SHORT REPORT

Anti-MAG/SGPG associated neuropathy does not commonly cause distal nerve temporal dispersion

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Patients with anti-myelin associated glycoprotein (anti-MAG) neuropathy have uniform slowing without temporal dispersion, but do usually have disproportionately distal slowing. We evaluated distal compound muscle action potential (CMAP) dispersion in 29 patients with anti-MAG/sulphated glucuronyl paragloboside (SGPG) neuropathy (titres ≥ 12800). Among 138 motor responses, 15% (tibial), 7.3% (peroneal), 10.7% (median) and 13.8% (ulnar) had distal CMAP duration >9 ms. Disproportionate distal slowing with normal distal CMAP duration in the arms may be useful to differentiate chronic inflammatory demyelinating polyneuropathy from anti-MAG/SGPG associated neuropathy.

Anti-myelin associated glycoprotein (anti-MAG) neuropathy is typically a slowly progressive predominantly sensory ataxic neuropathy associated with an IgM monoclonal protein.^{1,2}

Unlike other acquired demyelinating neuropathies, electrophysiological studies typically show uniform slowing, without temporal dispersion or conduction block. There is disproportionate slowing of conduction in distal segments, with a length dependent process and centripetal evolution.^{1,2}

More recently, a new method for evaluation of temporal dispersion has been validated in patients with chronic inflammatory demyelinating polyneuropathy (CIDP).³ Quantification of the distal dispersion of the compound muscle action potential (CMAP) has been proposed as an adjunctive electrodiagnostic criterion for CIDP.³ In this study, since the measurement of the distal CMAP duration would measure temporal dispersion in the distal segment, which is preferentially involved, we asked whether the distal CMAP showed temporal dispersion in anti-MAG patients. We also compared the electrophysiological findings from anti-MAG neuropathy with our own cohort of CIDP patients.

PATIENTS AND METHODS

We conducted a computer guided search using the keywords anti-MAG and sulphated glucuronyl paragloboside (SGPG) neuropathy at the Peripheral Neuropathy Center Patient Databank, Cornell University. A total of 41 medical charts with these characteristics were found and reviewed. Patients with anti-MAG or anti-SGPG titres $<12\,800$ were excluded to avoid the inclusion of patients exhibiting cross reactivity against MAG/SGPG in the setting of a more widespread autoimmune disorder ($n = 8$). This study was approved by the Weill Medical College of Cornell University Institutional Review Board.

The presence of demyelination was determined by evaluating all nerve conduction studies and/or nerve biopsies, performed in the centre or by outside medical facilities (a third of the tests), according to standard criteria.^{4,5} The distal CMAP duration from the initial negative phase to the return to baseline of the last negative phase that rises above baseline was

measured in all cases, with the waveform set at 500 μ V/division.³ Conduction block was defined as a drop in the area of the proximal compared with the distal CMAP of 50% or more.⁶ Abnormal temporal dispersion of the proximal segments was defined as greater than 30% of the proximal CMAP duration, compared with the distal duration for each nerve segment, marking the waveform from the onset to the return to baseline after the last negative peak, above the baseline.³

Descriptive statistics were used to report the clinical and electrodiagnostic features of the patients. In addition, comparisons between the current electrodiagnostic findings and a cohort of 11 CIDP patients seen at our centre were performed using odds ratio analysis and the χ^2 test, and were considered to be significant at $p < 0.05$. Patients with CIDP were identified as those with proximal and distal weakness, with at least one demyelinating finding on nerve conduction studies⁴ or findings of demyelination on a nerve biopsy.

RESULTS

We found 14 women and 19 men with anti-MAG or anti-SGPG titres $\geq 12\,800$ and compared them with 11 patients with CIDP. Mean age at neuropathy presentation was 61.8 (3.8) years. Sensory complaints (numbness or pain) and/or abnormal sensory examination were present in all patients. Significant gait involvement (history of falls or abnormal gait evaluation) was evidenced in 57.5% of the patients. Tremor was present in eight patients. Three men and one woman did not have the waveforms or the distal CMAP duration available for complete neurophysiology analysis and therefore were excluded from the distal CMAP duration analysis.

