Tremor in inflammatory neuropathies

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ABSTRACT

Background Tremor is known to occur in patients with neuropathies although its reported prevalence varies widely. Tremor has been shown to cause disability in children with Charcot–Marie–Tooth disease but no data exist about the disability caused by tremor in inflammatory neuropathies. Little is known about the response of neuropathic tremor to treatment and why it selectively occurs in some people and not others.

Methods This case control study investigates the presence and severity of tremor in 43 consecutively recruited patients with inflammatory neuropathies at the National Hospital for Neurology and Neurosurgery, London. Clinical assessment, including Fahn–Tolosa–Marin Scale for tremor, sensory scores, power scores and Overall Neuropathy Limitations Scale, were recorded. Results of nerve conduction studies were retrieved and assessed. Nine patients’ tremors were recorded with accelerometry.

Results Tremor was most common in IgM paraproteinaemic neuropathies, as previously reported, but also occurred in 58% of those with chronic inflammatory demyelinating polyradiculoneuropathy and 56% of those with multifocal motor neuropathy with conduction block. We describe, for the first time, tremor in all of these patients seems generally refractory to treatment except in a small number of cases where tremor improves with treatment of the underlying neuropathy. We provide evidence that tremor may add to disability in patients with inflammatory neuropathy. Mean tremor frequency was 6 Hz and did not vary with weight loading. We demonstrate for the first time that although tremor severity correlates with F wave latency, it is not sufficient to distinguish those with, from those without, tremor.

Conclusion Tremor in inflammatory neuropathies is common, adds to disability and yet does not often respond to treatment of the underlying neuropathy. When present, tremor severity is associated with F wave latency.

INTRODUCTION

It has been recognised for many years that tremor can be an accompanying feature of peripheral neuropathy.1 2 This neuropathic tremor was first described in hereditary neuropathies as part of Roussy–Levy syndrome3 which has since been shown to be a genetically heterogeneous entity.4 5 In inflammatory neuropathies, tremor is found in up to 80% of patients with IgM paraproteinaemic neuropathy (IgMPN),2 6 7 in the recovery phase of Guillain–Barré syndrome6 and is occasionally reported in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).9 No relationship seems to exist between the development of tremor and the severity of the neuropathy, proprioceptive loss, weakness or fatigue10 11 but it may relate to disease activity.12 13 Thus it is not clear why only a subset of patients develop tremor. Tremor in neuropathies has been described as disabling but no formal study of this has been undertaken,7 except in paediatric Charcot–Marie–Tooth disease where it has been shown to be one of the strongest independent determinants of reduced quality of life12; successful treatment in this context would likely have a substantial effect on quality of life. Tremor in this population also predicts other disabling symptoms.13 Currently, there is no consensus on the best way to treat neuropathic tremor, or why only some patients seem to be at risk of developing it. Certainly, some cases of tremor in inflammatory neuropathies are very disabling, necessitating both medical and invasive surgical approaches to treatment.14–16

In this case control study we gathered consecutive and clinically well characterised patients with inflammatory neuropathy with the main aims of (1) documenting the incidence and nature of tremor, (2) assessing the additional disability that might be present in patients with tremor and (3) determining the predictors of tremor onset and its subsequent severity.

METHODS

Patients

All patients with a diagnosis of an inflammatory neuropathy made by a neuromuscular expert (MMR, MPL and HM) and who were receiving regular intravenous immunoglobulin treatment at the National Hospital for Neurology and Neurosurgery, London, UK, were approached to take part in the study. Those taking drugs known to commonly cause tremor were excluded. Written informed consent was obtained from all patients and the study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki.

