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ORIGINAL COMMUNICATION

Characteristics of single ocular motor nerve palsy associated with anti-GQ1b antibody

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Abstract

To define the prevalence and characteristics of single ocular motor nerve palsy (OMNP) associated with positive serum anti-GQ1b antibody. We performed a prospective multicenter study that recruited 82 patients with single OMNP without identifiable causes from the history and neuroimaging in six neurology clinics of university hospitals. We measured serum anti-GQ1b antibody in all participants. Twelve patients with multiple OMNP and 30 with identifiable causes served as the controls. Overall, the prevalence of anti-GQ1b antibody syndrome was 10% (8/82) in patients with single OMNP and 6% (5/78) in those with single OMNP in isolation. None of the 14 patients with OMNP with identifiable causes showed positive serum anti-GQ1b antibody. The prevalence of anti-GQ1b antibody syndrome was much higher in patients with multiple OMNP than in those with single OMNP (50% vs. 10%, $p<0.01$). Patients with single OMNP and positive anti-GQ1b antibody are younger (42 ± 16 vs. 58 ± 15, $p<0.05$) and had a significantly higher frequency of preceding infection (75 vs. 19%, $p<0.05$) and other neurological signs (38 vs. 1%, $p<0.05$) than those with negative antibody. Eight patients with single OMNP and positive serum anti-GQ1b antibody involved the abducens ($n=6$), trochlear ($n=1$), or oculomotor nerve ($n=1$). Single OMNP accompanying other neurological signs and multiple OMNP are more likely to be associated with anti-GQ1b antibody. Anti-GQ1b antibody syndrome should be considered even in patients with single OMNP, especially when antecedent infection was associated in younger patients.

Keywords Acquired ocular motor nerve palsy · Isolated ocular motor nerve palsy · Anti-GQ1b antibody · Anti-ganglioside antibody · Fisher syndrome

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Introduction

Anti-GQ1b antibody has been found in Guillain–Barre' syndrome with ophthalmoplegia, Fisher syndrome (FS), and Bickerstaff brainstem encephalitis (BBE) [1–4]. Recently, acute ophthalmoplegia without ataxia (AO) was added to the clinical spectrum of anti-GQ1b antibody syndrome [5–7]. The ophthalmoplegia in FS and AO is usually bilateral and symmetric [1], but may be isolated and unilateral [5]. In these instances, the ophthalmoplegia may mimic single ocular motor nerve palsy (OMNP), which would necessitate pursuit of other etiologies and remain idiopathic without measurement of serum anti-GQ1b antibody. Previous reports on single OMNP associated with anti-GQ1b antibody have been mostly limited to anecdotal case reports [8–11], and few studies have systematically investigated the prevalence and clinical features of anti-GQ1b antibody syndrome presenting single OMNP.

This study aimed to determine the prevalence and characteristics of single OMNP associated with anti-GQ1b antibody by adopting a prospective multi-center design.

Subjects and methods

We performed a prospective multicenter study that had recruited 82 patients with a single OMNP without identifiable causes in six neurology clinics of university hospitals in Korea between September 2015 and February 2016. The inclusion criteria were (1) acquired binocular diplopia within 14 days of onset, (2) diplopia due to a single OMNP, and (3) no alternative causes on MRIs and clinical and laboratory tests. We excluded the patients with a prior history of strabismus, preceding head trauma, orbital diseases, diplopia due to extraocular muscle, neuromuscular junction, nuclear or supranuclear disorders, inability to undergo MRIs, and incomplete data.

For comparison, we additionally recruited 30 patients with acquired OMNP due to known causes, and 12 with multiple OMNP including four with a clinical diagnosis of FS. The known causes included Tolosa–Hunt syndrome ($n=14$), head trauma ($n=3$), tumor ($n=4$), cerebral infarction ($n=3$), myasthenia gravis ($n=2$), carotid cavernous fistula ($n=2$), and sarcoidosis ($n=2$).

