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Atypical clinical manifestations of Miller Fisher syndrome

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Abstract

Miller Fisher syndrome (MFS) is characterized by a clinical triad of ophthalmoplegia, ataxia, and areflexia, and is closely associated with serum anti-GQ1b antibody. Although the clinical triad is the cardinal diagnostic clue, a variety of other symptoms and signs beyond the triad have been reported. To elucidate the frequency and characteristics of atypical clinical manifestations of MFS, we recruited 38 patients with MFS and evaluated the symptoms or signs beyond the classic triad. Eleven (29%) of 38 patients had atypical clinical manifestations of MFS such as headache ($n = 6$), delayed facial palsy ($n = 3$), divergence insufficiency ($n = 2$), and taste impairment ($n = 2$). Headache was localized to the periorbital ($n = 3$), temporal ($n = 2$), or whole ($n = 1$) area. Only one of them showed bilateral papilledema and an elevated opening pressure in cerebrospinal fluid analysis. Delayed facial palsy developed after the other signs have reached nadir ($n = 1$) or started to improve ($n = 2$), and did not follow a pattern of descending paralysis with other cranial neuropathies. Two patients showed divergence insufficiency without external ophthalmoplegia, and another two had taste impairment over the entire tongue without the other signs of facial and glossopharyngeal nerve involvements. Our study shows that approximately 30% of MFS patients can have atypical clinical manifestations beyond the classic triad. These results reflect the broad clinical spectrum of MFS, and might be associated with the presence of additional antiganglioside antibodies besides anti-GQ1b in patients with MFS.

Keywords Miller Fisher syndrome · Headache · Delayed facial palsy · Anti-GQ1b antibody

Introduction

Miller Fisher syndrome (MFS) is an acute self-limiting disorder characterized by a clinical triad of ophthalmoplegia, ataxia, and areflexia [1, 2]. It is considered a variant of Guillain-Barré syndrome (GBS), and can overlap with the pharyngeal-cervical-brachial (PCB) variants of GBS or Bickerstaff brainstem encephalitis (BBE) in the clinical course [3, 4]. The antibody to ganglioside GQ1b is well known as biomarkers of MFS [5]. The GQ1b epitope is strongly expressed in ocular motor nerves, dorsal root ganglion neurons, and muscle spindles, and these localizations of the epitope can explain the classic triad of symptoms seen in patients with MFS [6].

Although the clinical triad of ophthalmoplegia, ataxia, and areflexia is the cardinal diagnostic clue in MFS, a variety of other symptoms and signs beyond the triad have been reported. These atypical clinical features include headache [7, 8], delayed facial palsy [9, 10], optic neuropathy [11], taste impairment [12, 13], and micturition disturbance [14]. Their presence can lead to difficulties in the diagnosis of MFS, but expand our understanding to the clinical spectrum and pathogenesis of MFS. The aim of this study was to elucidate the frequency and characteristics of atypical clinical manifestations beyond the clinical triad in MFS.

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Methods

Thirty-eight patients with MFS were consecutively recruited from Pusan National University Yangsan Hospital between 2012 and 2017. All patients initially exhibited the triad of ophthalmoplegia, ataxia, and areflexia. Based on the new diagnostic classification, pure MFS was defined as the presence of only the triad and the absence of limb weakness and hypersomnolence [2]. If there was absence of one feature among the triad, it was assigned to incomplete MFS such as acute ophthalmoparesis (AO) or acute ataxic neuropathy (AAN). When additional features such as bulbar palsy, limb weakness, or hypersomnolence were present throughout the course of the disease, they were classified as overlapping MFS including MFS/PCB, MFS/GBS, and MFS/BBE, as previously described [3].

To determine the presence of ganglioside antibodies, serum samples were obtained from the patients during the acute phase. Immunoglobulin G (IgG) antibodies against the gangliosides GQ1b, GM1, and GD1b were measured using an ELISA or line immunoassay at commercial specialty laboratories (Green Cross Reference Laboratory, Seoul, Korea), as described previously [9, 15].

