Tremor is often associated with anti-myelin-associated glycoprotein (anti-MAG) peripheral neuropathy (PN), but its physiology has never been accurately described. This study quantified the physiological characteristics of tremors in patients with anti-MAG demyelinating PN. Eighteen patients with tremor and PN with demyelinating features (ages 30–86, mean = 66.5 years) were evaluated for anti-MAG antibodies (positive considered ⩾1:3200) and for tremor amplitude, frequency, side-to-side relationships, and electromyographic (EMG) activation patterns. Thirteen patients had anti-MAG titers >1:3200 and 8 had both positive anti-MAG titers and tremors. Anti-MAG PN patients revealed tremors higher in amplitude, lower in frequency, with greater side-to-side amplitude ratios, greater amplitude variability, and more consistent cocontracting antagonist EMG patterns that do not attenuate with inertial loading. We conclude that anti-MAG PN tremor is not due only to exaggerated physiologic mechanisms but may reflect a distinctive form of neurogenic tremor.
Key words: tremor • neuropathy • demyelination • myelin-associated glycoproteins

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PHYSIOLOGICAL TREMOR ANALYSIS OF PATIENTS WITH ANTI-MYELIN-ASSOCIATED GLYCOPROTEIN ASSOCIATED NEUROPATHY AND TREMOR

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Patients with peripheral neuropathy and evidence of demyelination may complain of tremor. While the characteristics and prevalence of tremor in patients with chronic inflammatory demyelinating polyneuropathy (CIDP) and hereditary motor–sensory neuropathies (HMSN) have been documented,[1,5] how often tremor occurs in patients with other acquired neuropathies having demyelinating features remains unclear, as does the nature of the relationship between the symptoms of neuropathy, tremor, and associated immunologic disorders. Little has been written on these topics, and virtually no in-depth physiologic studies have been performed on groups of patients with both peripheral neuropathy (PN) and tremor. Thus the role tremor plays in an underlying neuropathy and the quantitative characteristics of this tremor have yet to be determined.

In this study, we evaluated patients using computerized tremor analyses in order to quantify the physiological characteristics of tremors found in patients with anti-myelin-associated glycoprotein (anti-MAG) PN, and more precisely determine the relationship between neuropathy and tremor.

MATERIALS AND METHODS

Nine men and 9 women with neuropathy having demyelinating features according to electrophysiologic criteria[3] were selected for study (all right-handed, ages 30–86 mean = 66.5 years). All patients had neuropathy documented clinically and by electromyography (EMG)/nerve conduction studies. The patients were all evaluated for anti-MAG antibodies using the enzyme-linked immunosorbent assay (ELISA) as described previously[17,18] and were considered anti-MAG antibody positive with titers ⩾1:3200.

Tremor Analysis Technique. Ultra-light piezoresistive triaxial miniature accelerometers (±25 g, 0.5 g each) with linear sensitivities of approximately 4.5

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mV/g in the physiologic range, attached over the distal third knuckle on the dorsum of the hands, were used to measure hand tremors at the wrist. Silver/silver chloride surface EMG electrodes simultaneously recorded wrist flexor and extensor muscle activity. Accelerometric and EMG signals were digitized at 500 Hz and stored in eight trials during four conditions: at rest, with arms extended with and without 300-g inertial loading, and during finger-to-nose movements. This tremor analysis technique has been shown to be consistently accurate up to 6 months of testing and retesting individual subjects, valid in distinguishing clinical disorders from a database of over 900 cases, and sensitive in determining side-to-side differences in clinical trials.[9,16,19]

The tremor acquisition setup allowed for relatively unrestrained activity of both arms and hands throughout the tests. By not limiting movements with mechanical restraints, tremors were measured as close to the clinical state as possible, although care was taken to restrict recordings to measurement only at the wrist. Rest data were obtained with the arms 90° flexed and kept stationary at the elbow to prevent transmitted movements from the upper arm. The forearm was supported by the side of the chair with the hand freely resting over the end. In the arms extended condition, both arms were flexed at the shoulders with the forearms, hands, and fingers held straight in a horizontal plane level with the shoulders. With the finger-to-nose movements, the patient was instructed to begin in the arms extended position pointing toward the examiner's finger, touch his nose with the index finger, and return to the target. Inertial weighting was conducted with 300-g weights applied over the dorsum of the hands throughout those trials. Data were collected over approximately 1–2 h to capture tremor variability over time. Stress factors during data acquisition were kept to a minimum during the entire procedure.