The serum was obtained from all participants within 2 weeks from the symptom onset and before any treatment. The serum was analyzed for the presence of IgM/IgG antibodies against GQ1b with the GanglioCombi ELISA (BÜHLMANN Laboratories, Switzerland). The serum was considered positive for anti-GQ1b Ab when the antibody titer was above 50% of the reference value.

Patients with anti-GQ1b antibody-associated single OMNP received medical treatments or were followed up without a specific treatment. All the patients were followed up at least for 1 year, and the outcome was considered resolved when both the tropia and diplopia disappeared.

We compared the clinical characteristics and the prevalence of anti-GQ1b antibody syndrome using Fisher's exact and Mann–Whitney *U* tests between the patients with single and multiple OMNPs, patients with positive and negative serum anti-GQ1b antibody in single OMNP, and among the patients with a single OMNP involving each ocular motor nerve. We performed statistical analyses using SPSS (version 18.0, Chicago, IL, USA) and $p<0.05$ was considered significant.

This study followed the tenets of Declaration of Helsinki and was approved by the Institutional Review Boards of Pusan National University Hospital (1605-001-041).

Results

Eighty-two patients with single OMNP included 56 men (68%) with the age range from 15 to 81 years (mean 57.7 ± 15.6). Of them, 78 patients (95%) had single OMNP in isolation while the remaining 4 (5%) showed other neurological signs that included ataxia ($n=3$), areflexia ($n=3$), or dysarthria ($n=1$).

We found positive serum anti-GQ1b antibody in 8 (10%) of the 82 patients with single OMNP and in 5 (6%) of the 78 patients with isolated single OMNP (Tables 1, 2). In contrast, none of the 30 patients with identifiable causes of OMNP showed positive serum anti-GQ1b antibody. The prevalence of anti-GQ1b antibody syndrome in multiple OMNP was higher than in single OMNP (50% vs. 10%, $p<0.01$).

Table 1 Prevalence of anti-GQ1b antibody syndrome in acquired OMNP

Acquired OMNP	Anti-GQ1b antibody syndrome, *n* (%)
Single OMNP ($n=82$)	8 (10)
With neurological signs ($n=4$)	3 (75)
Isolated ($n=78$)	5 (6)
III ($n=16$)	0 (0)
IV ($n=20$)	1 (5)
VI ($n=42$)	4 (10)
Multiple OMNP ($n=12$)	6 (50)
OMNP with identifiable causes ($n=14$)	0 (0)

OMNP ocular motor nerve palsy, *III* oculomotor nerve palsy, *IV* trochlear nerve palsy, *VI* abducens nerve palsy

Table 2 Characteristics of eight patients with single OMNP due to anti-GQ1b antibody syndrome

Patients	Sex	Age, years	Preceding infection	Headache or ocular pain	OMNP	Ataxia	Areflexia	Additional features
Single OMNP plus other findings ($n=3$)								
1	M	66	+	−	Single, 3rd	+	+	−
2	M	31	+	−	Single, 6th	+	+	Dysarthria
3	M	29	+	−	Single, 6th	-	+	−
Isolated single OMNP ($n=5$)								
4	F	46	−	+	Single, 4th	−	−	−
5	M	33	−	−	Single, 6th	−	−	−
6	M	65	+	−	Single, 6th	−	−	−
7	M	40	+	−	Single, 6th	−	−	−
8	M	22	+	+	Single, 6th	−	−	−

OMNP ocular motor nerve palsy, *B* bilateral, *GEN* gaze-evoked nystagmus

Compared to the patients with single OMNP and negative serum anti-GQ1b antibody ($n=74$), the patients with positive anti-GQ1b antibody ($n=8$) are younger (42 ± 16 vs. 58 ± 15, $p<0.05$) and had a higher frequency of preceding infection (75 vs. 19%, $p<0.05$) and other neurological signs (38 vs. 1%, $p<0.05$) (Table 3).

Serum anti-GQ1b antibody was positive in 14% (6/44) of the patients with single OMNP involving the abducens nerve, 6% (1/18) of those involving the oculomotor nerve, and 5% (1/20) of those involving the trochlear nerve. The prevalence of anti-GQ1b antibody syndrome did not differ among the patients with single OMNP involving each ocular motor nerve ($p>0.05$).