We reviewed the medical records of all patients. In particular, we evaluated atypical clinical manifestations of MFS, which were defined as the symptoms or signs beyond the classic triad (ophthalmoplegia, ataxia, areflexia) and the features of overlapping MFS (bulbar palsy, limb weakness, hypersomnolence). These included headache, delayed facial palsy, divergence insufficiency, and taste impairment. We analyzed demographic information, neurological examination findings, pattern of clinical evolution, the results of laboratory evaluation, treatment, and outcome.

All experiments followed the tenets of the Declaration of Helsinki and were approved by the Institutional Review Board of Pusan National University Yangsan Hospital. Informed contents were obtained after the nature and possible consequence of this study had been explained to participants.

Results

Detailed demographic and clinical profiles of the patients are described in Table 1. All 38 patients initially developed the classic triad of MFS. Of them, 26 (68%) had pure MFS throughout the disease course including AO ($n = 10$) and AAN ($n = 1$), whereas the remaining 12 (32%) showed overlapping syndrome: MFS/PCB in six, MFS/GBS in four, and MFS/BBE in two. Thirty-four patients (89%) had an antecedent illness prior to developing MFS. Twenty-six (68%) exhibited positivity to the serum anti-GQ1b IgG antibody, and five had additional ganglioside antibodies: anti-GM1 ($n = 1$, case 8), anti-GD1b ($n = 3$, case 26, 31, 32), and anti-GM1/GD1b

($n = 1$, case 5). Twenty-nine patients (76%) were treated with intravenous immunoglobulin (IVIG), whereas the remaining nine received conservative treatments without immunotherapy because they refused IVIG treatment due to a high cost. In 32 patients with regular follow-ups, the ophthalmoplegia improved markedly within 5 months after the disease onset.

Atypical clinical manifestations

Eleven (29%) of 38 patients had atypical clinical manifestations of MFS such as headache, delayed facial palsy, divergence insufficiency, and taste impairment.

Six patients (16%) had headache with moderate severity (mean Wong-Baker FACES Pain Rating Scale, 5.5 ± 2.3; Table 2) before use of IVIG. It occurred prior to ($n = 3$), concurrent with ($n = 2$), or following ($n = 1$) the onset of ophthalmoplegia. Five of them had the localized pain to the periorbital ($n = 3$) or temporal ($n = 2$) area, while one had generalized headache involving the whole head. The character of pain was variable, which described as dull, tight, splitting, pressing, sharp, or shooting. All had normal findings on brain MRI. Only one (case 30) showed bilateral papilledema and an elevated opening pressure in cerebrospinal fluid (CSF) analysis (Fig. 1). CSF protein was normal in all. Anti-GQ1b IgG antibody was positive in three (case 4, 19, 28). The use of oral nonsteroidal anti-inflammatory drugs failed to relieve pain satisfactorily in most patients, but the pain disappeared within 2 weeks after the onset before the resolution of ophthalmoplegia (mean 2.6 months).

Three patients (8%) developed delayed facial palsy after the other neurological signs have reached nadir (case 29) or start to improve (case 10, 18) (Table 3). The onset of facial palsy was 10–16 days after disease onset. The facial palsy was unilateral in two patients (case 18, 29) and bilateral in one (case 10). The patients showed variable patterns of clinical evolution during the disease course. In all, facial nerve involvement occurred only after the development of the upper cranial nerves (3rd, 4th, 6th cranial nerve). However, one (case 10) of them developed bulbar palsy during the disease course before the involvement of facial nerve. Furthermore, two (case 10, 29) had an earlier involvement of the 6th cranial nerve which was followed by involvement of other ocular motor nerves (3rd or 4th cranial nerve). Anti-GQ1b IgG antibody was positive in only one (case 18). The facial palsy resolved completely with the improvement of ophthalmoplegia within 2 months.

Two patients (case 5, 27) showed divergence insufficiency without external ophthalmoplegia (Fig. 2). All presented with horizontal diplopia only at distance, ataxia, and areflexia after antecedent illness. Ocular duction and version were normal without limited abduction, but one (case 5) of them had dilated pupils unreactive to light. Prism cover test revealed 10 (case 5) and 4 (case 27) prism diopters of esotropia only at distance.

