SHORT REPORT

Acute oropharyngeal palsy is associated with antibodies to GQ1b and GT1a gangliosides

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Abstract
Three patients with acute oropharyngeal palsy had high titre anti-GQ1b and anti-GT1a IgG antibodies. No patients had ophthalmoplegia or ptosis. In all patients limb ataxia or areflexia were present without notable limb weakness. These patients describe an oropharyngeal variant of Guillain-Barré syndrome in terms of anti-GQ1b antibody reactivity and show that high titre anti-GQ1b antibodies, serologically indistinguishable from those found in Miller Fisher syndrome, can occur in a clinical setting without ophthalmoplegia. The anti-GQ1b and anti-GT1a antibody assays may be helpful tests when considering the differential diagnosis of acute oropharyngeal palsy.

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Several regional variants of Guillain-Barré syndrome have been described occurring either as isolated syndromes or as transitional illnesses that either overlap each other or evolve into generalised Guillain-Barré syndrome.[1] Of these, the most widely recognised is the Miller Fisher syndrome,[2] in which serum antibodies to GQ1b are found in over 90% of patients.[3-5] Anti-GQ1b antibodies are also present in patients with Guillain-Barré syndrome who exhibit ophthalmoplegia.[6 7] These clinicoserological studies have led some authors to suggest that anti-GQ1b antibodies are a marker for ophthalmoplegia. This conclusion is also supported by the finding that GQ1b is highly enriched in human oculomotor nerves compared with peripheral nerve.[7]

Acute oropharyngeal palsy is another regional variant of Guillain-Barré syndrome. It may occur in isolation, as part of the Miller Fisher syndrome, or with mild proximal upper limb weakness, when it has been referred to as the pharyngeal-cervical-brachial variant, comprising 2% of patients with Guillain-Barré syndrome.[1] One such patient, transitional with generalised Guillain-Barré syndrome, has been reported in association with anti-GT1a and GD1a antibodies.[8] Acute oropharyngeal palsy

can also occur with ataxia and tendon reflex abnormalities, as described here. When ophthalmoplegia completes the triad these patients are usually referred to as having Miller Fisher syndrome.

Here we report three patients with acute oropharyngeal palsy without ophthalmoplegia, in whom high titre anti-GQ1b and GT1a antibodies were detected. This clinicoserological association has not previously been reported and shows a further regional variant of Guillain-Barré syndrome with a readily identifiable antiganglioside antibody phenotype.

Case reports and assay methods
Table 1 summarises the clinical features of the three patients. The initial symptoms in all patients were of dysarthria and dysphagia. At no time did any patient complain of double vision or have clinically evident ophthalmoplegia. In each patient there was no significant functional involvement of other sites although minor symptoms and signs, including paraesthesiae, limb weakness, ataxia, and areflexia were variably present. One patient required tube feeding and two required dietary modification to tolerate an oral intake. All patients made a good recovery. The preceding infections were unidentified upper respiratory tract infections in two patients and serologically established *Campylobacter jejuni* enteritis in the other patient. Peripheral nerve electrophysiology was abnormal in all patients showing both motor and sensory nerve conduction abnormalities.

A control group of 10 consecutive patients with Miller Fisher syndrome, with the triad of ophthalmoplegia, ataxia, and areflexia, was studied for comparison (summarised in table 1). Nine of these patients with Miller Fisher syndrome had craniopharyngeal weakness without notable limb weakness, this being the typical pattern of Miller Fisher syndrome seen locally. All patients had preceding unidentified upper respiratory tract infections and abnormal electrophysiological studies compatible with the diagnosis of Miller Fisher syndrome.