Lower extremities

In the MAG patients, among the 81 motor responses analysed in the legs (40 tibial and 41 peroneal), the distal CMAP duration was greater than 9 ms in 15% of the tibial (6/40) and in 7.3% (3/41) of the peroneal responses. Only two of the six tibial responses >9 ms had an evoked response amplitude greater than 0.5 mV (3.2 and 1 mV). Prolonged distal CMAP duration was not more prevalent in patients with a low terminal latency index. Table 1 compares the data from MAG and our cohort of CIDP patients for the different nerves and parameters studied. A χ^2 comparison for the per cent of prolonged distal CMAP duration between the present cohort of MAG patients and our cohort of patients with CIDP (12 tibial and 11 peroneal responses) revealed significant differences for the tibial (15 vs 42%; $p < 0.001$) and peroneal (7.3 vs 38%; $p < 0.001$) nerves. The tibial terminal latency index was 0.44 (0.35). In three peroneal responses, we observed proximal temporal dispersion (duration increase in the proximal responses $>30\%$). One of the peroneal responses >9 ms was

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; CMAP, compound muscle action potential; MAG, myelin associated glycoprotein; SGPG, sulphated glucuronyl paragloboside

Table 1 Electrodiagnostic features of patients with anti-MAG/SGPG associated neuropathy

Demyelinating CMAP findings						
Nerve	dCMAP duration (%)		Proximal TD (%)		CV slowing	
	MAG	CIDP	MAG	CIDP	MAG	CIDP
Tibial	15 (6)	41.6 (5)*	0 (0)	0 (0)	37.5 (15)	36.4 (4)
Peroneal	7.3 (3)	27.3 (3)**	7.3 (3)	36.4 (4)	26.8 (11)	9.1 (1)
Median	10.7 (3)	23.1 (3)***	0 (0)	16.7 (2)	47.8 (13)	50 (6)
Ulnar	13.8 (4)	14.3 (2)	3.4 (1)	30.8 (4)	43.5 (13)	53.8 (7)
	Dem DL (%)		TLI		TLI <0.25 (n)	
	MAG	CIDP	MAG	CIDP	MAG	CIDP
Tibial	32.5 (13)	36.4 (4)	0.44 (0.35)	0.49 (0.03)	2	0
Peroneal	31.7 (13)	27.3 (3)	0.35 (0.03)	0.35 (0.06)	2	2
Median	53.5 (15)	41.7 (5)	0.27 (0.01)	0.37 (0.04)	10	4
Ulnar	37.9 (11)	30.8 (4)	0.4 (0.02)	0.51 (0.05)	1	2

CIDP, chronic inflammatory demyelinating polyneuropathy; dCMAP, distal compound muscle action potential; Dem, demyelinating; MAG, myelin associated glycoprotein; NCV, nerve conduction velocity; SGPG, sulphated glucuronyl paragloboside; TD, temporal dispersion; TLI, terminal latency index.

* $p < 0.001$, 95% CI 5.7 to 14.9; ** $p < 0.001$, 95% CI 2.3 to 8.7; *** $p < 0.004$, 95% CI 4.3 to 17.9.

TLI values are mean (SD).

The frequency of each finding per nerve is followed by the absolute number of patients with demyelinating features in parentheses.

1.5 mV, while the other two were 0.05 mV. Peroneal terminal latency index was 0.35 (0.03). Prolonged distal CMAP duration was not more prevalent in patients with a low terminal latency index. Forty-five per cent of the tibial and 39% of the peroneal responses were absent. No conduction block was observed. Distal latencies were in the demyelinating range in 32.5% of the tibial and 31.7% of the peroneal responses. Conduction velocities were in the demyelinating range in 37.5% of the tibial and 26.8% of the peroneal responses. Tibial F waves ($n = 33$) were absent in 72.7% ($n = 24$) and in the demyelinating range in 12.1% of the responses ($n = 4$). Peroneal F waves ($n = 32$) were absent in 71.9% ($n = 23$) and in the demyelinating range in 12.5% ($n = 4$). Sural sensory responses ($n = 37$) were absent in 81.1% of the nerves tested ($n = 30$). H reflexes were absent in 90.6% of the responses tested and in the demyelinating range in 6.7%.

