of Miller Fisher syndrome with unilateral 3rd nerve palsy and rapid recovery following intravenous immunoglobulin

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Abstract

Miller Fisher syndrome (MFS) is an immune mediated neuropathy commonly triggered by an infection. It is considered as a variant of Guillain-Barre syndrome. Although bilateral ophthalmoplegia is the commonest ocular involvement in MFS, there are reported cases of unilateral ophthalmoplegia. MFS has a benign course and treatment is not required in majority of cases unless there is a life-threatening complication.

We report an unusual case of MFS, presented with isolated right sided oculomotor nerve palsy with pupillary involvement, ataxia and areflexia. Patient was treated with intravenous immunoglobulin (IVIG) achieving a remarkable recovery by five days of treatment. We believe this is a treatment effect rather than the natural course of her illness. Although it is rare, MFS should be included in the differential diagnosis of unilateral 3rd nerve palsy with pupillary involvement, especially when associated with ataxia or areflexia. Having a low threshold to initiate IVIG in MFS may accelerate the recovery with a positive impact on patient's functional status.

Key words: Miller Fisher syndrome, unilateral, ophthalmoplegia, third nerve palsy, intravenous immunoglobulin

Introduction

Miller Fisher syndrome (MFS) is considered as a variant of Guillain-Barre syndrome (GBS). It is characterized by cardinal features of ophthalmoplegia, ataxia and areflexia. Aetiology of MFS is thought to be due to an aberrant acute autoimmune response to a preceding infection. Anti GQ1b is positive in majority of patients supporting the underlying pathophysiology of molecular mimicry.[1] Ocular manifestations are distinctive in MFS in contrast to other variants of GBS. Usually MFS is associated with bilateral ophthalmoplegia, but in a case series, 27.3% of 34 patients had unilateral ophthalmoplegia.[2] However, isolated oculomotor nerve with pupillary involvement is seldom reported and extensive work up is required to ascertain the etiology in such presentations.

Prognosis of MFS is excellent and immune therapy is not required owing to its' self-limiting nature. There is equivocal evidence to support the use of IVIG or plasmapheresis in MFS. However, there are case reports where IVIG has been used successfully in severe cases with swallowing or breathing difficulties.

We report a case of MFS presenting with isolated third nerve palsy with pupillary involvement along with ataxia and areflexia. We had a low threshold to treat her with IVIG. Interestingly she had a speedy recovery following treatment.

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Case presentation

A 62-year-old woman who was previously healthy apart from the recent diagnosis of hypertension presented to us in early 2022 due to drooping of right eyelid followed by unsteadiness in gait. She had fever with myalgia for two days and on the third day she noted right eyelid drooping which became complete by the end of the day. Next day (day 4) she was unsteady in her gait leading to falls which persuaded her to seek medical attention.

Examination revealed evidence of complete ptosis with external ophthalmoplegia compatible with 3rd nerve palsy on the right side. Pupil was dilated and the direct and indirect light reflexes were sluggish in right eye. Abduction and intorsion were full. Left eye examination and bilateral optic nerve assessments were completely normal. She did not have other cranial nerve palsies (Figure 1).

Rest of the neurological examination revealed normal tone and power of the limbs. Upper limb reflexes were brisk but lower limb reflexes were absent. Plantar reflexes were flexor. Sensation was normal, but she was markedly ataxic with positive Romberg test and gait was broad-based with tendency to fall to either side. There were no other cerebellar signs.

Her fever continued for five days and aborted. She had watery diarrhoea for two days which settled by its own. Neurological signs remained stable since admission. Investigations revealed, white cell count 4.5 x 10^3 with lymphocytes 56% and neutrophils 42%, hemoglobin 11.8 g/dL and platelets 148 x 10^3. The blood picture was compatible with ongoing viral infection. C-reactive protein was 20mg/dl and erythrocyte sedimentation rate was 15mm/1st hour. Both COVID-19 PCR and dengue NS1 antigen test were negative. Stool analysis was normal with no pus or red cells and culture was negative for pathogenic organisms. We could not perform campylobacter jejuni nucleic acid amplification test or PCR in stools due to the unavailability of the test in the government sector.