Critical physiologic information obtained included tremor amplitude (±0.005 mm), frequency (±0.24 Hz), side-to-side relationships, and EMG activation patterns using semiautomatic interactive software developed in our laboratory. To simplify calculations of maximum tremor displacement, the highest amplitude accelerometric signal was selected for the final analysis in each set of trials. Tremor amplitude was derived from double integration of accelerometric data after filtering out low-frequency drift (<2 Hz) and averaging. A fast Fourier transform algorithm to generate autocorrelation spectra was used to calculate tremor frequencies. EMGs were full-wave rectified and demodulated before processing with the accelerometric data. Statistical analyses were performed using Student's *t*-tests.

Nerve Conduction and EMG. Motor nerve conduction studies of the median, ulnar, peroneal, and tibial nerves and orthodromic sensory nerve conductions of the median, ulnar, superficial peroneal, and sural nerves were performed using Viking II EMG machines (Nicolet Biomedical, Madison, WI). Concentric needle EMG examination of first dorsal interosseus, abductor pollicis brevis, and extensor digitorum communis in both arms and vastus lateralis, tibialis anterior, and medial gastrocnemius in both legs of each subject included noting the presence of spontaneous activity, and analysis of motor unit potential forms and recruitment patterns at low and high levels of effort.

RESULTS

The distribution of tremor in non-anti-MAG and anti-MAG patients is shown in Table 1. Thirteen patients had a postural or action tremor; none had a significant rest tremor. Thirteen patients were found to be anti-MAG positive, 8 of whom had tremors. Non–anti-MAG patients had either Guillain–Barré syndrome ($n = 3$) or an indeterminate demyelinating PN ($n = 2$). Of the anti-MAG associated PN patients with tremor, 3 had immunoglobulin (Ig) M_k monoclonal gammopathies, 2 had only IgM_l, 1 patient had both an IgM_l and an IgG_l monoclonal gammopathy, and 2 were not determined. EMG, nerve conduction data, other immunologic data, and clinical information are summarized in Table 2.

Postural and action tremors in anti-MAG neuropathy patients were higher in average amplitude ($P < 0.05$), lower in frequency ($P < 0.001$), and tended to be more asymmetric compared to non–anti-MAG PN patients. Physiologic data highlighting these differences from example anti-MAG and non–anti-MAG PN patients are illustrated in Figures 1 and 2.

Average tremor amplitude data for all conditions are summarized in Figure 3. Anti-MAG patient tremors exhibited higher amplitude variability but more consistent cocontracting antagonist EMG firing patterns compared with non–anti-MAG patients, where

Table 1. Patient tremor distribution.

	Non-anti-MAG		Anti-MAG		Total	
	n	(%)	*n*	(%)	*n*	(%)
Tremor	5	27.8%	8	44.4%	13	72.2%
No tremor	0	0.0%	5	27.8%	5	27.8%
Total	5	27.8%	13	72.2%	18	100%

Table 2. EMG, immunologic, and clinical summaries.

