Neurological Sciences
https://doi.org/10.1007/s10072-021-05157-7

ORIGINAL ARTICLE

Characteristics of pupil palsy in miller-fisher syndrome: case reports and review of the literature

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Received: 17 January 2021 / Accepted: 26 February 2021

Abstract
Pupil palsy has been a frequent finding in Miller Fisher syndrome (MFS), but its clinical characteristics have not been clearly defined. The basis for differential diagnosis with other diseases with pupil palsy has also remained vague. We report cases of four MFS patients with bilateral pupil palsy and specify pupil characteristics of light-near dissociation (LND), cholinergic super-sensitivity, vermiform movements, and prognosis. We conducted a literature review to compare with our cases and investigate common findings of pupil palsy in MFS patients. We suggest that the acute generalized pupil palsy without vermiform movements can serve as a key finding for the diagnosis of pupil palsy associated with MFS. However, the presence of LND and cholinergic super-sensitivity was not distinctive clinical findings in MFS patients who had pupil palsy and did not prove useful for differential diagnosis. The prognosis of pupil palsy in MFS patients was good in our 4 cases and the literature review.

Keywords Pupil · Miller Fisher syndrome · Tonic pupil · Mydriasis

Introduction

Miller Fisher syndrome (MFS) [1] is an acute self-limiting disorder characterized by a clinical triad ophthalmoplegia, ataxia, and areflexia [2]. However, many atypical clinical manifestations beyond the classic triad are considered for the differential diagnosis between various neuro-ophthalmic diseases [3].

Pupil palsy has been one of the signs often present in patients with MFS, although not part of the classical triad. Berlit and Rakicky conducted a review on all reported cases of classical MFS since 1956 [4], and the prevalence of pupil palsy was nearly half in the cases reported. Since then, several case reports have continuously reported the high frequency of pupil palsy in MFS patients [5–7], but in most of the cases describing pupillary involvement in MFS reported to date, its characteristics such as the presence of light-near dissociation (LND), cholinergic super-sensitivity or vermiform movements, and clinical course of pupil palsy have not been specifically addressed. Not only did this vagueness cause uncertainty in assessing and predicting pupil palsy in MFS, but it also caused difficulty in differentiating MFS from other diseases with pupil palsy. Herein, we investigated the clinical course and the features of pupil palsy in four patients with MFS and conducted a review of the literature in order to specify the characteristics of pupil palsy in MFS.

Material and method

This retrospective, case–series study included patients diagnosed with MFS at Seoul National University Hospital (SNUH). The study protocol was reviewed and approved by the Institutional Review Boards of Seoul National University Hospital. The study procedures were conducted in accordance with the tenets of the Declaration of Helsinki.

Subjects

We retrospectively reviewed the medical records of the patients with MFS between January 2018 and December 2019. The diagnoses of MFS and subtyping were categorized as follows: (1) classic MFS: ophthalmoplegia, ataxia, and areflexia; (2) incomplete MFS: acute ophthalmoparesis (AO), ataxic neuropathy, ptosis, or mydriasis; (3) Bickerstaff brainstem encephalitis

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Published online: 06 April 2021

(BBE): ophthalmoplegia, ataxia, and hypersomnolence; and (4) overlapping MFS: overlap with Guillain-Barre syndrome (GBS) variants [2].

The data in the records revealed that all patients underwent neuro-ophthalmologic examinations including best-corrected visual acuities, presence of eyelid drooping, presence of extraocular muscle palsy, presence of pupil palsy, presence of ataxia, and presence of tendon reflex. Furthermore, we collected the data of preceding infection history, anti-GQ1b antibody positivity, and additional neurologic symptoms or signs beyond classic MFS symptom triad. We excluded patients who had a previous neurological illness or less than 6-month follow-up. In addition, the cases of patients diagnosed as BBE were excluded because pupil dysfunction arising from damage of the brainstem could be misdiagnosed as pupil palsy.

Pupil testing

Pupil testing was performed on the MFS patients who had sluggish pupil movements or presumed to have deficits of light reflex. An automatic binocular pupillometry system (Mon CV3; Metrovision, Perenchies, France) was used to measure the pupil size quantitatively and to check the pupil constriction velocity in response to light stimulation. Pharmacologic testing was performed with 0.1% pilocarpine and the presence of LND was also tested. Slit-lamp examination was conducted to observe the paralytic nature of the pupil palsy and to check its movement under light by changing the light intensity from dim to bright.