Non-contrast computer tomography (NCCT) and MRI of brain were normal. Nerve conduction studies (NCS) showed reduced conduction velocities, conduction blocks and F wave abnormalities in upper and lower limbs suggestive of acute demyelinating polyneuropathy. Lumbar puncture performed on the ninth day of the illness showed CSF protein 92mg/dl and 08 lymphocytes/mm^3 with absent polymorphs. There were no facilities available to check for anti GQ1b antibodies.

Patient was managed conservatively, and she remained stable for 4 days. As she was severely disabled due to ataxia, it was decided to commence intravenous immunoglobulin (IVIG) 0.4g/kg on the fifth day of hospitalization. She had a remarkable improvement with IVIG and by the third day of treatment, 3rd nerve palsy was almost completely resolved. She could walk independently on day four of treatment and she was completely asymptomatic at the time of discharge (Figure 2).

Figure 1. Eye movement examination on admission showing complete third nerve palsy on the right side. (Right eyelid is supported during the examination to visualize right eye movements.)

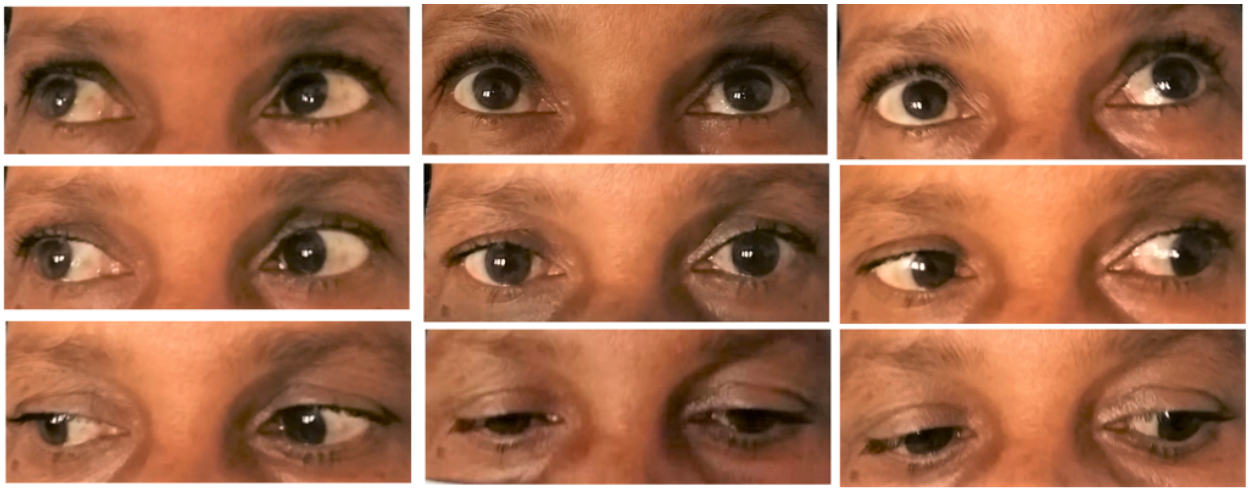

Figure 2. Eye movement examination 3 days after IVIG treatment.

Discussion

Guillain, Barre and Strohl first described GBS in 1916, based on two patients presented with areflexic tetraplegia and albumin-cytological dissociation in CSF analysis.[3] Later, many subtypes of GBS were described which included paraplegic form, spinal and mid brain form, mid brain form and hypersomnolence form.[4] About four decades later, in 1956, Miller Fisher described three patients with ataxia, areflexia and ophthalmoplegia, which had a close resemblance to mid brain variant of GBS described by Guillain.[5] Since then, many new phenotypes were described over the years, and various classification systems evolved to characterize this spectrum of immune mediated neuropathies.