Serum samples were collected four days (patient 1), 14 days (patient 2), and eight days (patient 3) after the onset of symptoms and before specific treatment was started. Samples were stored at −70°C until assayed. Antibody

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Table 1   Clinical features of the three oropharyngeal patients and the 10 Miller Fisher (MFS) patients

	Patient 1	Patient 2	Patient 3	10 MFS patients
Clinical features:				
Age/sex	39 F	49 M	52 M	17–57 (mean 34)
				M:F = 7:3
Preceding infection	URTI	C Jejuni enteritis	URTI	10/10
Symptoms at onset	Bulbar	Bulbar and sensory	Bulbar and sensory	6/10 ocular
				5/10 ataxia
				5/10 sensory
Dysarthria	+ +	+ +	+ +	9/10
Dysphagia	+ +	+ +	+ + +	9/10
Perioral paraesthaesia	–	–	+	5/10
Facial weakness	–	–	+ +	9/10
Ptosis	–	–	–	7/10
Ophthalmoplegia	–	–	–	10/10
Ataxia	–	+	–	10/10
Areflexia	Partial	Complete	Complete	10/10
Limp paraesthesiae	Distal	Distal	–	5/10
Limb weakness	No	No	Yes	6/10 No
(MRC grade)			(4)	4/10 grade 4
Ventilated	No	No	No	1/10 (4 days)
Tube fed	No	No	Yes	3/10
Specific treatment	None	None	HIg	9/10
				(6 × HIg, 3 × PE)

URTI = Upper respiratory tract infection; HIg = human immune globulin; PE = plasma exchange; + = mild; + + = moderate; + + + = severe; − = absent.

assays were performed with a panel of gangliosides comprising GM1, GM2, GM3, GDla, GDlb, GD3, GTla, GTlb, and GQlb in a standard enzyme linked immunosorbent assay (ELISA), and a thin layer chromatography (TLC) overlay technique as previously described.[9] Titres were calculated by end point dilution analysis. Our normal ranges for antiganglioside IgG antibodies are set at < 1/500 (2 SD above the mean of a panel of normal and disease control serum samples). IgG subclass analysis was performed as previously described.[10]

For statistical analysis the antibody titres were $\log_2$ transformed. Unpaired Student's t test was then used to assess the significance of the differences of the titres of anti-GQlb and anti-GTla antibodies between the group of three oropharyngeal patients and the 10 patients with Miller Fisher syndrome. The ratios (GQlb:GTla and GTla:GQlb) of the log transformed titres were estimated for each individual patient and the Mann-Whitney U test was used to assess the differences in the ratios between the two groups.

Results

IgG antibodies to GQlb and GTla gangliosides were found in high titres in all three patients (table 2). Reactivities found by ELISA were confirmed using TLC overlay (not shown). Raised antibodies to GD3 (two

patients) or GDlb (one patient) were also present but remained within the normal range. No patients had detectable antibodies to GTlb, GM1, or to the other gangliosides tested. IgG subclass analysis showed that both the anti-GQlb and anti-GTla IgG antibody reactivities resided in the IgG3 subclass in patients 1 and 2, and in the IgG1 subclass in patient 3 (data not shown).

All 10 patients with Miller Fisher syndrome had raised antibody titres (table 2) to GQlb and nine had raised GTla antibodies. The patient with Miller Fisher syndrome with a low GTla titre (1/220) had clearly raised titres to GQlb (1/2600) and to GTlb (1/3200). Many of the patients with Miller Fisher syndrome and oropharyngeal patients also had detectable antibody titres to structurally related gangliosides such as GDlb, GTlb, and GD3 (table 2). Although these titres were below 1/500 in many instances and would not be considered significant in isolation, the fact that they occurred in the presence of high titres to GTla and GQlb does suggest that they are a significant element of this acute immune response.

In the oropharyngeal patients the mean antibody titres to GTla (1/6500) were higher than those to GQlb (1/2250); by contrast with the patients with Miller Fisher syndrome the mean GTla titre (1/5000) was lower than the mean GQlb titre (1/8000). However, statistical analysis of the titres to either antigen showed no significant differences between the patients with oropharyngeal palsy and patients with Miller Fisher syndrome (P = 0·19 for GQlb; P = 0·78 for GTla). Similarly analysis of the ratios of the paired values between both groups just failed to achieve significance at the 5% level (0·05 < P <0·10).

