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CASE REPORT AND LITERATURE REVIEW

Pupillary Involvement in Miller Fisher Syndrome

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ABSTRACT

Miller Fisher Syndrome is characterised by the classical triad of ophthalmoplegia, ataxia, and areflexia. Ophthalmoparesis without ataxia, without areflexia, or with neither have been attributed as atypical forms of MFS. We report two patients with MFS who had tonic pupils and raised anti-GQ1b antibody titres. Bilateral dilated pupils (either tonic or fixed) can be a manifestation of MFS and anti-GQ1b immunoglobulin G (IgG) antibodies are useful to confirm the diagnosis in unexplained cases. The site of involvement is thought to be the ciliary ganglion or short ciliary nerves.

Keywords: Internal ophthalmoplegia, Miller Fisher syndrome, mydriasis, pupil

INTRODUCTION

Miller Fisher Syndrome (MFS) is characterised by the classical triad of ophthalmoplegia, ataxia, and areflexia with a good prognosis in most cases.[1] The anti-GQ1b antibody was initially defined as a marker for MFS.[2,3] Then, elevation of immunoglobulin G (IgG) anti-GQ1b antibodies was found to be associated with acute paresis of extraocular muscles without the triad of MFS.[4,5] Since then, the anti-GQ1b antibody syndrome includes Guillain-Barré syndrome (GBS), MFS, Bickerstaff's brainstem encephalitis (BBE), and acute ophthalmoplegia without ataxia (AO).[4,6] Diplopia is the most common initial symptom in MFS.[7] Although pupillary involvement has been reported in large series of MFS cases,[8,9] the site of involvement is not well clarified. Herein we review the literature concerning pupillary involvement in MFS and report two patients with mydriasis and raised anti GQ1b antibody titres.

CASE 1

A 17-year-old male was admitted to our hospital with chief complaint of diplopia. There was no history of an infectious disease before the onset. On examination of eye movements he had limited abduction bilaterally. The other cranial nerves were intact. The next day, eye movements were limited in all directions and he had mydriasis with no reaction to light (Figure 1). Pupils constricted slowly to a near stimulus. The rest of the neurological examination was normal. He was found to have neither have ataxia nor areflexia. Magnetic resonance imaging (MRI) of the brain with gadolinium was normal. Cerebrospinal fluid (CSF) examination showed no cells and had normal protein-glucose levels. Nerve conduction studies with F-wave stimulation in all limbs and repetitive nerve stimulation were normal. MFS with neither ataxia nor areflexia was considered the diagnosis and raised titres of anti-GQ1b antibodies in serum were detected. Treatment with intravenous immunoglobulin (IVIg) was started at the dosage of 0.4 g/kg for five consecutive days. The patient's symptoms improved rapidly after IVIg administration.

CASE 2

A 66-year-old male was admitted with a 2-week history of diplopia and ataxia. Two weeks prior to his admission, he had had diarrhoea for 1 week. He had a

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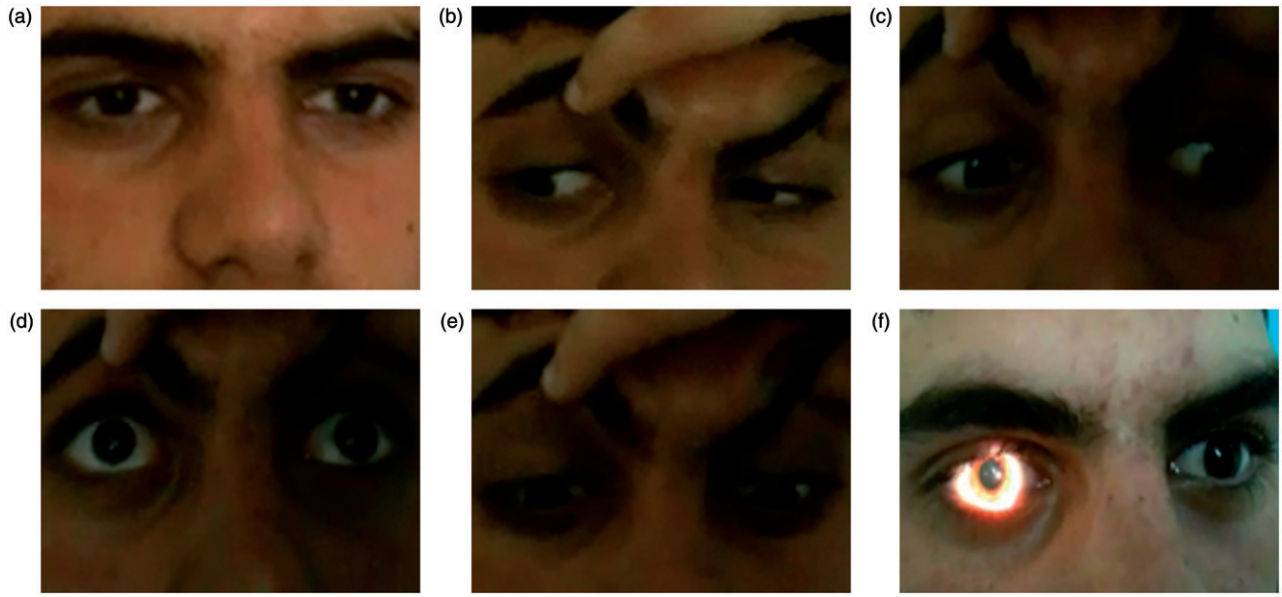

