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【 CASE REPORT 】

Acute Oropharyngeal Palsy Following Bilateral Adie's Tonic Pupils Associated with Anti-GT1a and GQ1b IgG Antibodies

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Abstract:
A 36-year-old man was admitted to our hospital with complaints of dysphagia and photophobia. A neurological examination showed oropharyngeal palsy and bilateral mydriasis with loss of light reflexes in the absence of external ophthalmoplegia. Bilateral pupils were supersensitive to pilocarpine 0.1%, which was compatible with Adie's tonic pupils. Serum IgG reacted with GQ1b, GT1a, GalNAc-GD1a, and GD3. Intravenous high-dose immunoglobulin therapy improved his neurological symptoms within three weeks. To our knowledge, there is no medical literature describing acute oropharyngeal palsy with Adie's tonic pupils. We recommend evaluating antiganglioside antibodies to clarify the cause of oropharyngeal palsy and Adie's tonic pupils.

Key words: acute oropharyngeal palsy, Adie's tonic pupils, isolated internal ophthalmoplegia, GT1a, GQ1b

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Introduction

Acute oropharyngeal palsy (AOP) has been described as a rare variant of Guillain-Barré syndrome (GBS) or Miller Fisher syndrome (MFS) in the absence of neck or limb weakness with a high titer of IgG anti-GQ1b and anti-GT1a antibodies (1). External ophthalmoplegia is one of the most common concomitant neurological findings with AOP during the disease course, and several cases of AOP with severe external ophthalmoplegia have concomitantly presented with internal ophthalmoplegia (2). However, only one case of AOP with internal ophthalmoplegia in the absence of external ophthalmoplegia has been reported, and there has been controversy as to whether or not AOP-related isolated internal ophthalmoplegia is compatible with Adie's tonic pupils (3).

We herein report a case of AOP with bilateral Adie's tonic pupils and discuss the association of clinical phenotypes with anti-ganglioside antibodies.

Case Report

A previously healthy 36-year-old man was admitted to our hospital with a nasal voice, nasopharyngeal reflux, difficulty in swallowing, photophobia, and numbness in the distal extremities starting 4 days before admission. He had no antecedent infections before the development of neurological symptoms.

On admission, he was afebrile and mentally alert. A neurological examination showed bilateral mydriasis (6.0 mm in diameter) with loss of direct and consensual light reflexes and normal near reaction, i.e. light-near dissociation. His distant visual acuity was normal, and his near acuity was not tested. External ocular movements were intact. There was bilateral paralysis of the soft palate and loss of pharyngeal reflexes.

A sensory examination showed decreased vibratory sensation in the bilateral distal lower limbs but preserved sensation in the proximal lower limbs and upper limbs. Position sensation was preserved in the limbs and trunk. Patella ten-

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Table 1. Results of Nerve Conduction Studies.

	MCV (m/s)	CMAP (mV)	F wave occurrence (%)	FWCV (m/s)	SCV (m/s)	SNAP (μV)
Median, L	57.4	19.4	94	64.0	50.7	15.5
Ulnar, L	58.6	15.1	100	66.5	50.9	10.5
Tibial, L	46.1	17.9	100	45.8	N/A	N/A
Peroneal, L	46.5	17.9	N/A	N/A	N/A	N/A
Sural, L	N/A	N/A	N/A	N/A	44.4	15.3

MCV: motor conduction velocity, CMAP: compound muscle action potential, FWCV: F wave conduction velocity, SCV: sensory conduction velocity, SNAP: sensory nerve action potential, L: left, N/A: not available

Table 2. Antiganglioside Antibody Results in the Present Case.