Upper extremities

Among the 57 motor responses analysed in the arms (28 median and 29 ulnar), the distal CMAP duration was greater than 9 ms in 10.7% of the median (3/28) and in 13.8% (4/29) of the ulnar responses. Proximal temporal dispersion (duration increase in the proximal responses $>30\%$) was present in only one ulnar response, while no proximal temporal dispersion was observed among the median nerve studied. The χ^2 comparison for the per cent of prolonged distal CMAP duration between the present cohort of MAG patients and our cohort of patients with CIDP (13 median and 14 ulnar responses) revealed significant difference for the median (10.7 vs 23%; $p < 0.003$) but not for the ulnar nerve (13.8 vs 14%; NS). Median terminal latency index was 0.27 (0.01), while ulnar terminal latency index was 0.4 (0.02). Prolonged distal CMAP duration was not more prevalent in patients with low terminal latency index. Only one median and one ulnar CMAP response was absent. No conduction block was observed. Distal latencies were in the demyelinating range in 53.5% of the median and 37.9% of the ulnar responses. Conduction velocities were in the demyelinating range in 47.8% of the median and 43.5% of the ulnar responses. Median F waves ($n = 29$) were in the demyelinating range in 68.1% of the responses ($n = 15$). Ulnar F waves ($n = 28$) were in the demyelinating range in 59.1% ($n = 13$). Sensory responses were absent in 54.5% of the median and 61.9% of the ulnar nerves tested.

DISCUSSION

Polyneuropathies associated with IgM antibodies reacting against a carbohydrate epitope shared by MAG, SGPG and sulphated glucuronyl lactosaminyl paragloboside occur more frequently in older individuals, have a slow course, long median time to the nadir of disease, distal and symmetrical distribution and earlier leg involvement.¹⁻⁸

Previous studies comparing the electrophysiology in idiopathic CIDP and anti-MAG/SGPG polyneuropathy have described a disproportionate slowing of conduction in distal segments, with a length dependent process and centripetal evolution.¹ Nerve conduction studies reveal uniform slowing with distal predominance. Conduction block and temporal dispersion are not seen using strict criteria for conduction block¹⁻⁸ but some investigators have reported conduction block using less stringent definitions.⁹⁻¹⁰

More recently, different methods for evaluation of demyelination have been validated in patients with CIDP.³ Quantification of the distal dispersion of the distal CMAP is one of these novel techniques, and has been proposed as an adjunctive electrodiagnostic criterion for CIDP.³ To our knowledge, distal CMAP dispersion has not been assessed in patients with anti-MAG/SGPG polyneuropathy. In this study, comparison with our cohort of CIDP patients revealed that patients with anti-MAG neuropathy were less likely than patients with CIDP to exhibit prolonged distal CMAP duration in the arms and legs, except for the ulnar nerve, where similarly prolonged distal CMAP durations were observed. In addition, comparison with the CIDP cohort published by Thaisetthawatkul *et al*³ also yielded similar results: the odds ratio of finding prolonged distal CMAP duration in anti-MAG versus CIDP patients was 14.7 for the tibial nerve (95% CI 3.2 to 71.1, χ^2 18.4; $p < 0.001$), 6.3 for the peroneal nerve (95% CI 0.8 to 49.7, χ^2 5.5; $p < 0.2$), 13 for the median nerve (95% CI 2.6 to 81.8, χ^2 14.3; $p < 0.01$) and 5.7 for the ulnar nerve (95% CI 1.6 to 28.9, χ^2 7.2; $p < 0.02$). Anti-MAG antibodies are thought to be pathogenic. Anti-MAG neuropathy with the typical pathological features, including widened myelin lamellae, can be reproduced in an animal model,¹¹ and removal of the antibody results in improvement.¹¹

How the anti-MAG antibody causes neuropathy is uncertain. Deposits of IgM and complement are noted on myelin sheaths,⁷ suggesting an immune mediated attack resulting from the anti-MAG antibodies. The predominantly distal involvement could

be due to the relatively impaired blood nerve barrier at the nerve terminal. Alternatively, the antibody may also interfere with the role of MAG in neurofilament spacing, which can disturb axonal transport and impair axonal survival.¹² The lack of temporal dispersion, which is a rare event, even at the distal site, suggests a uniform involvement of fibres.

In summary, in patients with anti-MAG/SGPG associated neuropathy, prolonged distal CMAP duration is not common, despite the presence of a disproportionate slowing of the distal segments of the motor nerves. Therefore, the combination of disproportionate distal motor slowing and normal distal CMAP duration may be a useful tool to clinically differentiate patients with CIDP and anti-MAG/SGPG associated neuropathy.

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