FIGURE 1 Ocular movements of Case 1 showing limitation in all directions. (a) Primary position. (b) Right gaze. (c) Left gaze. (d) Up gaze. (e) Down gaze. (f) Bilaterally dilated pupils with no response to light (***Note*:** Figures 1 and 2 of this article are available in colour online at www.informahealthcare.com/oph).

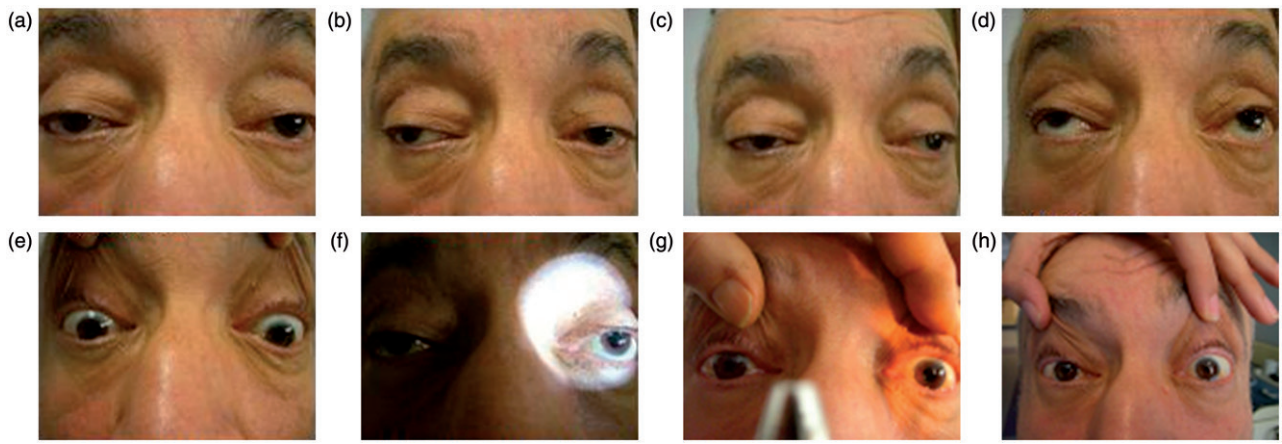

FIGURE 2 Ocular movements of Case 2 showing limitation in all directions. (a) Primary position. (b) Right gaze. (c) Left gaze. (d) Up gaze. (e) Down gaze. (f) Bilaterally dilated pupils with no response to light. (g) Slow response to near reflex. (h) Miosis after 0.125% pilocarpine administration.

history of hypertension, diabetes mellitus, hypothyroidism, and hairy cell leukaemia, which was diagnosed a year prior to presentation. He had been treated with cladribine and a remission was obtained after the treatment. On initial examination he had bilateral mydriasis with no light reaction and slow reaction to near. Examination of ocular movements revealed severe limitation of adduction, abduction, elevation, and depression bilaterally. Pharmacological testing with 0.125% pilocarpine caused miosis in both eyes supporting the diagnosis of tonic pupil (Figure 2). Deep tendon reflexes were absent and truncal ataxia was present. Blood studies including complete blood count, liver and renal function tests, and paraneoplastic antibody analysis were normal except for a mild thrombocytopaenia. CSF analysis showed no cells, elevated protein (58 mg/dL), and normal glucose levels. Cranial MRI was normal. Raised titres of anti-GQ1b antibodies in serum were detected and he was diagnosed as MFS. After a 5-day treatment using IVIg (with the dosage of 0.4 gr/kg/day), truncal ataxia improved gradually, but the pupils remained dilated for 3 more months.