Clinical evaluation

Details regarding demographic and medical history were obtained from patients directly and corroborated with their medical notes. A standardised clinical examination was performed. In particular,
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careful examination for parkinsonian signs and signs of functional tremor\(^{15}\) were sought. Tremor where present was distinguished from other spontaneous movements, including fasciculations and myokymia. A summed Medical Research Council score (MRC score)\(^{20}\) was calculated (maximum score 70) as well as a sensory sum score.\(^{21}\) Tremor was assessed using the Fahn–Tolosa–Marin Scale\(^{22,23}\) with higher scores attributed to worse tremor. Tremor severity in the limbs was specifically assessed with Archimedes spirals and using the Bain and Findley spiral score (rated 0–10 with 10 representing the most severe tremor)\(^{24}\) to rate these. Patients were divided into two groups for subsequent analysis depending on the presence, clinically, of pathological tremor (tremulous group) or absence (non-tremulous group). Disability was assessed with the Overall Neuropathy Limitations Scale (ONLS).\(^{25}\) It has separate subscales for arms and legs with higher scores indicating more functional impairment. Results of patients’ most recent nerve conduction studies were obtained and correlations of clinical features of tremor to median nerve conduction alone were made on onset was 57.6 (11.6) years. Mean duration of disease before tremor onset was 5.8 (7.2) years. There were more men in the tremulous group (table 1) but this did not reach statistical significance (p=0.14). One patient had onset of tremor during a relapse of his MMNCB, 6 years after the clinical onset of his neuropathy. One non-tremulous patient had a previous episode of tremor during her first Guillain–Barré syndrome-like presentation. A precipitating event prior to tremor onset was recalled in 10 of 27 patients: six were at the onset of the neuropathy, two were with relapses and two were at the time of general medical complications (one with a pulmonary embolus and intensive therapy unit admission and the other with a pulmonary embolus, but neither had abnormal structural MRI brain scans to account for the onset). Of the tremulous patients, four reported tremor in one first degree relative (one of these reported it in two first degree relatives). Of these, two were in the context of a diagnosis of Parkinson’s disease in old age, one in the context of substantial alcohol misuse and the other reported hand tremor in his father with no known secondary cause. Of those with tremor, seven had trialled medical treatments specifically for tremor (propranolol (n=5), atenolol (n=1), levodopa (n=1), clonazepam (n=1), trihexyphenidyl (benzhexol) (n=1), topiramate (n=1), gabapentin (n=1), pregabalin (n=2), primidone (n=1)), all without benefit. Only one reported possible benefit with alcohol. Five patients reported benefit to tremor from treatment given for their neuropathy (three with intravenous immunoglobulin, one with CHOP-R chemotherapy and one with rituximab) while the remaining 22 patients reported no benefit from treatment of their neuropathy (all of these patients had only received intravenous immunoglobulin treatment apart from one who was also treated with rituximab).

Of the non-tremulous group, we obtained neuroradiology reports of four that had previous brain imaging (sometimes for incidental purposes) with MRI and one with CT. Three of four with MRI had changes consistent with mild or moderate small vessel disease. The patient with CT had evidence suggesting small vessel disease. Of the tremulous group of patients, we were able to obtain imaging reports of eight with MRI and two with only CT. Five of those with MRI had mild or moderate changes consistent with small vessel disease, one with frontoparietal atrophy bilaterally and two reported as normal. Of those who had CT, one was reported as normal and one reported as suggesting small vessel disease. The overall proportion of those with abnormal imaging versus those with normal imaging were seated in a comfortable chair. A triaxial accelerometer transducer (sensitivity ±100 mV/G, Biometrics ACL500, Biometrics Ltd, Cwmfelinfach, UK) was attached to the dorsal surface of the middle phalanx of the index finger bilaterally. Recordings were performed (a) with arms/wrists outstretched at shoulder level (posture) and (b) with a similar posture but a 500 g mass also attached to the wrists. Accelerometry was recorded and analysed for 30 s. The accelerometry traces were stored in a laboratory computer for display and offline analysis using customised Spike V2.

Accelerometry
Nine patients with tremor (five CIDP, two multifocal motor neuropathy with conduction block (MMNCB) and two IgMPN) took part in this evaluation. Subjects were seated in a comfortable chair. A triaxial accelerometer transducer (sensitivity ±100 mV/G, Biometrics ACL500, Biometrics Ltd, Cwmfelinfach, UK) was attached to the dorsal surface of the middle phalanx of the index finger bilaterally. Recordings were performed (a) with arms/wrists outstretched at shoulder level (posture) and (b) with a similar posture but a 500 g mass also attached to the wrists. Accelerometry was recorded and analysed for 30 s. The accelerometry traces were stored in a laboratory computer for display and offline analysis using customised Spike V2.