			Nerve conduction/EMG results														
			Sensory NCV (m/s) dl (ms)				Motor NCV (m/s) dl (ms)										
Patient	Sex	Age (years)	Med	U	P	S	Med	U	P	T	Axonal changes	Serum IgM (mg/dL)	Serum IgG (mg/dL)	Anti-MAG titers	SPE	Tremor	Clinical
1	F	30	43.8	47.1	—	41.5	59.5	64.7	47.4	45.6	None	nl	nl	nl	nl	+	GBS with tremor in all limbs.
			3.0	2.4		2.2	3.9	3.1	5.4	6.3		233	1010				
2	M	75	43	42.4	—	—	51.5	NR	43.8	NR	1 + fibs and psw	nl	nl	nl	IgG_l	+	GBS with tremor and weakness.
			3.6	2.9			4.7		2.4			114	1260				
3	M	48	57	—	—	45	69	—	50.9	48.8	None	nl	nl	nl	—	+	Indeterminate PN with tremor.
			2.4			2.2	3.4		4.6	6.7		98	927				
4	F	58	45.9	40.8	NR	40.3	55	50	41	43	None	nl	nl	nl	—	+	Indeterminate PN with numb, tingling limbs and tremor.
			2.7	2.3		2.8	3.0	2.3	5.0	4.2		137	1010				
5	F	71	54	—	—	39	51.4	49.2	47.1	42.1	Rare fasciae	HI	nl	nl	nl	+	GBS with weakness and tremor.
			3.2			7.8	3.0	—	5.3	8.3	and CRDs	705	854				
6	M	86	NR	NR	—	NR	NR	NR	NR	NR	2+ fibs and psw	HI	nl	HI	IgM_l	+++	Demyelinating PN with tremor and weakness.
												1620	706	1.6 million			
7	M	67	NR	NR	—	NR	18	21	13	NR	—	HI	nl	HI	IgM_k	++	Severe PN with tremor.
							12.2	7.5	10.3			673	789	50,000			
8	F	68	42	50	—	—	21	10	61	35	1+ fibs and	—	—	HI	—	++	Motor PN with tremor and weakness.
			2.4	2.2			4.2	3.3	7.5	5.6	CRDs			6400			
9	M	63	NR	NR	—	NR	18	17	NR	NR	psw, fibs,	HI	nl	HI	IgM_k	++	PN with sensory loss, weakness, and tremor.
							16.5	7.1			rare fasciae	682	1024	1.6 million			
10	F	74	45	39	—	NR	39	42	20	23	—	HI	Low	HI	IgM_l	++	PN with numbness of feet and tremor.
											—	361	635	6400			
11	M	72	48	44	—	41	53	50	41	41	nl	HI	nl	HI	—	–	Sensory PN.
			2.9	2.4		3.0	3.8	2.2	4.0	5.2		351	1300	6400			
12	M	66	37	46	—	NR	27	38	40	NR	1+psw and	nl	nl	HI	small	–	PN with difficulty walking and poor balance.
			3.9	2.7			6.1	4.1	3.5		fibs	293	1430	102,400	IgM_k		
13	F	67	46	59	—	NR	52	54	27	21	—	HI	nl	HI	IgM_k	+	PN with tremor.
			2.8	2.2			5.9	3.6	10.0	20.0		605	726	12,800			
14	M	61	—	—	—	—	—	—	—	—	—	HI	nl	HI	IgM_k	–	PN secondary, Waldenstrom's macroglobulinemia.
												523	1294	102,400			
15	F	80	33	20	14	NR	44	—	31	NR	nl	HI	nl	HI	—	+++	Sensory–motor PN with numbness and rigidity.
			4.2	4.5	7.3		5.0		5.1			588	1350	6400			
16	F	74	NR	30	—	NR	48	35	12	31	—	HI	nl	HI	IgM_l	+	Demyelinating sensory–motor PN with tremor.
				3.7			9.5	4.7	11.4	11.0		325	942	25,600	and IgG_k		
17	M	58	46	—	—	37	43.9	—	31.4	33.3	psw, fibs,	HI	nl	HI	IgM_k	–	PN with sensory loss, weakness, and painful paresthesias.
			3.3			2.6	3.6		6.4	4.3	fasciae +3	416	975	3200			
18	F	79	—	—	NR	NR	—	—	31	37.2	Fibs	HI	nl	HI	IgM_l	–	PN with numbness in legs.
									9.6	8.4	+3	506	965	6400			

M, male; F, female; dl, distal latency; Med, median nerve; U, ulnar; P, peroneal; S, sural; T, tibial; NR, no response at site indicated; —, not tested; nl, normal; HI, high/abnormal; SPE, serum protein electophoresis; ++–+++, level of clinically assessed tremor; –, no clinically assessed tremor; PN, peripheral neuropathy, GBS, Guillain–Barré syndrome; NCV, nerve conduction velocity.

EMG firing patterns were less regular and often revealed both co- and alternating antagonist EMG bursts. EMG activity did not attenuate with inertial loading in the more involved arms in anti-MAG patients and was reduced or completely obliterated in non–anti-MAG cases.

When asymmetric, the tremor asymmetric (measured by average worse-side to better-side amplitude ratios) was greater in anti-MAG tremor patients during all conditions tested (Fig. 4). This worse-to-better side asymmetry ratio increased from 5.6 in postural tremors and to over 20 times ($P < 0.01$) in anti-MAG associated neuropathy patients.