Literature review

We performed the PubMed (Medline) databases searching for literature review. We searched the articles published up to November 2020 including the search terms: "pupil palsy," "mydriasis," and "internal ophthalmoplegia" in combination with "Miller Fisher syndrome," "Miller-Fisher syndrome," and "MFS." Additional articles referred to in such articles were also included in the literature search. Case reports or series about pupil palsy in MFS were included. Studies written in non-English language and studies that had the full text unavailable were excluded for accuracy. Cases that did not report signs of pupil abnormalities were excluded for the purpose of our research. Each article obtained from the search was investigated to determine its potential inclusion in the review.

Result

Clinical characteristic of pupil palsy in MFS

We identified a total of four patients with MFS who showed clear signs of pupil palsy. Demographic and clinical features of these patients are listed in Table 1. The average age at onset

Table 1 Demographic and clinical characteristics of 4 patients with Miller Fisher syndrome

Patient no.	Sex	Age	Classification	Preceding infection	External ophthalmoplegia	Ptosis	Extraocular muscle limitation	Ataxia	Areflexia	Light-near dissociation	Pilocarpine test	Segmental palsy	Atypical symptom	Presence of anti-GQ1b
1	M	31	AO	(+)	B	(-)	Bilateral abduction deficit	(-)	(-)	(-)	(+)	(-)	(-)	(-)
2	M	33	Classic MFS	(+)	B	(+/B)	Bilateral abduction deficit	(+)	(+)	(-)	(-)	(-)	(-)	(-)
3	F	31	Classic MFS	(+)	B	(-)	Bilateral abduction deficit	(+)	(+)	(-)	(-)	(-)	Facial sensory deficit	(-)
4	F	18	Classic MFS	(+)	B	(-)	Total external ophthalmoplegia	(+)	(+)	(-)	(-)	(-)	Facial palsy	(-)

was 28.25 years (range 18–33), and two were males, two were females. All patients complained about blurred vision at reading distance and photophobia outdoor. Three revealed symptoms of the triad of ophthalmoplegia, ataxia, and areflexia and were diagnosed as classical MFS, while one patient developed only ophthalmoplegia and was diagnosed as AO. All of them were reported to have undergone an antecedent infection. Upon extraocular movement testing, three patients showed bilateral abduction deficits while one had bilateral total ophthalmoplegia. Ptosis was absent in all except one patient. Serum anti-GQ1b IgG antibody was negative in all cases.

The presence of pupil palsy was bilateral in all cases. No signs of vermiform movement and segmental palsy were observed upon slit-lamp examination in all four patients, but iris movement was paralyzed in all 360 degrees, which we termed as "generalized palsy" (Fig. 1a). Pupillometry test demonstrated dilated pupil and absence of pupil constriction under light stimulation (Fig. 1b). LND was also negative in all four patients. Pharmacologic testing using 0.125% pilocarpine caused miosis in only one patient, while the rest did not show any significant change in pupil size. All patients underwent intravenous immunoglobulin treatment, and pupil palsy was resolved before the remission of diplopia, ranging from 2 weeks to 2 months.

Literature review of pupil palsy in MFS

We reviewed 27 cases between January 1977 and November 2020 in which features of pupil palsy were described. The clinical features of each cases are summarized in Table 2 [5, 7–19]. All cases had bilateral pupil involvement. Nine in 25 cases (36.0%) revealed signs of LND, while two did not mention response to light or near responses in their reports. Only 13 cases out of 27 (48.1%) mentioned results of pharmacological testing on their subjects, ten of which (76.9%) showed significant miosis in response. Checking for vermiform movements were described in only six cases, and all of them revealed no sign of vermiform movements. In 11 out of 27 cases (40.7%), the prognosis of pupil palsy and the classical triad was respectively described, and in ten of them (90.9%), pupil palsy showed an earlier recovery than diplopia.