Statistical analysis
For accelerometry data, a Fourier analysis of the signals derived from accelerometry was performed to define peak tremor frequency. Statistical analysis was performed using PASW Statistics 19 (SPSS Inc, Chicago, Illinois, USA). All results are expressed as mean (SD) or median (range) where assumptions of parametric data were not met. Baseline tremor characteristics were compared between tremulous and non-tremulous controls by independent sample t test or Mann–Whitney test where assumptions of parametric distributions were not met. For categorical data, group analysis was performed using Pearson’s coefficient or Kendall’s τ where data could not be transformed to fulfil assumptions for parametric distributions. A p value <0.05 was considered to indicate statistical significance except where indicated, in which case Bonferroni correction for multiple comparisons was employed.

RESULTS
From a total group of 44 patients, 45 patients agreed to take part. Clinical and demographic details are summarised in table 1.

Clinical evaluation
Twenty-seven (65%) patients had tremor. Mean age at tremor onset was 57.6 (11.6) years. Mean duration of disease before tremor onset was 5.8 (7.2) years. There were more men in the tremulous group (table 1) but this did not reach statistical significance (p=0.14). One patient had onset of tremor during a relapse of his MMNCB, 6 years after the clinical onset of his neuropathy. One non-tremulous patient had a previous episode of tremor during her first Guillain–Barré syndrome-like presentation. A precipitating event prior to tremor onset was recalled in 10 of 27 patients: six were at the onset of the neuropathy, two were with relapses and two were at the time of general medical complications (one with a pulmonary embolus and intensive therapy unit admission and the other with a pulmonary embolus, but neither had abnormal structural MRI brain scans to account for the onset). Of the tremulous patients, four reported tremor in one first degree relative (one of these reported it in two first degree relatives). Of these, two were in the context of a diagnosis of Parkinson’s disease in old age, one in the context of substantial alcohol misuse and the other reported hand tremor in his father with no known secondary cause. Of those with tremor, seven had trialled medical treatments specifically for tremor (propranolol (n=5), atenolol (n=1), levodopa (n=1), clonazepam (n=1), trihexyphenidyl (benzhexol) (n=1), topiramate (n=1), gabapentin (n=1), pregabalin (n=2), primidone (n=1)), all without benefit. Only one reported possible benefit with alcohol. Five patients reported benefit to tremor from treatment given for their neuropathy (three with intravenous immunoglobulin, one with CHOP-R chemotherapy and one with rituximab) while the remaining 22 patients reported no benefit from treatment of their neuropathy (all of these patients had only received intravenous immunoglobulin treatment apart from one who was also treated with rituximab).

Of the non-tremulous group, we obtained neuroradiology reports of four that had previous brain imaging (sometimes for incidental purposes) with MRI and one with CT. Three of four with MRI had changes consistent with mild or moderate small vessel disease. The patient with CT had evidence suggesting small vessel disease. Of the tremulous group of patients, we were able to obtain imaging reports of eight with MRI and two with only CT. Five of those with MRI had mild or moderate changes consistent with small vessel disease, one with frontoparietal atrophy bilaterally and two reported as normal. Of those who had CT, one was reported as normal and one reported as suggesting small vessel disease. The overall proportion of those with abnormal imaging versus those with normal imaging

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tremulous patients</th>
<th>Non-tremulous patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>27 (63%)</td>
<td>15 (37%)</td>
</tr>
<tr>
<td>Disease (n (%))</td>
<td>15 (58)</td>
<td>11 (42)</td>
</tr>
<tr>
<td>CIDP</td>
<td>5 (56)</td>
<td>4 (44)</td>
</tr>
<tr>
<td>MMNCB</td>
<td>7 (88)</td>
<td>1 (12)</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>6/21</td>
<td>7/9</td>
</tr>
</tbody>
</table>

Age of patients (years)

| Mean*                                                                  | 63.3 (11.0)        | 60.5 (12.0)            |
| Median                                                                 | 63.0 (34.0–83.0)   | 59.0 (44.0–85.0)       |

Disease duration (years)

| Mean*                                                                  | 12.8 (8.9)         | 14.3 (9.2)             |
| Median                                                                 | 10.0 (2.0–30.0)    | 12.5 (2.0–33.0)        |

Values are mean (SD), median (range) and number (%).

*Denotes the use of either the mean or median for pairwise comparison.