DISCUSSION

The diagnosis of MFS is mainly based on clinical findings. Relatively symmetric ophthalmoplegia and ataxia progressing for up to 4 weeks, hyporeflexia or areflexia, and limb strength of 5 or 4 on the Medical Research Council scale are required for diagnosis. History of infectious symptoms within 4 weeks before the onset of neurological symptoms, CSF

albuminocytologic dissociation, and the presence of anti-GQ1b IgG antibody ware considered features highly supportive of the diagnosis.[10] The anti-GQ1b antibody is present in more than 90% of patients with MFS.[2] MFS, GBS with ophthalmoparesis, BBE, and AO are closely related diseases. The anti-GQ1b antibodies have high diagnostic specificity and sensitivity for this group of disorders. It is absent in normal control subjects and is found less often in patients with GBS without ophthalmoplegia.[5,11]

Lack of areflexia and ataxia in the first patient and history of a malignancy in the second patient made the diagnosis difficult. In the first patient, bilateral acute ophthalmoplegia without ataxia and areflexia, and presence of dilated pupils were a challenging condition. The differential diagnosis is wide and includes brainstem lesions (tumours, Bickerstaff's encephalitis, demyelinating disease, etc.), myasthenia gravis, GBS, MFS, and botulism. We ruled out these causes with CSF analysis, neuroimaging, and electrophysiological studies. Although antecedent infection was not reported by the patient, high titre of anti-GQ1b antibodies confirmed the diagnosis of an atypical MFS or acute ophthalmoparesis (AO) without ataxia. In the second patient, the clinical manifestations and the history of diarrhoea were suggestive of the diagnosis of MFS. The dilated pupils with no light reaction and the presence of history of hairy cell leukaemia required an investigation to rule out an infiltration or a paraneoplastic condition. No leukaemic infiltration was detected and the results showed that the disease was in remission at that time. The high titre of anti-GQ1b antibodies confirmed the diagnosis of MFS.

Ophthalmoparesis without ataxia, without areflexia, or with neither has been described as an atypical form of MFS.[4] Yuki described anti-GQ1b antibody positive patients with ophthalmoplegia and no ataxia and designated the condition as ''acute ophthalmoparesis'' (AO).[5] Odaka et al. proposed a diagnostic criteria for AO.[10] Progressive, relatively symmetrical ophthalmoplegia up to 4 weeks and absence of ataxia and limb weakness are the mandatory criteria. History of infectious symptoms within 4 weeks prior to the onset of neurological symptoms, CSF albuminocytologic dissociation, and the presence of anti-GQ1b IgG antibody were defined as the features that strongly supportive of the diagnosis. In 2001, Yuki et al. published clinical features of 21 patients with AO.[12] None of the patients had pupillary areflexia. The authors suggested that AO can be considered as a mild form of Miller Fisher syndrome. Lee et al. studied 11 patients with AO and about half of their patients had internal ophthalmoplegia.[13] There are a few reports with internal opthalmoplegia as the sole initial manifestation[14] or as almost the sole sign of MFS.[15–18]

Tonic pupil in MFS was first described in 1977.[19,20] In 1992, Berlit and Rakicky reviewed all cases with MFS reported since 1956. A complete ophthalmoplegia including parasymphatetic fibres to the pupil sphincter was described in nearly half of the patients.[7] One year later, Yuki et al. described clinical features in 16 cases of MFS, 7 of them had sluggish or absent pupillary reflexes.[12] Najim Al-Din et al. observed pupillary involvement in 40% of their patients and none of them had light-near dissociation by clinical examination.[21] The same authors reviewed neuro-ophthalmic manifestations of MFS in 243 cases from the literature.[9] Internal ophthalmoplegia was observed in nearly half of the patients and cholinergic hypersensitivity was found when the pupils were studied pharmacologically in a few of them. Mori et al. reported mydriasis and sluggish light reflexes in 21 of 50 patients with MFS.[22] Ten of these patients had anisocoria, suggesting unequal involvement of both pupils. Ito et al. analysed clinical profiles of patients with MFS and Bickerstaff's brainstem encephalitis and they observed that 35% of patients had internal ophthalmoplegia in the MFS group.[23] Response to a near stimulus wasn't mentioned in both studies. Keane reviewed 31 cases with complete ophthalmoplegia, MFS and GBS being the leading causes. Five of 13 patients with MFS showed fixed dilated pupils, whereas the pupils were partially involved in 6 and spared in 2 patients. The meaning of partial involvement was not disclosed.[24] Nitta et al. reported 27 patients with MFS, only 4 of them presented with mydriasis.[25] Two of these patients with mydriasis showed light-near dissociation and marked miosis after installation of 0.125% pilocarpine, whereas the other two did not respond to light and near stimuli or pilocarpine. They suggested that denervated iris sphincter muscles, which was supersensitive to the cholinergic transmitter had an important role in the expression of the light-near dissociation in MFS. Recently, Mori et al. collected 118 patients from 5 case series and mydriasis was observed in 38% of these patients.[26] Table 1 summarises the frequency of pupillary involvement in cases of MFS from the literature. Mydriasis is recorded in all cases but the type of involvement, whether tonic or fixed, was not addressed in most of them (Table 1). It is difficult to determine the distribution of fixed unreactive and tonic pupils from the literature published to date.