Table 1 Demographic and clinical characteristics of 38 patients with Miller Fisher Syndrome

Patient no.	Age/ sex	Classification	Ophthalmoplegia			Ataxia	Areflexia	Atypical clinical manifestation	Ganglioside antibodies	Treatment
			EO	IO	Ptosis					
1	50/M	Pure MFS	V(B), H(B)	(−)	(−)	(+)	(+)	Taste impairment	Anti-GQ1b (+)	IVIG
2	30/F	Pure MFS	V(L), H(B, ab)	(−)	L	(+)	(+)	(−)	Anti-GQ1b (+)	IVIG
3	60/F	Pure MFS	V(B), H(B)	(−)	(−)	(+)	(+)	(−)	Anti-GQ1b (+)	IVIG
4	55/F	Pure MFS	V(B), H(B)	B(s)	B	(+)	(+)	Headache (WB7)	Anti-GQ1b (+)	IVIG
5	27/F	Pure MFS	(−)	B(n)	R	(+)	(+)	Divergence insufficiency	Anti-GQ1b/GM1/GD1b (+)	IVIG
6	26/M	MFS/GBS	V(R, u), H(B)	B(s)	B	(+)	(+)	(−)	Anti-GQ1b (+)	IVIG
7	51/M	MFS/PCB	V(B), H(B)	B(s)	B	(+)	(+)	(−)	Anti-GQ1b (+)	IVIG
8	46/F	Pure MFS	V(B), H(B)	B(n)	B	(+)	(+)	(−)	Anti-GQ1b/GM1 (+)	IVIG
9	79/M	MFS/PCB	V(B), H(B)	(−)	B	(+)	(+)	(−)	Anti-GQ1b (+)	IVIG
10	23/M	MFS/PCB	V(B), H(B, ab)	(−)	R	(+)	(+)	Delayed facial palsy	(−)	IVIG
11	19/F	Pure MFS	H(B, ab)	(−)	(−)	(+)	(+)	(−)	(−)	IVIG
12	19/M	Pure MFS	V(B), H(B)	(−)	(−)	(+)	(+)	Headache (WB5)	(−)	IVIG
13	76/F	Pure MFS	V(B), H(B)	B(s)	(−)	(+)	(+)	(−)	(−)	IVIG
14	64/F	Pure MFS	V(B), H(B)	(−)	(−)	(+)	(+)	(−)	(−)	IVIG
15	54/M	Pure MFS	V(B), H(B)	(−)	(−)	(+)	(+)	(−)	Anti-GQ1b (+)	Conservative
16	56/M	Pure MFS	V(B), H(B)	(−)	(−)	(+)	(+)	(−)	Anti-GQ1b (+)	Conservative
17	46/M	Pure MFS	V(B), H(B)	B(s)	(−)	(+)	(+)	(−)	Anti-GQ1b (+)	IVIG
18	50/M	Pure MFS	V(B), H(B)	(−)	B	(−)	(+)	Delayed facial palsy	Anti-GQ1b (+)	IVIG
19	45/M	Pure MFS	V(B), H(B)	B(s)	B	(−)	(+)	Headache (WB4)	Anti-GQ1b (+)	IVIG
20	64/F	MFS/PCB	V(B), H(B)	(−)	(−)	(−)	(+)	(−)	Anti-GQ1b (+)	IVIG
21	66/F	Pure MFS	V(R), H(B)	(−)	(−)	(−)	(−)	(−)	Anti-GQ1b (+)	Conservative
22	35/M	Pure MFS	H(R, ab)	(−)	(−)	(−)	(−)	(−)	Anti-GQ1b (+)	Conservative
23	38/M	Pure MFS	V(B), H(B)	B(n)	(−)	(−)	(+)	(−)	Anti-GQ1b (+)	Conservative
24	40/M	Pure MFS	H(B, ab)	(−)	(−)	(−)	(+)	(−)	Anti-GQ1b (+)	Conservative
25	56/F	Pure MFS	H(B, ab)	(−)	(−)	(−)	(+)	(−)	Anti-GQ1b (+)	Conservative
26	60/M	Pure MFS	H(R, ab)	(−)	(−)	(−)	(−)	(−)	Anti-GQ1b/GD1b (+)	Conservative
27	36/M	Pure MFS	(−)	(−)	(−)	(+)	(+)	Divergence insufficiency	Anti-GQ1b (+)	IVIG
28	17/F	MFS/PCB	V(R), H(B)	B(s)	R	(+)	(−)	Headache (WB7), taste impairment	Anti-GQ1b (+)	IVIG
29	57/M	Pure MFS	V(B), H(B)	B(n)	L	(−)	(+)	Headache (WB3), delayed facial palsy	(−)	IVIG
30	47/F	Pure MFS	V(B), H(B)	B(n)	L	(−)	(−)	Headache (WB4)	(−)	IVIG
31	64/M	MFS/GBS	H(B, ab)	(−)	(−)	(+)	(+)	(−)	Anti-GQ1b/GD1b (+)	IVIG/PP
32	79/M	MFS/GBS	V(B), H(B)	B(s)	B	(+)	(+)	(−)	Anti-GQ1b/GD1b (+)	IVIG
33	31/M	MFS/GBS	H(B, ab)	B(s)	(−)	(−)	(+)	(−)	(−)	IVIG
34	21/F	Pure MFS	H(B, ab)	(−)	(−)	(+)	(+)	(−)	(−)	Conservative
35	29/M	Pure MFS	V(B, u), H(B, ab)	(−)	(−)	(+)	(−)	(−)	(−)	IVIG
36	25/M	MFS/BBE	V(B, u), H(B)	(−)	(−)	(+)	(−)	(−)	(−)	IVIG
37	16/M	MFS/BBE	H(L, ab)	(−)	(−)	(+)	(+)	(−)	(−)	IVIG
38	45/F	MFS/PCB	V(B), H(B)	(−)	B	(+)	(+)	(−)	(−)	IVIG