Even though the incidence of GBS is the same across Caucasians and Asians, MFS is more prevalent in East Asia. When only 1-5% of GBS cases were MFS in western countries, 19% and 25% cases were MFS among total GBS cases reported in Taiwan and Japan respectively.[6,7,8] Unfortunately, there are no data on MFS in Sri Lanka.

Similar to GBS, MFS is usually preceded by an infection. Bacterial infections such as *clostridium jejuni* and *hemophilus influenzae* have been reported. Preceding infections lead to the underlying pathophysiology mediated by molecular mimicry between organisms and perineural cells. Presence of anti GQ1b antibodies among patients with MFS further supports the hypothesis of molecular mimicry. In our patient, as the fever and diarrhoea was present at the same time as neurological symptoms, we assumed that the diarrhoea was a coincidence rather than an aetio-pathological association.

Cranial nerves 3rd, 4th and 6th are known to have a higher concentration of GQ1b ganglioside making them vulnerable to demyelination in this disease entity.[2] Anti GQ1b antibodies cross react with GT1a, GD3, GD1b and GT1b which are structurally similar to GQ1b gangliosides. Those are predominantly expressed in other cranial nerves, cerebellum, and dorsal root ganglia.[9] Ataxia seen in MFS is due to loss of proprioceptive inputs and the exact site of defect is debated. Reactive epitopes were found in dorsal root ganglia, intrafusal apparatus of muscle spindles as well as in cerebellum, and all such involvements can cause ataxia.[10] Surprisingly joint position sense is not impaired in most patients despite profound ataxia.[11]

Cardinal clinical features of MFS are ophthalmoplegia, ataxia and areflexia. According to a case series of 50 patients, other less frequently reported symptoms were paresthesia of limbs (14%), dysphagia (2%), photophobia (2%), and blepharoptosis (2%).[11] Facial palsy is also a well described feature. In this case series, 21 patients out of 50 (42%) showed mydriasis.

Ophthalmoplegia is classically bilateral in MFS whereas marked laterality should raise the possibility of an alternative diagnosis. Less commonly reported ophthalmic manifestations are internuclear ophthalmoplegia, convergence spasm, convergence failure, defective vestibulo-ocular reflex, Parinaud's syndrome, areflexic mydriasis, and acute angle closure glaucoma. Unilateral ophthalmoplegia is reported rarely in medical literature and we could find only a few such case reports. Kundaje et al described a patient with partial right sided 3rd and 6th nerve palsy.[12] Another case of marked asymmetrical right sided ptosis and ophthalmoplegia was reported by Uchihara et al.[13] Keichiro et al

described a case of left sided near complete ophthalmoplegia with ptosis, which was interestingly associated with ataxia and areflexia limited to left side.[14] In another case series which included 34 patients, unilateral ophthalmoplegia was found in 27.3% cases.[1]

Isolated 3rd nerve involvement as the sole ocular manifestation was even rarer.[15] Tatsuya et al reported a 68-year-old patient with unilateral oculomotor palsy without ataxia and the patient improved over 3 months.[15] We found our patient to be unique among reported cases as she had unilateral oculomotor involvement with mydriasis. Surprisingly she showed rapid recovery by day 10 of the illness. Her speedy recovery must have been accelerated by IVIG therapy. MFS generally has a good prognosis and can be managed conservatively. No robust evidence exists for immunoglobulin treatment in MFS. However, in severe cases with swallowing and respiratory difficulties, IVIG should be considered. In a case series of 28 patients with MFS, median times of recovery from ataxia and ophthalmoplegia were 12 days (3 to 41) and 15 days (3 to 46) respectively.[9]

Conclusions

Our patient emphasizes the importance of knowing different presentations of MFS, especially unilateral ophthalmoplegia. Further, this case may shed light to have a lower threshold to initiate immunotherapy in MFS. Even though MFS usually has a benign and self-limiting course, active treatment may significantly shorten the recovery time in carefully selected patients. It is more important in cases where the patient's functional status is affected due to ataxia or diplopia. However, further studies, preferably case control randomized studies may give clear guidance to this uncertain aspect of MFS.