Tremor frequencies varied in the anti-MAG neuropathy group from 2.4 to 7.5 Hz in the more affected side and from 2.0 to 7.5 Hz in the less affected side with arms extended. Frequencies found in the non–anti-MAG neuropathy patients ranged from 6.5 to 12.2 Hz on the more affected side and from 5.0 to 7.9 Hz on the less affected side. Neither average fre-

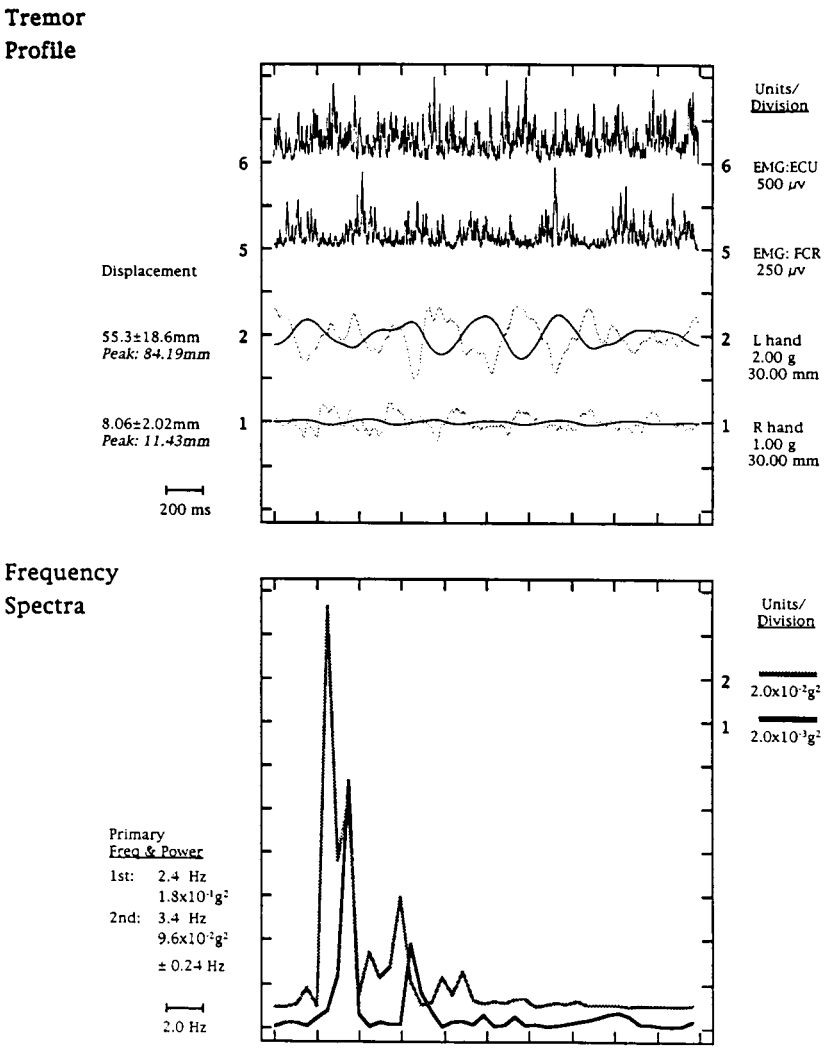

FIGURE 1. Sample tremor and EMG data for example patient with anti-MAG PN. Tremor profile, top, shows a 2-s sample with four channels of data. Channels 1–2: accelerometry (stippled lines) and derived amplitudes (solid lines); channels 5–6: demodulated surface EMG of extensor carpi ulnaris (ECU) and flexor carpi radialis (FCR). Frequency spectra, bottom, shows Fourier transforms of channels 1 and 2. Left side labels show primary and secondary frequency peaks with their corresponding powers, right labels indicate power units per division.

quencies nor frequency ratios (worse-side frequency to better-side frequency) varied significantly between trials for anti-MAG patients (5.3 ± 1.9 Hz, 1.2 for arms extended; 5.6 ± 1.5 Hz, 0.9 ± 0.2 for inertial weighting, $P > 0.05$; 4.4 ± 2.0 Hz, 0.9 for finger-to-nose), nor was the frequency ratio for anti-MAG positive patients with tremor in the arms extended position significantly different from that of the anti-MAG negative tremor patients (1.2 vs. 1.4, $P > 0.05$). However, the average tremor frequency of anti-MAG patients was significantly lower ($P < 0.05$) in the arms extended position than that of non–anti-MAG neuropathy patients (Fig. 5).