The GQ1b ganglioside is highly enriched in the paranodal regions of extramedullary portion of the human oculomotor, trochlear, and abducens nerves.[4] Specific binding of the antiGQ1b IgG to the paranodal myelin of those three cranial nerves may, therefore, underlie the pathogenesis of ophthalmoplegia in MFS.[27] Neuromuscular junctions (NMJs) have also been shown by in vitro studies to be one of the potential targets of antiGQ1b IgG antibodies. It was reported that antiGQ1b antibodies binding to NMJs

TABLE 1 Frequency of the pupillary involvement in cases of MFS in the literature.

Study (year)	Cases with MFS, n	Pupil involvement, n	Fixed dilated n (%)	L-N dissociation n. (%)
Berlit and Rakickly.[7] (1992)	223	109 (48%)	109 (48%)	0 (0%)
Yuki et al.[12] (1993)	16	7 (43%)	N/A	N/A
Najim Al-Din et al.[21] (1994)	20	8 (40%)	8 (40%)	0 (0%)
Najim Al-Din et al.[9] (1994)	243	123 (50%)	N/A	N/A
Mori et al.[22] (2001)	50	21 (42%)	N/A	N/A
Keane et al.[24] (2007)	13	11 (84%)	5 (38%)	N/A
Nitta et al.[25] (2007)	27	4 (14%)	2 (7%)	2 (7%)
Ito et al.[23] (2008)	466	163 (35%)	N/A	N/A
Mori et al.[26] (2012)	118	45/46 (38%)	N/A	N/A

N/A = Not addressed.

induce massive quantal release of acetylcholine from nerve terminals and eventually block neuromuscular transmission.[28,29] The pathogenesis of ataxia in MFS is not well understood. Both peripheral and central mechanisms have been implicated. Some studies supported the idea that the ataxia is proprioceptive in origin.[28,30] Involvement of muscle spindle afferents and/or the dorsal root ganglia may cause ataxia and may also be responsible for areflexia. Muscle spindle bodies and dorsal roots are immunostained with antibodies against GQ1b.[31,32] On the other hand, presence of anti-cerebellar antibodies was detected in the sera of patients with MFS and the serum of patients with MFS reacted with the molecular layer and Purkinje cells of the cerebellum.[33,34] Further studies are needed to clarify the pathophysiology of ataxia in MFS.

Although both of our patients had tonic pupils with light near dissociation, some reported cases are associated with fixed dilated pupils reactive to neither light nor near stimuli.[24,25,35] Fixed dilated pupils are a result of involvement of the preganglionic pathway parasympathetic from Edinger-Westphal nucleus to the ciliary ganglion. Tonic pupils are thought to be due to damage of the ciliary ganglion or short ciliary nerves. In fact, the near reflex is not spared but restored with the aberrant regeneration due to subsequent collateral sprouting, resulting in the iris sphincter being almost entirely innervated by accommodative elements.[36] So, completely unreactive dilated pupils might be seen in the initial stage of tonic pupils. We assumed that the anti-GQlb antibodies developed their blocking effect at the level of the ciliary ganglion in our patients or at the muscle endplate of the pupillary sphincter muscle. The findings of anti-GQ1b antibodies in the sera of patients with isolated internal ophthalmoplegia suggests that these epitopes may also be present in the ciliary ganglia.[4,12,15] Another site for bilateral dilated pupils with light-near dissociation could be the tectal area, which seemed to be structurally intact from MRI of our patients.[14,37,38]

Intravenous immunoglobulin is the treatment of choice for the alleviation of ophthalmoplegia and ataxia but does not affect the final outcome.[39] Although AO has a good prognosis without treatment, the quality of life in these patients can be severely affected. Papanikolaou et al. reported a case with acute bilateral ophthalmoparesis and fixed dilated pupils in MFS with a recovery within 10 weeks after IVIg treatment.[40] Our first case had a rapid improvement after IVIg administration. He had complete recovery 1 week after the treatment. In the second case, first the ataxia, then the ophthalmoparesis and pupils improved gradually in 2 months after IVIg therapy.

In conclusion, bilateral tonic or dilated fixed pupils can be a manifestation of MFS and pupillary involvement can occur in approximately 50% of MFS patients. Tonic pupils are thought to be due to damage of the ciliary ganglion or short ciliary nerves in our patients. Anti-GQ1b IgG antibodies are useful to confirm the diagnosis in unexplained cases and treatment with IVIg can accelerate recovery period. We believe that future studies with more rigorous testing techniques will reveal more information about characteristics and distribution of pupillary involvement in MFS.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

***Note*:** Figures 1 and 2 of this article are available in colour online at www.informahealthcare.com/oph.

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