Consent for publication

Informed written consent was taken from the patient to publish images and the clinical details.

Competing interests

None.

Authors' contributions

All authors were involved in the management of the patient. IR did the initial literature review and wrote the first draft. JW reviewed the first draft after IR. SS did the final correction before submission. All authors have read and approved the final manuscript.

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References

1. Lyu RK, Tang LM, Cheng SY, Hsu WC, Chen ST. Guillain-Barré syndrome in Taiwan: a clinical study of 167 patients. *J Neurol Neurosurg Psychiatry* 1997; **63**: 494-500.
2. Lee SH, Lim GH, Kim JS, et al. Acute ophthalmoplegia (without ataxia) associated with anti-GQ1b antibody. *Neurology* 2008; **71**(6): 426-9.
3. Guillain G, Barré JA, Strohl A. Sur un syndrome de radiculonévrite avec hyperalbuminose du liquide céphalo-rachidien sans réaction cellulaire: remarques sur les caractères cliniques et graphiques des réflexes tendineux [French]. *Bull. Mem. Hop. Paris.* 1916; **40**: 1462-70.
4. Guillain, G. Les polyradiculonévrites avec dissociation alumbinocytologique et á evolution favorable (syndrome de Guillain et Barré) [French]. *J. Belge Neurol. Psychiatr.* 1938; **38**: 323-29.
5. Fisher, M. An unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia and areflexia). *N. Engl. J. Med*. 1956; **255**: 57-65.
6. Arnason GBW. Acute inflammatory demyelinating polyneuropathy. In: Dyck PJ, Thomas PK, Griffin JW, Low PA, Poduslo JF, eds. Peripheral neuropathy. 3rd ed. Philadelphia: *Saunders* 1993: 1437-97.
7. Mori M, Kuwabara S, Fukutake T, Yuki N, Hattori T. Clinical features and prognosis of Miller Fisher syndrome. *Neurology* 2001; **56**(8): 1104-6.
8. Chiba A, Kusunoki S, Obata H, et al. Serum anti-GQ1b IgG antibody is associated with ophthalmoplegia in Miller Fisher syndrome and Guillain-Barre´syndrome: clinical and immunohistochemical studies. *Neurology* 1993; **43**: 1911-17.
9. Willison HJ, O'Hanlon GM. The immunopathogenesis of Miller Fisher syndrome. *J. Neuroimmunol*. 1999; **100**(1-2): 3-12.
10. O'Leary CP, Veitch J, Durward WF, Thomas AM, Rees JH, Willison HJ. Acute oropharyngeal palsy is associated with antibodies to GQ1b and GT1a gangliosides. *Journal of Neurol. Neurosurg. Psychiatry* 1996; **61**(6): 649-51.
11. Kuwabara S, Asahina M, Nakajima M, Mori M, Fukutake T, Hattori T, Yuki N. Special sensory ataxia in Miller Fisher syndrome detected by postural body sway analysis. *Ann Neurol.* 1999; **45**(4): 533-6.
12. Kundaje GN, Ramesh S, Shubha K. An Unusual Case of Miller-Fisher Syndrome. *JAPI*. 1983; **31**(6): 383.
13. Uchihara T, Ikeda M, Tsukagoshi H. Recurrent Fisher's syndrome with immunological abnormalities and replicated laterality. *Eur J Neurol.* 1991; **31**(4): 270-2.
14. Susuki K, Yuki N, Muramatsu M, Hirata K. Unilateral ophthalmoparesis and limb ataxia associated with anti-GQ1b IgG antibody. *J Neurol*. 2000; **247**(8): 652.
15. Ueno T, Kon T, Kurihara AI, Tomiyama M. Unilateral oculomotor nerve palsy following campylobacter infection: a mild form of Miller Fisher syndrome without ataxia. *Internal Medicine*. 2017; **56**(21): 2929-32.