The EMG tremor generator patterns for anti-MAG positive patients were predominantly cocontracting while for non–anti-MAG patients mixed co- and alternating contracting muscle patterns were found, particularly in the arms extended position. In the finger-to-nose trials, all patients tested exhibited predominant cocontracting muscles, except patient 6, whose bursts were mixed. Inertial weighting either attenuated or completely obliterated discrete EMG bursts or resulted in no clear pattern for non–anti-MAG patients; however, the majority of anti-MAG neuropathy patients exhibited cocontracting muscle bursts.

DISCUSSION

We have found that among those patients with neuropathy studied, those with high anti-MAG titers and

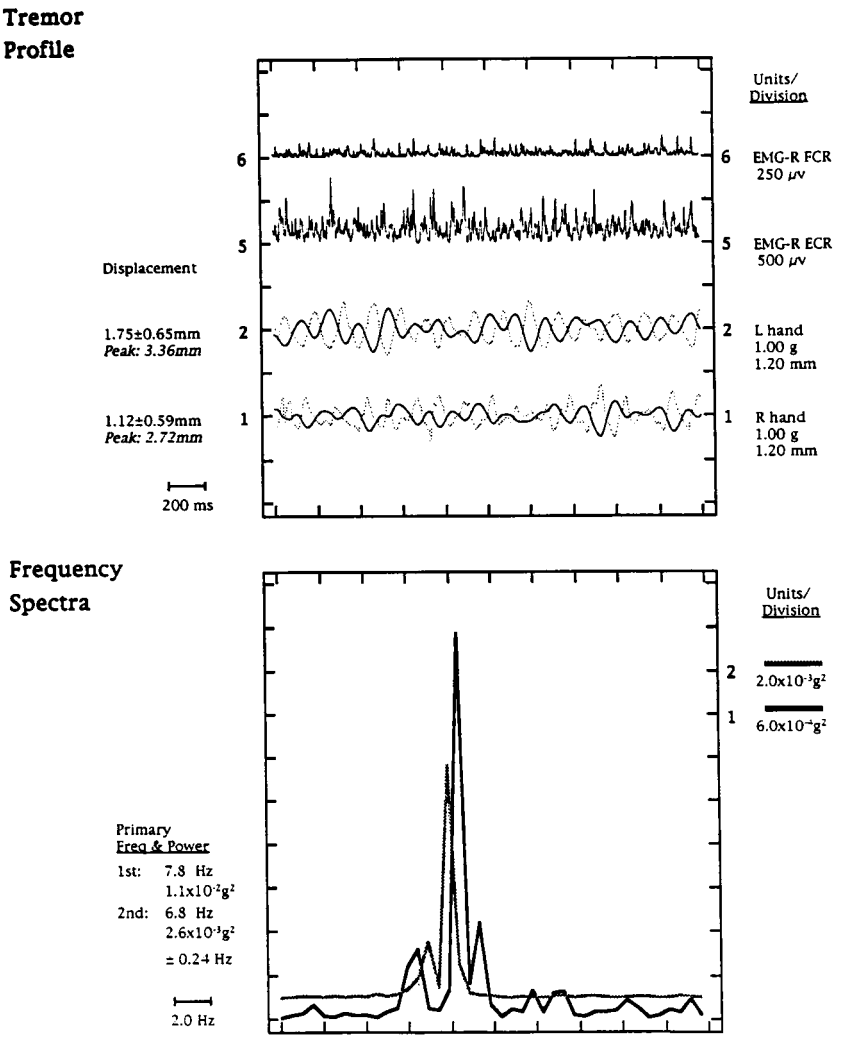

FIGURE 2. Sample tremor and EMG data for example patient with non–anti-MAG PN. Tremor profile, top, and Frequency spectra, bottom, shows similar 2-s samples of accelerometry, amplitudes, and demodulated surface EMG of extensor carpi radialis (ECR) and flexor carpi radialis (FCR). Note the less active EMGs, more symmetric and lower-amplitude tremor tracings, and higher peak frequencies.