ab abduction palsy only, *B* bilateral, *BBE* Bickerstaff brainstem encephalitis, *EO* external ophthalmoplegia, *F* female, *GBS* Guillain-Barré syndrome, *H* horizontal, *IO* internal ophthalmoplegia, *IVIG* intravenous immunoglobulin, *L* left, *M* male, *MFS* Miller Fisher syndrome, *n* nonreactive, *PCB* pharyngeal-cervical-brachial variant, *PP* plasmapheresis, *R* right, *s* sluggish, *u* upgaze palsy only, *V* vertical, *WB* Wong-Baker FACES Pain Rating Scale

Table 2 Headache characteristics and laboratory results of six patients with Miller Fisher Syndrome and headache

Patient no.	Sex/ age	Classification	Headache				Papilledema	CSF		Response to NSAID
			Onset	Location	Characteristics	Severity†		Opening pressure	Protein	
4	F/55	Pure MFS	2 days before onset of diplopia	Retro-orbital (L)	Dull	7	No	120	43.3	No
12	M/19	Pure MFS	Concurrent with diplopia	Whole	Tight	5	No	180	24	No
19	M/45	Pure MFS	Concurrent with diplopia	Retro-orbital (B)	Splitting	4	No	150	39	No
28	F/17	Pure MFS	3 days before onset of diplopia	Temporal (B)	Pressing	7	No	220	13	Self-limited
29	M/57	Pure MFS	1 day before onset of diplopia	Temporal (L)	Sharp	3	No	135	29	Slightly
30	F/47	Pure MFS	3 days after onset of diplopia	Periorbital	Shooting	4	Yes	250	30.4	Slightly

†The severity of headache is based on the Wong-Baker FACES Pain Rating Scale

B bilateral, *CSF* cerebrospinal fluid, *F* female, *L* left, *M* male, *MFS* Miller Fisher syndrome, *NSAID* nonsteroidal anti-inflammatory drug

Video-oculography exhibited normal amplitude and velocity of abducting saccades. They did not develop external ophthalmoplegia during the disease course. After IVIG treatment, horizontal diplopia and esotropia at distance resolved within 2 months.