Bonferroni corrected significance value of 0.025 was used, and p values where relevant are reported in the manuscript.

CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; IgMPN, IgM paraproteinaemic neuropathy; MMNCB, multifocal motor neuropathy with conduction block.
Measures of tremor severity
The median Fahn–Tolosa–Marin Scale score in tremulous patients was 14.0 (9.8–18.3). The Fahn–Tolosa–Marin Scale score includes components assessing disability and tremor in body parts other than the arms. Using spiral scores is a purer measure of tremor amplitude in the upper limb and thus of value in correlating with upper limb clinical and electrophysiological measures. Nevertheless, there was a strong correlation between both measures of tremor (Kendall’s τ=0.59; p<0.001). There was also a difference between the median score for spirals in those with tremor (3.0) compared with those without tremor (1.0) (U=16, Z=−4.5, p=0.001, r=−0.75). Spirals in non-tremulous patients were often abnormal but typically lacked periodic oscillatory patterns. To investigate whether other symptoms of neuropathy were confounding the spiral score, we correlated spiral scores to strength and sensory deficit (using a Bonferroni corrected significance level of 0.0167 to adjust for three comparisons). In those with tremor, higher spiral scores did not correlate with worse MRC scores (see table 2) (p=0.45) or worse sensory scores (p=0.98). In those with tremor, there was a correlation between higher (more severe) ONLS arm scores and higher spiral scores (Kendall’s τ=0.44; p=0.01).

Correlation of tremor with electrophysiological markers
A number of variables measured are dependent on conduction velocity but principal component analysis was not used given the inadequately low Keiser–Meyer–Olkin measure of sampling adequacy (0.43). There was no difference in F wave latencies between the tremulous and non-tremulous groups (see table 3). However, with individual correlation of variables (using a Bonferroni corrected significance level of 0.025 for two comparisons), using spiral scores, there was a correlation between spiral scores and median nerve F wave latency (p=0.02) (see figure 1). Given this, ulnar nerve F wave latency was examined post hoc and a similar but stronger correlation was found with spiral scores (p=0.003) (see figure 1). F wave latency was only calculated for those in whom it could be measured. Where F waves were not seen, the mean spiral score was 3.5 (3.0). There was no correlation between spiral scores and median nerve motor conduction velocity (p=0.49) or median nerve sensory conduction velocity (p=0.36).

Correlation of tremor with clinical features of neuropathy
Those with tremor had better MRC scores than those without tremor (t (16.8)=−2.6; p=0.018), yet they had similar disability scores measured by ONLS (see table 1). Using spiral scores as a measure of tremor severity, there was a correlation with ONLS arm subscores in tremulous patients (Kendall’s τ=0.44; p=0.01 using a Bonferroni corrected significance level of 0.01 to adjust for five comparisons), demonstrating an association between increasing tremor severity and increasing disability. There was no correlation of tremor severity measured by spiral scores with disease (neuropathy) duration (p=0.67), MRC score (p=0.45), overall sensory score in the arms (p>0.99) or arm proprioception score (p=0.68). With regard to hypotheses of tremor pathophysiology in these disorders, there was no difference in the proportion of tremulous patients who had a serum paraprotein (44%) from the proportion of non-tremulous subjects (51%) with a paraprotein (p=0.52). There was also no difference in the proportion of tremulous patients who demonstrated pseudoathetosis (22%) compared with the proportion of non-tremulous patients with pseudoathetosis (13%) (p=0.69).

Accelerometric measure of tremor
In all nine patients recorded with accelerometry, a bilateral rhythmic tremor was noted during posture. There was no significant difference in tremor frequency between left and right hands (p=0.53). The mean frequency of tremor in both hands in all nine patients was 6.1 (1.6) Hz, with the highest recorded frequency at 10.0 Hz and the lowest frequency at 3.5 Hz. There was no significant difference in tremor frequency between the three groups of patients (CIDP, MMNCB, IgMPN) (p=0.53). Weight loading did not alter mean tremor frequency (p=0.25). A sample of tremor recording is demonstrated in figure 2.