Discussion

Pupil palsy has been often involved in MFS, but its features have not been clearly specified, leaving its differential diagnosis open to question. Keane reported two cases of MFS in which LND and cholinergic super-sensitivity was evident and addressed the pupil palsy as tonic pupil [9]. He presumed that it was due to an incomplete reinnervation to ciliary and pupillary sphincter muscles that followed the recovery of damaged post-ganglionic parasympathetic fibers. However, vermiform movements have not been identified in his reports, leaving his diagnosis of the pupil palsy as tonic pupil questionable. Nitta et al. reported four patients with two showing mydriasis with apparent LND and cholinergic denervation super-sensitivity [7]. They concluded that cholinergic super-sensitivity and LND in their patients may be correlated but dismissed the possibility of the tonic pupil due to the transient nature of LND in their patients, as well as the absence of vermiform iris movements or a prominent delay of re-dilation of the pupils. Bae et al. also reported a patient that showed denervation super-sensitivity and LND but ruled out tonic pupil because there was no segmental palsy or anisocoria [13].

Because cholinergic super-sensitivity and LND are distinct findings in tonic pupils, the frequency of their involvement ought to be specified. Our patients have mostly shown negative results regarding both findings, while other cases of MFS reported up to date in the literature have a higher positive response ratio of the two. The variability in these results indicates that LND and cholinergic super-sensitivity are not absolute but rather supportive findings in MFS.

Segmental palsy is also a key finding of tonic pupil [20] and it has been suggested along with anisocoria as a basis on which it could be distinguished from the diagnosis of generalized neuropathy [21]. Although only a few cases have paid attention to this feature when examining patients with MFS, all of them including ours have affirmed its absence. This suggests that signs of segmental palsy could be used in the differential diagnosis of MFS from tonic pupils. Since tonic pupil is a chronic disorder which shows slow progression [22], the tonic nature of the damage in pupillary nerve fibers may reflect its distinct pupil findings [23]. Delayed degeneration would result in LND since undamaged fibers remain, and

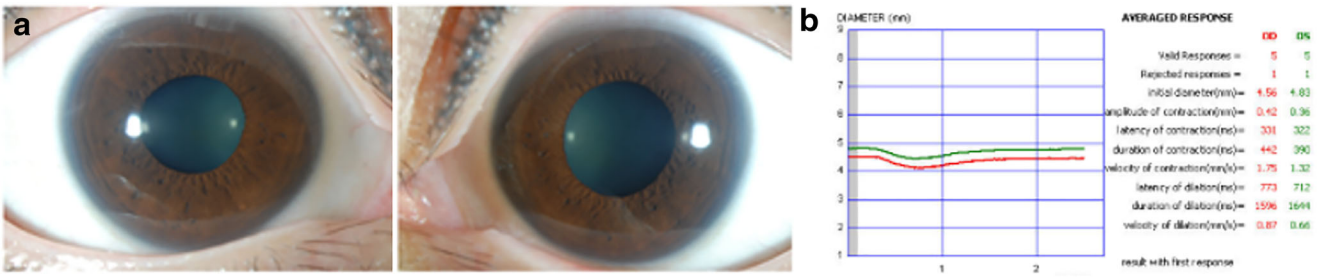

Fig. 1 Case 3. **a** Nine gaze photographs showed bilateral adduction deficit. **b** Anterior segment photographs demonstrated bilateral generalized pupil palsy without segmental palsy. **c** Pupillometry revealed limited and delayed pupil constriction to bright light stimulation

Table 2 Review of the clinical features of Miller Fisher syndrome including pupil findings from the literature [5, 7–19]