Two patients (case 1, 28) complained of taste impairment without facial nerve palsy during the disease course. They did not recognize any sensation of taste over the entire tongue, including sweetness, sourness, saltiness, and bitterness. Their taste impairment resolved completely within 1 month before the resolution of ophthalmoplegia.

Discussion

In our study, approximately 30% of MFS patients had atypical clinical manifestations beyond the classic triad. These included headache, delayed facial palsy, divergence insufficiency,

Fig. 1 Nine-gaze photograph and fundus photograph of case 30 presenting with headache. **a** The patient has ptosis in the left eye and complete external ophthalmoplegia in the nine cardinal position of gaze. **b** Fundus photograph shows grade 2 (Frisén grading system) papilledema in both eyes
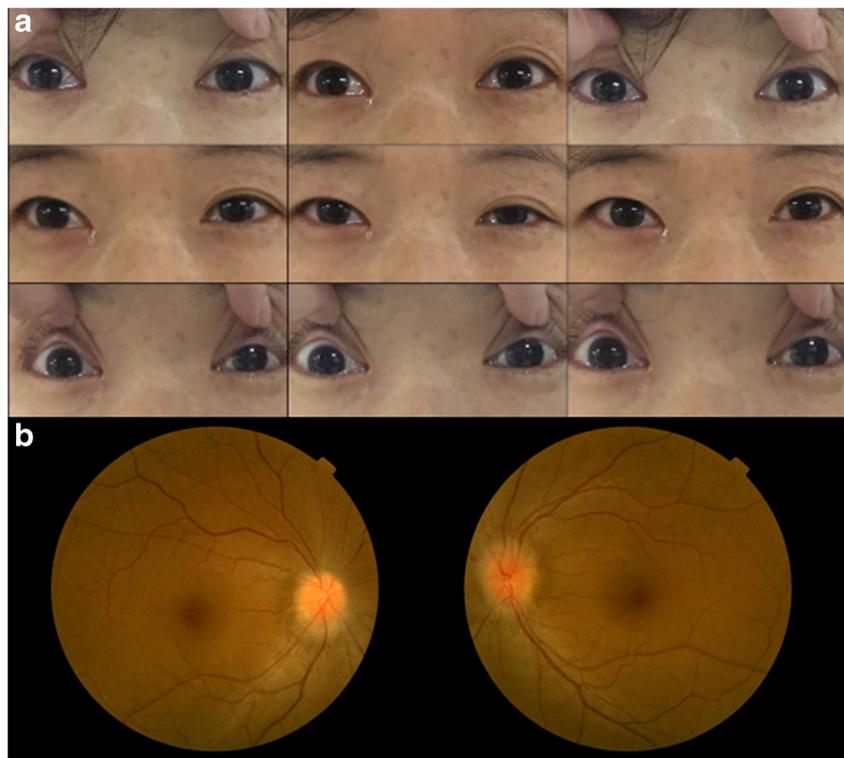
Table 3 Clinical features of delayed facial palsy in three patients with Miller Fisher Syndrome

	Case 10	Case 18	Case 29
Age/sex	23/M	50/M	57/M
Classification	MFS/PCB	Pure MFS	Pure MFS
Antecedent illness	(+)	(+)	(−)
Symptoms/signs			
Ophthalmoplegia	(+)	(+)	(+)
Ptosis	(+)	(+)	(−)
Mydriasis	(−)	(−)	(+)
Ataxia	(+)	(−)	(−)
Areflexia	(+)	(+)	(+)
Bulbar palsy	(+)	(−)	(−)
Dysesthesia	(+)	(−)	(−)
Immunotherapy	IVIG	IVIG	IVIG
Day of neurological nadir	7	4	9
Day of neurological improvement	11	7	20
Day of onset of facial palsy	16	10	15
Side of facial palsy	Bilateral	Left	Right
Consecutive involvement of CN	CN3,6 ➜ bulbar palsy ➜ CN4 ➜ CN7	CN3,4,6 ➜ CN7	CN6 ➜ CN3,4 ➜ CN7

CN cranial nerve, *F* female, *IVIG* intravenous immunoglobulin, *L* left, *M* male, *MFS* Miller Fisher syndrome, *PCB* pharyngeal-cervical-brachial variant

and taste impairment. The presence of these atypical features reflects the wild clinical spectrum of MFS and expands its pathogenesis. Furthermore, recognizing atypical features of MFS can help avoid unnecessary examinations.