Discussion

The oropharyngeal variant of Guillain-Barré syndrome may occur in isolation but usually occurs as a transitional syndrome with other features of either Guillain-Barré syndrome or Miller Fisher syndrome. Although these three patients may fit into a transitional category as

Table 2   Laboratory features of the three oropharyngeal patients and the 10 Miller Fisher patients

	Patient 1	Patient 2	Patient 3	10 MFS patients
CSF protein (g/l)				
(NR 0·1–0·5 g/l)	0·44	0·55	0·86	7/10* (0·64)
IgG antiganglioside titres				
(upper limit of normal = 1/500) (No +ve (mean titre)):				
GQlb	1/3100	1/2600	1/1500	10/10 (1/8000)
GTla	1/2900	1/7600	1/12500	9/10 (1/5000)
GTlb	–	–	–	6/10 (1/750)
GDla	–	–	–	0/10 –
GDlb	–	1/240	–	2/10 (1/1000)
GD3	1/480	–	1/570	6/10 (1/500)
GM1	–	–	–	0/10 –

*CSF examined in 7/10 patients; − = negative.

each one had minor symptoms or signs elsewhere, the major clinical manifestations define a clearly identifiable phenotype. None of these patients closely resemble Ropper's description of pharyngeal-cervical-brachial Guillain-Barré syndrome in that all had sensory symptoms, none had ptosis, and proximal upper limb weakness was mild if present.[1] The most striking clinical feature of these patients was the absence of ophthalmoplegia and ptosis, particularly when other features of Miller Fisher syndrome were present, such as in patient 3. These patients clearly show that the anti-GQ1b antibody need not necessarily be associated with clinically evident ophthalmoplegia and that these antibodies should be sought in any patient with acute craniopharyngeal palsy of unknown cause.

The clinical expression of anti-GQ1b antibody associated syndromes may show geographic variation: in their series of 19 and six patients with Miller Fisher syndrome, Chiba et al[7] and Yuki et al[4] reported oropharyngeal weakness as minimal or absent. By contrast, nine of the last 10 consecutive anti-GQ1b antibody positive patients with Miller Fisher syndrome admitted to our institute had symptomatic oropharyngeal weakness which in three patients was severe enough to require tube feeding or mechanical ventilation. All 10 patients exhibited the clinical triad of ophthalmoplegia, ataxia, and areflexia without limb weakness. Thus our local experience is that the motor manifestations of Miller Fisher syndrome are not restricted to the extraocular muscles but invariably involve the oropharynx. This does not seem to be the pattern of illness seen in Japan despite similar antiganglioside antibody serology. The explanation(s) for these geographic variations is unknown but may include racial differences in the ganglioside content of different cranial nerves, immunogenetic variations in the host, or structural variations in the provoking antigen(s). Alternatively this may simply represent bias in case ascertainment and reporting.

The fine specificity of the antiganglioside antibodies, as assessed by relative titres to GQ1b and GT1a and reactivity with other structurally similar disialosyl containing gangliosides such as GD1b, GD3, and GT1b, is compatible with many previous studies.[3-5 8-10] The IgG subclass data suggest that the population of antibiodies reacting with GQ1b is also reacting with GT1a and vice versa, although this has not been formally established by cross absorption studies. The difference in relative titres to GQ1b and GT1a may be accounted for by a partial preference for one or other ganglioside and is consistent with their very close structural similarity. The absence of reactivity with GT1b indicates that a terminal disialylated galactose (common to both GQ1b and GT1a but absent on GT1b) is an essential feature of the reactive epitope. The relative reactivity with GQ1b and GT1a does not statistically correlate with the clinical pattern of craniopharyngeal involvement in the Miller Fisher syndrome or oropharyngeal patient groups. However, the data tend towards the GT1a/GQ1b titre ratio being higher in the oropharyngeal group than in the Miller Fisher syndrome group, suggesting that anti-GQ1b and anti-GT1a antibodies may be markers for ophthalmoplegia and pharyngeal palsy respectively. In addition, the presence of anti-GD1b or anti-GD3 antibodies seems to be associated with more prominent sensory involvement, as previously suggested.[11] The few patients studied preclude detailed statistical analysis but these concepts are compatible with previously published data.[8-11] Although the relative amount of GQ1b in human oculomotor nerves compared with peripheral nerve has been analysed and found to be high,[7] its quantitative relation with GT1a and other disialylated gangliosides throughout the craniobulbar region is unknown.

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