	IgM	IgG	IgG Glycolipid+PA
GM1	-	-	0.244
GM2	-	-	-
GM3	-	-	-
GD1a	-	-	-
GD1b	-	-	0.162
GD3	-	0.368	0.249
GT1b	-	-	-
GQ1b	-	0.673	0.148
Gal-C	-	-	-
GalNAc-GD1a	-	0.661	0.356
GT1a	-	0.862	0.290
GD1a/GD1b	-	-	-

Results are displayed as the OD value based on the ELISA response. The reference OD value is less than 0.1. PA: phosphatidic acid, Glycolipid+PA: complex of glycolipid with PA, GD1/GD1b: complex of GD1a with GD1b, ELISA: enzyme-linked immunosorbent assay, OD: optic density

don reflexes were slightly depressed, and he had flexor plantar responses. The patient had a sensory ataxic gait with positive Romberg's sign. There was no weakness of the facial, neck, or limb muscles, and there was no cerebellar ataxia. The results of laboratory studies, including a complete blood count, routine biochemical tests, hemoglobin A1c, thyroid function, tumor markers, antinuclear antibodies, antineutrophil cytoplasmic antibodies, and anti-SS-A/SS-B antibodies, were unremarkable. A cerebrospinal fluid analysis revealed 3 cells/μL (100% mononuclear cells) and 29 mg/dL of protein. The pupils of both eyes were supersensitive to pilocarpine 0.1%. Orthostatic hypotension and sphincter dysfunction were not found.

There were no abnormalities on brain magnetic resonance imaging (MRI). Nerve conduction studies showed no abnormalities, including sensory nerve action potentials (SNAP) and sensory nerve conduction velocity (SCV) (Table 1). An enzyme-linked immunosorbent assay showed that the patient's serum IgG reacted with GQ1b, GT1a, GD3, GalNAc-GD1a, and complex of GM1 or GD1b with phosphatidic acid (PA) (Table 2).

The patient received intravenous high-dose immunoglobulin (IVIg) treatment for 5 days (0.4 g/kg/day) from day 4 of hospitalization. His photophobia improved immediately after starting IVIg treatment. At the end of IVIg treatment (day 8 of hospitalization), his light reflexes, decreased vibratory sensation in distal lower limbs, depressed patella tendon reflexes, and sensory ataxic gait were completely normalized, and Romberg's sign disappeared. Furthermore, his nasal voice, nasopharyngeal reflux, difficulty swallowing, and numbness in the distal extremities completely recovered by day 22 of hospitalization. A somatosensory evoked potentials (SEP) test was not done because of his immediate recovery from decreased vibratory sensation in distal lower limbs. His neurological symptoms did not recur within four months after his complete recovery.

Discussion

The main clinical features of our patient were oropharyngeal palsy and internal ophthalmoplegia without external ophthalmoplegia. MRI revealed no abnormalities in the brain or brainstem. Botulism was excluded owing to no history of causative food intake. The monophasic disease course with a full recovery was suggestive of a GBS/MFS-like disorder. Identification of antiganglioside antibodies confirmed this diagnosis.

Acute oropharyngeal palsy has been described as a very rare regional variant of GBS showing bulbar palsy without limb weakness (1). A recent literature review examining 28 cases of AOP showed that external ophthalmoplegia (20 cases, 71.4%), areflexia/hyporeflexia (18 cases, 64.3%), facial palsy (17 cases, 60.7%), gait ataxia (14 cases, 50.0%), sensory abnormality (14 cases, 50.0%), internal ophthalmoplegia (4 cases, 14.3%), and masticatory muscle and tongue weakness (2 cases, 7.1%) occur during the disease course (2). Of the four cases with internal ophthalmoplegia, three concomitantly had external ophthalmoplegia; only one case lacked external ophthalmoplegia, which was reported by Wakerley et al. (3). That patient had bilateral mydriasis with loss of light reflexes, impairment of the near response, and no hypersensitivity to 0.1% pilocarpine, suggesting that AOP-related internal ophthalmoplegia should not be confused with Adie's tonic pupils (3). However, our patient had bilateral Adie's tonic pupils due to the presence of bilateral dilated pupils, light-near dissociation, and cholinergic denervation hypersensitivity. To our knowledge, this is the first case of AOP with bilateral Adie's tonic pupils in the absence of external ophthalmoplegia, although a language bias is

present, as we only searched for publications in English.