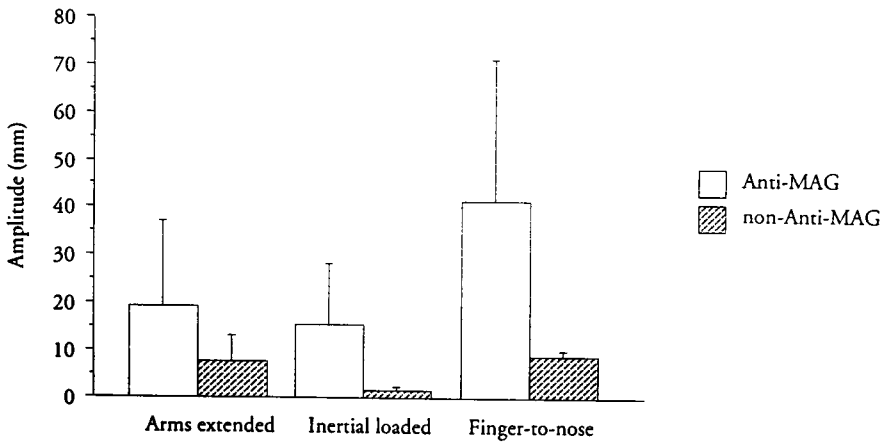

FIGURE 3. Average ± SD ratios of tremor amplitudes in anti-MAG vs. non–anti-MAG patients.

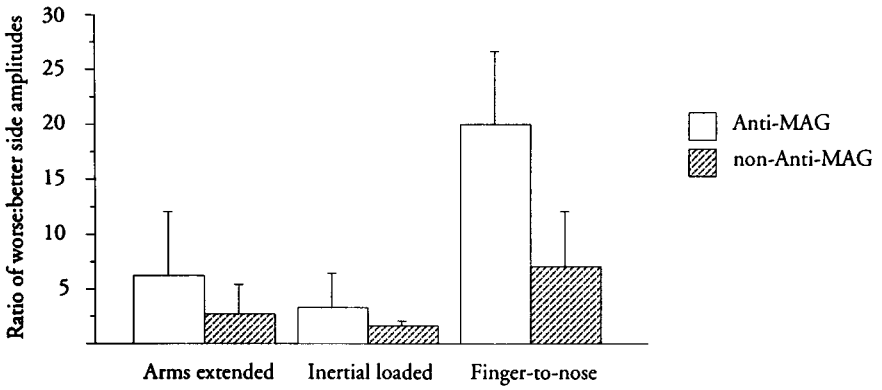

FIGURE 4. Average ± SD ratios of worse side to better side tremor amplitude in anti-MAG vs. non–anti-MAG patients.

tremor can be differentiated on the basis of their postural and action tremor characteristics. In our study, patients with anti-MAG associated neuropathy revealed relatively higher amplitude, lower frequency, irregular, and often asymmetric tremors with predominantly cocontracting antagonist EMG firing patterns that did not attenuate with inertial loading. These findings are more characteristic of neurogenic tremor, not exaggerated physiologic tremor (EPT), as has been previously reported in anti-MAG patients.[5,10]

Said et al.[10] assert that the tremor often found in patients with demyelinating neuropathy is basically EPT caused by weakness and alteration of stretch reflex mechanisms. They performed both conduction studies and nerve biopsies on 14 patients with both tremor and acquired demyelinating neuropathy, concluding that demyelination is not a primary cause of tremor, as it was not found in nerve biopsies of all patients, but tremor amplitude is greatly affected by the changes in the stretch reflex.

In a study involving 11 patients with CIDP or dysgammaglobulinemic polyneuropathy who were evaluated clinically and tested for the presence of tremor, Dalakas et al. found that the tremor associated with neuropathy has no relationship to weakness or loss of proprioception, although it does resemble EPT.[5] In addition, several studies have documented that tremor improves in neuropathy patients treated with high doses of prednisone, immunosuppressants, or intravenous immunoglobulin infusions,[2,4,5,7] suggesting a correlation between the tremor and the underlying neuropathy. In studies of initially 12 then expanded to 18 patients a decade later,[12,13] Smith et al. observed similar findings of significant tremor and ataxia in patients with chronic demyelinating neuropathy and benign paraproteinemia.