We would like to highlight that headache is not uncommon in MFS. In our study, 16% of the patients experienced headache during the acute phase of MFS. In MFS, headache appears to be considerably less common than other symptoms,

Fig. 2 Nine-gaze photograph and Hess screen test of case 5 presenting with divergence insufficiency. **a** The patient has no limitation of the extraocular muscles in the nine cardinal position of gaze. **b** Hess screen test shows esotropia without paresis of both lateral rectus muscles and lateral incomitancy
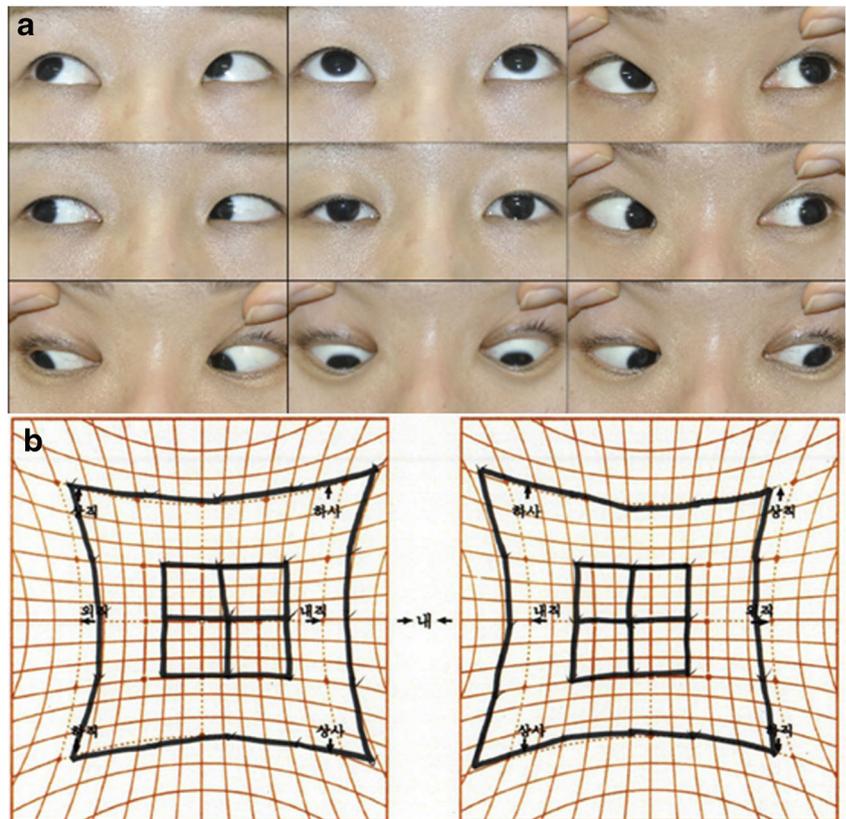
and a few patients have been reported having headache in the literature [1, 7, 8]. However, two of three patients in Fisher's original report complained of headaches during the acute phase, which was aggravated by coughing [1]. In case series of 27 patients with MFS, three (11%) reported having headache around the orbit early in their disease course [7]. The authors described that periorbital pain may be characteristic of MFS, leading to differentiate MFS from Tolosa-Hunt syndrome or ophthalmoplegic migraine. In our study, however, the location of headaches was variable including periorbital, temporal, or whole area. The pathogenesis of headache in MFS is uncertain. Although headache associated with posterior reversible encephalopathy syndrome (PRES) has been reported in GBS [16], our patients with headache had no evidence of PRES on brain MRIs. Elevated intracranial pressure (ICP) due to increased CSF protein concentration could be considered as a potential cause of headache, but headache usually started days before the elevation of CSF protein [17]. In our study, only one patient showed headache and papilledema associated with elevated ICP, but CSF protein level was within normal range. Another potential explanation may be antibody-mediated effects on the trigeminovascular pain pathway [8]. The GQ1b ganglioside is strongly expressed in the oculomotor, trochlear, and abducens nerves, but the other cranial nerves including trigeminal nerve also contain the GQ1b with a small amount [6]. The GD3 and GD1b are major gangliosides of all cranial nerves along with the ventral and dorsal roots of the spinal cord [6]. Thus, demyelination of the cervical and cranial sensory nerves by antiganglioside antibodies may result in activation of the trigeminovascular pain pathway, leading to headache [8].