Author(s), year	Age/ sex	Presence of anti-GQ1b	External ophthalmoplegia	Pupil findings			Ataxia	Areflexia/ hyporeflexia	Preceding infection	Clinical course of pupil palsy
				Light-near dissociation	Cholinergic supersensitivity	Segmental palsy				
Okajima et al. [8]	78/F	NA	(+)	NA	(+/U)	NA	(+)	(+)	NA	Light reflex recovery (3 months), Complete recovery (4 months)
Keane, J. R. [9]	20/F	NA	(+)	(+)	(+/B)	NA	(+)	(+)	(+/URI)	4 years of F/U, LND, and pilocarpine test still (+)
	27/M	NA	(+)	(+)	(+/B)	NA	(+)	(-)	NA	3 1/2 months of F/U, LND, and pilocarpine test still (+)
Najim Al-Din et al. [5]	9/M	NA	(+)	(-)	NA	NA	(+)	(+)	(+)	Full recovery
	33/M	NA	(+)	(-)	NA	NA	(+)	(+)	(-)	EO and IO recovered by 12 weeks.
	25/M	NA	(+)	(-)	NA	NA	(+)	(+)	(-)	Full recovery
	60/M	NA	(+)	(-)	NA	NA	(+)	(+)	(-)	Full recovery
	30/M	NA	(+)	(-)	NA	NA	(+)	(+)	(-)	Full recovery
	60/F	NA	(+)	(-)	NA	NA	(+)	(+)	(-)	Pupils palsy recovered by one month, EO recovered after two months.
	29/F	NA	(+)	(-)	NA	NA	(+)	(+)	(+)	Pupil palsy recovered within 3 days, full recovery took 2 months.
	46/F	NA	(+)	(-)	NA	NA	(+)	(+)	(+)	Full recovery
Radziwill et al. [10]	33/M	(+)	(+)	(+)	(+/B)	NA	(+)	(-)	(+)	Conservative Tx., Sx. almost disappeared on day 20 at discharge.
Yuki et al. [11]	36/M	(+)	(+)	(-)	NA	NA	(-)	(+)	(-)	Sx. including pupil palsy recovered by day 22.
Chan et al. [12]	35/F	(+)	(+)	(+)	NA	NA	(-)	(-)	(+/URI)	Pupil palsy recovered by day 5, ophthalmoplegia persisted until 3 months.
Nitta et al. [7]	62/F	(+)	(+)	(+)	(+/B)	(-)	(+)	(+)	NA	Pupil returned to normal by 15th day, EO and ataxia persisted until 55th day.
	50/F	NA	(+)	(+)	(+/B)	(-)	(+)	(+)	(+)	The pupil recovered by 18th day, EO and ataxia persisted until 107th day.
	56/M	NA	(+)	(-)	(-)	(-)	(+)	(+)	(+/URI)	The pupil recovered by the 25th day, EO and ataxia persisted until 40th day, DTR remained absent.
	36/M	NA	(+)	(-)	(-)	(-)	(+)	(+)	(+/URI)	The pupil recovered by 23rd day, EO and ataxia persisted until 114th day.
Bae et al. [13]	22/F	(+)	(+)	(+)	(+/B)	(-)	(+)	(+)	(+/GI)	Tx. with IVIG for five days. Pupil returned to normal during the following 3 weeks, EO and ataxia persisted for about another month.
Yıldız et al. [14]	36/F	(-)	(+)	(-)	(+/U)	(-)	(+)	(+)	(-)	Light and near reaction of pupils improved after Tx. with IVIg for 5 days. Sx. free after 6 wks.
Bulder et al. [15]	41/M	(+)	(+)	(-)	(-)	NA	(-)	(+)	(+/RI (RSV))	5 months F/u, photophobia, pupillary reactions gradually returned to normal.

Table 2 (continued)

Author(s), year	Age/ sex	Presence of anti-GQ1b	External ophthalmoplegia	Pupil findings			Ataxia	Areflexia/ hyporeflexia	Preceding infection	Clinical course of pupil palsy
				Light-near dissociation	Cholinergic supersensitivity	Segmental palsy				
Kaymakamzade et al. [16]	17/M	(+)	(+)	(+)	NA	NA	(-)	(-)	(-)	Sx. improved rapidly after Tx. with IVIg for 5 consecutive days.
	66/M	(+)	(+)	(+)	(+/B)	NA	(+)	(+)	(+/GI)	Tx. with IVIg for 5 days improved ataxia, but pupils remained dilated for 3 months.
López et al. [17]	74/F	(-)	(+)	(-)	NA	NA	(+)	(+)	(+/URI)	Complete remission after 2 months.
Sato et al. [18]	28/M	(+)	(+)	(-)	(+)	NA	(-)	(+)	(+/URI)	Tx. with steroids, pupils returned to normal on day 18.
	29/M	NA	(+)	(-)	NA	NA	(-)	(-)	(+/GI)	Pupil size returned to normal, with normal light reflex noted on day 98.
Man, B. L. [19]	46/F	(+)	(+)	NA	NA	NA	(+)	(+)	(+/URI)	Tx. with IVIg, ophthalmoplegia markedly improved after Tx.
Total	27	10(83.3%)/12	27(100%)/27	9(36.0%)/25	10(76.9%)/13	0(0%)/6	21(77.8%)/27	24(75.0%)/32	16(66.7%)/24	