Antiganglioside antibodies are linked to a wide variety of pathologies, including notable inflammatory neuropathies, such as GBS and MFS (4). Several antiganglioside antibodies are associated with certain clinical phenotypes (5). Serum anti-GT1a IgG antibodies have been detected in GBS with bulbar palsy, the pharyngeal-cervical-brachial variant of GBS, and AOP (6). GT1a ganglioside is expressed in the glossopharyngeal and vagal nerves, and IgG anti-GT1a antibodies have a pathogenic role in the development of bulbar palsy in certain patients with GBS/MFS (7). In contrast, high sensitivity to anti-GQ1b antibodies has been confirmed in MFS, GBS, and Bickerstaff's brainstem encephalitis (8-10). Abundant GQ1b exists in the paranodal regions of the oculomotor, trochlear, and abducens nerves, and IgG anti-GQ1b antibodies are associated with external ophthalmoplegia (11). While patients with high titers of anti-GQ1b IgG antibodies often experience external ophthalmoplegia, several cases of isolated internal ophthalmoplegia associated with anti-GQ1b IgG antibodies have been reported (12). Although the detailed mechanisms underlying the development of internal ophthalmoplegia in the absence of external ophthalmoplegia remain unclear, it has been speculated that anti-GQ1b antibodies impair the function of the ciliary ganglia or the short ciliary nerves due to cholinergic denervation hypersensitivity (13). Furthermore, immunohistochemical studies have shown that GQ1b is also expressed in group 1a neurons of the human dorsal root ganglia (14) and muscle spindles (15), so antibodies against GQ1b are related to ataxia and areflexia. In our case, the patient's serum IgG reacted with GQ1b, GT1a, GD3, GalNAc-GD1a, and complex of GM1 or GD1b with PA. GQ1b, GT1a and GD3 gangliosides have disialylated residues, so anti-GQ1b antibodies are recognized to cross-react with GT1a or GD3 (11, 16). Thus, we speculate that the GT1a activities of antibodies against GQ1b, GT1a, and GD3 were associated with oropharyngeal palsy, and the GQ1b activities were related to Adie's tonic pupils.

However, the pathological significance of IgG antibodies against GalNAc-GD1a or complex of GM1 or GD1b with PA in this neuropathy, including Adie's tonic pupils, is unclear. Recently, approximately half of MFS patients were found to have serum antibodies against ganglioside complexes (GSCs), suggesting that the clustered glycoepitopes of GSCs in peripheral nerves are targets for serum antibodies in MFS (17). To our knowledge, there are no reports describing the relationship between Adie's tonic pupils and GSCs. The patient's serum IgG did not react with complex of GD1a and GD1b (Table 2), but antibodies against GSCs containing GQ1b were not measured. Future studies should analyze the binding specificity of antibodies by absorption tests or detect other antibodies using GSCs and cholesterol-added glycolipid antigens.

MFS is characterized by the unique clinical triad of ophthalmoplegia, ataxia, and areflexia, whereas sensory impairment was infrequent; 23% had decreased vibratory sensation, and 19% had reduced pin-prick sensation (18). Sekiguchi et al. reported decreased SNAP amplitudes in 32% of MFS patients, suggesting that Wallerian-like degeneration in the distal axons leads to sensory impairment in MFS (18). However, nerve conduction studies showed no abnormalities in our case. We speculate that abnormalities in the dorsal roots proximal to the dorsal root ganglion caused sensory impairment, although an SEP test was not conducted because of the patient's prompt recovery. Furthermore, considering the prompt recovery of sensory ataxia and Romberg's sign after IVIg treatment, the pathophysiology of this patient's neuropathy seems to be functional conduction block, such as reversible conduction failure (19). In addition, reversible conduction failure may have occurred in the short ciliary nerves, resulting in Adie's tonic pupils, although the intraocular muscles are inaccessible in electrophysiological examinations.

In conclusion, we encountered a case of AOP following bilateral Adie's pupils associated with IgG anti-GT1a and GQ1b antibodies. We suggest that it is important to measure antiganglioside antibodies in order to clarify the cause of oropharyngeal palsy and Adie's tonic pupils. The detailed mechanisms underlying the involvement of antiganglioside antibodies in Adie's tonic pupils remain unclear, and further investigations should be performed.

The authors state that they have no Conflict of Interest (COI).

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