In this case series, three (8%) patients developed delayed facial palsy. The patients reached neurological nadir within 4–9 days, but the onset of facial palsy was 10–16 days after disease onset, which is similar to the onset days of other reports [9, 10]. The exact mechanism of delayed facial palsy remains unclear. Some authors speculated "reversible descending paralysis" from the consequent involvement of cranial nerves and good outcome [9]. They found that earlier involvement of the upper cranial nerves was followed by involvement of the lower cranial nerves. However, this hypothesis is not supported by the early presence of bulbar palsy that was observed in one patient of our series and other reported cases [10]. Furthermore, the involvement of ocular motor nerves did not follow the pattern of descending paralysis in two of our patients. Alternatively, the proximal conduction block and long length of facial nerve may be involved in the development of delayed facial palsy [9, 10]. These raise the possibility that it will take more time to develop clinically apparent facial weakness. The existence of other undetectable antibody may be another explanation. The facial nerve contained elevated concentrations of GD1a, GD1b, and GT1b, but significantly lower GQ1b than ocular motor nerves

[6]. Although anti-GD1b antibody was not detected in any patients with delayed facial palsy, other antibodies that have not yet been discovered may be associated with the pathogenesis of delayed facial palsy.

Interestingly, two patients in our study had horizontal diplopia due to divergence insufficiency. They showed an esotropia only at distance without external ophthalmoplegia. Although subtle abduction paresis should be considered, ocular duction and abducting saccade test were normal. In addition, there was no progression to external ophthalmoplegia during the disease course. Divergence insufficiency can be caused by a variety of underlying pathologies including pseudotumor cerebri, progressive supranuclear palsy, cerebellar ataxia, or myasthenia gravis [18]. In the literature, only two reports have mentioned divergence insufficiency as the clinical manifestation of MFS [19, 20]. Experimental studies in monkeys have shown that the supraoculomotor area, which is located adjacent to the oculomotor nucleus in the midbrain, encodes vergence movements [21]. This area is thought to receive input from the cerebellum such as the caudal fastigial nuclei (cFN) and the posterior interposed nucleus (PIN). Thus, a disruption of the cFN/PIN-supraoculomotor area-medial rectus motoneuron circuit can provide a convergence bias signal to the medial rectus muscle, resulting in esotropia at distance [22]. The GQ1b expression is also found in both cerebellum and brainstem, and hypermetabolism of these structures has been documented in MFS [23]. These findings indicate that antibody-mediated inflammatory process in central nervous system may contribute to divergence insufficiency without external ophthalmoplegia in MFS.

Taste impairment is a very rare clinical feature of MFS. Only a few cases with MFS presenting with taste impairment have been reported in the literature [12, 13]. Taste sensations of the anterior two thirds and posterior one third of the tongue are innervated by facial and glossopharyngeal nerves, respectively [24]. However, our patients showed taste impairment over the entire tongue without the other signs of facial and glossopharyngeal nerve involvements. This suggests that antiganglioside antibodies including anti-GQ1b may affect the afferent sensory nerves at the level of the taste buds, not the entire facial or glossopharyngeal nerves.

The present study has some limitations. Due to small sample size, we could not analyze the relationship between antiganglioside antibody and atypical clinical manifestations. Furthermore, we did not measure other antibodies such as anti-GT1a or anti-GD3 antibody. However, the diagnosis of MFS should be made by clinical features, not laboratory data [2].

In conclusion, we would like to emphasize that MFS can show atypical clinical manifestations beyond the classic triad. This reflects the broad clinical spectrum of MFS, and might be associated with the presence of additional antiganglioside antibodies besides anti-GQ1b.

Compliance with ethical standards

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