segmental palsy would be observed because only a portion of the fibers has been damaged. Slow degeneration would also lead to an aberrant regeneration of fibers, which could explain the positive response of tonic pupils to dilute anticholinergics [23]. On the other hand, MFS follows an acute course, showing a quick onset of symptoms and a rather fast complete remission. The presence of generalized pupil palsy without vermiform movements in all cases of MFS that have reported it thus far suggests that an acute paralysis of pupillary nerve fibers occurs in MFS [7, 13, 14]. On such a basis, the variable of segmental palsy with vermiform movements can be a key finding for distinguishing between the diagnosis of MFS and tonic pupil in patients with pupil palsy. In addition, the acute mechanism of paralysis in MFS would cause LND and cholinergic super-sensitivity to be less frequent compared to a disease of a chronic, slow nature such as tonic pupil, in which aberrant regeneration of fibers leads to the two signs.

Third nerve palsy is another disease in which pupillary involvement is often described [24]. However, the paralysis of extraocular muscles is typical in third nerve palsy, which were not observed in our patients [24]. Since most patients with third nerve palsy show a unilateral palsy, laterality is one factor that could be used in distinguishing between third nerve palsy and MFS [24], but the characteristic palsy of extraocular muscles alone suffices in their differential diagnosis. Nonetheless, CNS imaging should be performed in patients with third nerve palsy that have pupil palsy.

In addition, conditions of Botulinum toxin infection share certain characteristics with MFS such as diplopia, bilateral ophthalmoplegia, ptosis, dysphagia, proximal extremity weakness, and pupil palsy [25]. However, because Botulinum toxins interfere with the release of acetylcholine vesicles in the synapse and block neuromuscular transmission, which would cause a negative pupil response to both low and high concentrated pilocarpine [26]. Such response differs from MFS, which responds positively at least to highly concentrated pilocarpine if not both, yet the distinctive symptoms of Botulism toxin infection, bioassay of the toxin, and preceding history of Botulinum toxin exposure (contaminated canned food or contaminated wounds) should be the consideration of greater priority when distinguishing between the two diseases [27].

The clinical course of pupil palsy was acute in all our patients, showing complete remission within2 months. Its recovery preceded the recovery of external ophthalmoplegia, and all except one case in literature reported the same tendencies in prognosis. All these cases indicate that pupil palsy follows a good prognosis, with relatively rapid improvement compared to that of diplopia.

This study is not without limitations. First, the number of patients we have observed is limited, and conclusions drawn out from these observations lack support. To overcome such limitations, we have performed a review of the literature to increase the number of subjects. Second, the number of cases reporting details on the observation of pupil appearances is

very few. Although this was potentially due to a lack of attention on segmental palsy as a key finding in differential diagnosis, all cases that have mentioned it agree on its absence in MFS. Thus, if a pupil palsy is observed, detailed examinations using the slit-lamp is recommended. Third, high concentration eye drop tests were not done in our patients. Responses tohigh concentration pilocarpine could potentially aid in the accurate diagnosis of diseases in which pupil palsy is apparent.

In conclusion, pupil involvement is frequent in MFS and findings such as LND and cholinergic super-sensitivity may be observed. The generalized pupil palsy without vermiform movements could serve as the key finding in the differential diagnosis of MFS with other pupil involving disorders.Prognosis of pupil palsy in MFS is good, with an earlier recovery than symptoms of diplopia. We believe that this information might help in the accurate diagnosis of MFS in patients revealing signs of pupil palsy.

Acknowledgements Thankful to my family, who has always supported me up to this point (JHL).

Funding This work was supported by the New Faculty Startup Fund from Seoul National University (JHJ).

Data availability The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate This study was approved by the institutional research board (IRB) of the Seoul National University Hospital (SNUH, 2010-080-1164) and was performed in accordance with the ethical standards of the Declaration of Helsinki. All patients included in the study provided verbal informed consent. As this study was conducted retrospectively and all data was anonymized, the written informed consent procedures have been exempted under the provisions of IRB of SNUH.

Consent for publication Not applicable for this study.

Competing interests The authors declare no competing interests.

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