Elble and Koller[6] summarize the current understanding of PN and tremor by describing the sometimes contradictory results of over 25 years of research in this area. Neurogenic tremor has been described as resembling all types of tremor including essential, parkinsonian, and cerebellar tremor, and has been documented as occurring at rest and with action.[11]13 However, these reports neither utilized detailed physiological analysis of the tremor nor analyzed the extent of the relationship between neurop-

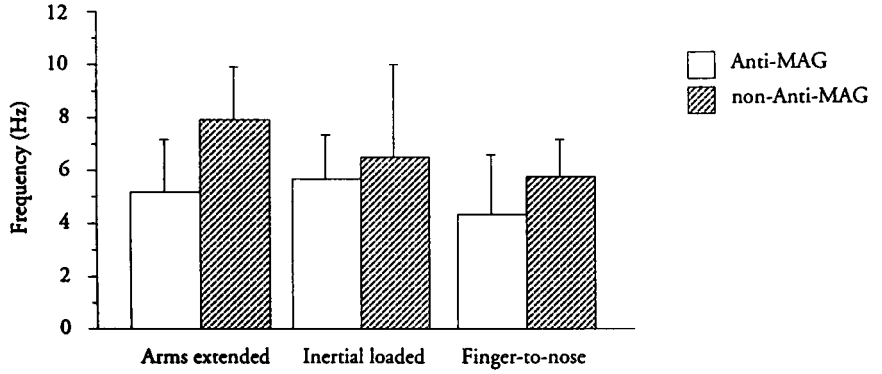

FIGURE 5. Average ± SD ratios of tremor frequencies in anti-MAG vs. non–anti-MAG patients.

athies, tremor, and immunologic disorders, such as the presence of anti-MAG antibodies or benign paraproteinemia.

According to the results of our study, we found that neurogenic tremor in anti-MAG PN can be characterized by large-amplitude, low-frequency wave patterns and is less affected by inertial weighting than is EPT. Our results also indicate that this neurogenic tremor tends to be asymmetric (worse on the side with more severe neuropathy) and more distal than proximal. The average frequency of the tremor found in anti-MAG patients in this study was significantly lower than was found in patients with more EPT-like tremor, who exhibited the 8–12-Hz tremors characteristic of EPT.[8] In some cases, the tremor found in our anti-MAG associated neuropathy patients was also more asymmetric, with tremor amplitudes almost five times worse on the more affected than the less affected side with arms extended and over 20 times worse with action. These tremors were also very irregular in comparison with non–anti-MAG neuropathy patients. In addition, we found that the tremors found in anti-MAG associated neuropathy patients worsened significantly with action, in agreement with the findings of an earlier report.[12]

The non–anti-MAG patients in our series exhibited the low-amplitude, high-frequency (8–12 Hz) symmetric, postural tremor and suppression of EMG burst pattern characteristic of EPT. The average frequency for these patients during the arms extended trial was 9.10 ± 1.09 Hz, which lies within the 8–12-Hz range of frequencies commonly seen in patients with EPT. The amplitudes for the non–anti-MAG patients were also very low. Four of the 5 non–anti-MAG tremor patients had amplitudes varying from 0.26 mm to 1.53 mm on the more affected side and showed much lower average worse-to-best side amplitude ratios, also supporting the diagnosis of a more EPT-like tremor.

Mechanisms underlying why anti-MAG associated PN tremors are more severe than other PN remain unclear. Central processing, sensory feedback abnormalities, or variability of involvement over the course of nerve fibers in anti-MAG neuropathies, with greater distal binding of anti-MAG antibodies to myelin sheaths,[14] may offer some explanations. Recently, Trojaborg et al.[15] showed that anti-MAG neuropathy patients with high titers ($\geq$1:12,000) can be differentiated from those with other types of neuropathy by their residual latency EMG parameters, and that the extent of the slowing of the residual latency is directly related to the severity of the anti-MAG titer. The relatively more abnormal distal conduction may cause improper feedback signaling or mismatches between intended and actual movements and result in some of the manifestations of neurogenic tremor found in our results, although these issues were not specifically investigated in this study. Further comparative analyses of tremors in patients with various forms of demyelinating and axonal neuropathies correlated with nerve conduction abnormalities are needed.

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