In one patient (patient 7), the initial single OMNP progressed into bilateral complete external ophthalmoplegia. Except one (patient 5) with a follow-up loss, six were treated with IV immunoglobulin ($n=2$, patients 1 and 2) or steroids ($n=4$) while the remaining one (patient 6) was followed up without a specific treatment. The ophthalmoplegia resolved within 6 months of symptom onset in 6 patients and by 1 year in the remaining patient ($n=1$, patient 7).

Discussion

This study showed that the overall prevalence of anti-GQ1b antibody syndrome was 10% in patients with single OMNP and 6% in patients with single OMNP in isolation. None of the 30 patients with other causes of OMNP showed positive serum anti-GQ1b antibody, convincing high specificity. Multiple OMNP and single OMNP accompanying other neurological signs or preceding infection were more often associated with positive serum anti-GQ1b antibody. In addition, patients with single OMNP associated with anti-GQ1b antibody were younger than those without antibody.

These results are similar to those of a recent study with small series of patients [12]. Serum anti-GQ1b antibody was positive in 11 of 12 patients with MFS, but only in one of the nine with single OMNP due to microangiopathy or

Table 3 Comparison of clinical characteristics between patients with isolated single OMNP having positive and negative serum anti-GQ1b antibody

	Single OMNP with anti-GQ1b antibody syndrome ($n=8$)	Single OMNP without anti-GQ1b antibody syndrome ($n=74$)	p value
Age, years, mean (SD)	42 (16)	58 (15)	0.006
Male, *n* (%)	7 (88)	49 (66)	0.425
Headache and/or ocular pain, *n* (%)	2 (25)	24 (32)	1.000
Other neurological signs, *n* (%)	3 (38)	1 (1)	0.002
Preceding infection, *n* (%)	6 (75)	14 (19)	0.002
Complete paralysis (III and VI), *n* (%)	3 (43)	12 (22)	0.157
Resolution within 6 months, *n* (%)	6 (86)[a]	66 (93)[b]	0.251

OMNP ocular motor nerve palsy, *III* oculomotor nerve palsy, *IV* trochlear nerve palsy, *VI* abducens nerve palsy

[a]We could not assess in one patient due to loss of follow-up evaluation

[b]We could not assess in three patients due to loss of follow-up evaluation

undetermined cause. Of interest, five patients in our study showed isolated single OMNP in association with anti-GQ1b antibody while one patient of the previous study had single OMNP, but in association with other multiple cranial neuropathy.

Although the possibility of secondary causes was believed to be higher in patients with single OMNP combined with additional neurological signs or multiple OMNP, identification of causes other than microvascular ischemia is challenging in isolated OMNP, especially when the history, routine laboratory evaluation and neuroimaging are unrevealing. Of the patients aged 50 years or more with isolated OMNP, 4 to 17% had causes other than microvascular ischemia [13, 14]. However, there has been no clinical guideline available for differentiation of other causes from presumed microvascular ischemia in isolated OMNP. Our results suggest that anti-GQ1b antibody syndrome should be considered in the differential diagnosis of acute single OMNP of undetermined etiology, especially when it occurs in young patients or is accompanied by antecedent infection.

In our study, anti-GQ1b antibody tended to involve the abducens nerve (14%) more often than the oculomotor (6%) or trochlear (5%) nerve although there was no statistical difference among the groups possibly due to small number of patients. This is in accordance with the results of previous studies. There have been several reports on abducens nerve palsy in association with anti-GQ 1b antibody, and one retrospective review also showed a higher incidence (25%) of anti-GQ1b antibody syndrome among 100 patients with isolated abducens nerve paresis [8, 9]. In contrast, isolated oculomotor or trochlear nerve palsy has been rarely reported in association with anti-GQ1b antibody syndrome [10, 11]. Immunohistochemical studies using an anti-GQ1b monoclonal antibody disclosed similar accumulation of GQ1b epitope in the paranodal regions of the oculomotor, trochlear and abducens cranial nerves [15]. The issue needs further investigation with a larger population of patients.

The present study has limitations because of a small sample size and selection bias. Since this study was based on the data from the neurology clinics of tertiary care hospitals, the results may not be generalized to the community hospitals or the ambulatory care units.

Compliance with ethical standards

Conflicts of interest We have no disclosure of any competing interest.

Ethical approval for research involving human participants and/or animals All experiments followed the tenets of the Declaration of Helsinki, and this study was approved by the Institutional Review Board of Pusan National University Hospital (1605-001-041).

References

1. Odaka M, Yuki N, Hirata K (2001) Anti-GQ1b IgG antibody syndrome: clinical and immunological range. J Neurol Neurosurg Psychiatry 70:50–55
2. Ito M, Kuwabara S, Odaka M, Misawa S, Koga M, Hirata K, Yuki N (2008) Bickerstaff's brainstem encephalitis and Fisher syndrome form a continuous spectrum: clinical analysis of 581 cases. J Neurol 255:674–682
3. Snyder LA, Rismondo V, Miller NR (2009) The Fisher variant of Guillain-Barre syndrome (Fisher syndrome). J Neuroophthalmol 29:312–324
4. Shahrizaila N, Yuki N (2013) Bickerstaff brainstem encephalitis and Fisher syndrome: anti-GQ1b antibody syndrome. J Neurol Neurosurg Psychiatry 84:576–583
5. Lee SH, Lim GH, Kim JS, Oh SY, Kim JK, Cha JK, Yun CH, Kang JK, Lee H, Song HK, Chung KC (2008) Acute ophthalmoplegia (without ataxia) associated with anti-GQ1b antibody. Neurology 71:426–429
6. Yuki N, Odaka M, Hirata K (2001) Acute ophthalmoparesis (without ataxia) associated with anti-GQ1b IgG antibody: clinical features. Ophthalmology 108:196–200
7. Sakurai Y, Mannen T, Kusunoki S (1998) Acute isolated ophthalmoplegia as a variant of Miller-Fisher syndrome. Muscle Nerve 21:1107
8. Tatsumoto M, Odaka M, Hirata K, Yuki N (2006) Isolated abducens nerve palsy as a regional variant of Guillain-Barre syndrome. J Neurol Sci 243:35–38
9. Kinno R, Ichikawa H, Tanigawa H, Itaya K, Kawamura M (2011) Unilateral abducens nerve palsy as an early feature of multiple mononeuropathy associated with anti-GQ1b antibody. Case Rep Neurol 3:82–85
10. Choi KD, Choi JH, Choi HY, Huh YE, Kim HJ, Oh SY, Jeong SH, Hwang JM, Kim JS (2013) Inferior rectus palsy as an isolated ocular motor sign: acquired etiologies and outcome. J Neurol 260:47–54
11. Ueno T, Kon T, Kurihara AI, Tomiyama M (2017) Unilateral oculomotor nerve palsy following campylobacter infection: a mild form of Miller Fisher syndrome without ataxia. Intern Med 56:2929–2932
12. Spatola M, Du Pasquier R, Schluep M, Regeniter A (2016) Serum and CSF GQ1b antibodies in isolated ophthalmologic syndromes. Neurology 86:1780–1784
13. Chou KL, Galetta SL, Liu GT, Volpe NJ, Bennett JL, Asbury AK, Balcer LJ (2004) Acute ocular motor mononeuropathies: prospective study of the roles of neuroimaging and clinical assessment. J Neurol Sci 219:35–39
14. Tamhankar MA, Biousse V, Ying GS, Prasad S, Subramanian PS, Lee MS, Eggenberger E, Moss HE, Pineles S, Bennett J, Osborne B, Volpe NJ, Liu GT, Bruce BB, Newman NJ, Galetta SL, Balcer LJ (2013) Isolated third, fourth, and sixth cranial nerve palsies from presumed microvascular versus other causes: a prospective study. Ophthalmology 120:2264–2269
15. Chiba A, Kusunoki S, Obata H, Machinami R, Kanazawa I (1997) Ganglioside composition of the human cranial nerves, with special reference to pathophysiology of Miller Fisher syndrome. Brain Res 745:32–36