Table 2 Clinical scores of the patients

<table>
<thead>
<tr>
<th>Clinical score</th>
<th>Tremulous patients</th>
<th>Non-tremulous patients</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean*</td>
<td>65.7 (3.9)</td>
<td>56.6 (13.4)</td>
<td>0.017†</td>
</tr>
<tr>
<td>Median</td>
<td>66.0 (58.0–70.0)</td>
<td>58.0 (29.0–70.0)</td>
<td></td>
</tr>
<tr>
<td>Sensory score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean*</td>
<td>39.9 (14.2)</td>
<td>42.3 (16.2)</td>
<td>0.63</td>
</tr>
<tr>
<td>Median</td>
<td>41.0 (8.0–56.0)</td>
<td>48.0 (3.0–56.0)</td>
<td></td>
</tr>
<tr>
<td>ONLS score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>3.7 (1.5)</td>
<td>4.5 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Median*</td>
<td>4.0 (0.0–6.0)</td>
<td>4.5 (1.0–10.0)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Values are mean (SD) and median (range).
*Denotes use of either the mean or median for pairwise comparison.
†Denotes significance.
MRC score, Medical Research Council score; ONLS score, Overall Neuropathy Limitations Scale score.

Table 3 Nerve conduction study results for patients

<table>
<thead>
<tr>
<th>Nerve conduction result</th>
<th>Tremulous patients</th>
<th>Non-tremulous patients</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median nerve MCV (m/s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>40.5 (19.7)</td>
<td>37.6 (10.1)</td>
<td></td>
</tr>
<tr>
<td>Median*</td>
<td>46.0 (10.0–97.0)</td>
<td>41.5 (21.0–56.0)</td>
<td>0.42</td>
</tr>
<tr>
<td>Median nerve CMAP (mV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean*</td>
<td>5.8 (3.1)</td>
<td>4.0 (3.2)</td>
<td>0.07</td>
</tr>
<tr>
<td>Median</td>
<td>5.5 (0.8–11.5)</td>
<td>3.3 (0.2–9.7)</td>
<td></td>
</tr>
<tr>
<td>Median nerve DML (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>7.0 (5.0)</td>
<td>5.8 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Median*</td>
<td>4.5 (3.0–18.4)</td>
<td>42.7 (19.7)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>28.5 (0.0–59.0)</td>
<td>50.0 (0.0–60.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Median nerve F wave latency (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>43.9 (24.7)</td>
<td>40.1 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Median*</td>
<td>31.3 (26.3–98.0)</td>
<td>36.9 (31.9–51.5)</td>
<td>0.22</td>
</tr>
<tr>
<td>Median</td>
<td>43.4 (20.5)</td>
<td>36.3 (6.2)</td>
<td></td>
</tr>
<tr>
<td>Median*</td>
<td>34.4 (27.7–96.5)</td>
<td>35.7 (29.7–46.6)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Values are mean (SD) and median (range).
*Denotes use of either the mean or median for pairwise comparison.
CMAP, compound motor action potential; DML, distal motor latency; MCV, motor conduction velocity; SCV, sensory conduction velocity.
We have described the clinical and electrophysiological characteristics of 43 patients with inflammatory neuropathies. This is the largest prospective cohort of patients with inflammatory neuropathy reported with the primary purpose of investigating tremor. We have highlighted that the majority of patients with inflammatory neuropathy in our cohort had tremor (63%), particularly those with IgMPN, but also the majority of patients with CIDP. We have also described, for the first time, tremor in the majority of patients with MMNCB. Tremor in all of these patients does not seem to improve with treatment of the underlying neuropathy except in a small number of cases. Specific treatments for tremor, where used in a few cases, also proved to be, in the majority of cases, unsuccessful. We have provided evidence that tremor may add to disability in patients with inflammatory neuropathy, as has been described in children with Charcot–Marie–Tooth.12 We have also demonstrated for the first time a correlation of tremor severity and ulnar F wave latencies.

**Impact of tremor on disability**

Patients with tremor scored similarly to patients without tremor on the ONLS, a validated disability score. Despite this, non-tremulous patients were weaker than tremulous patients. This suggests that the presence of tremor accounts for part of the disability measured by the ONLS, similarly suggested by Ahlskog et al.26 Interestingly, in multiple sclerosis tremor, as limb weakness progresses, tremor may improve, suggesting a necessary role for limb strength in generating tremor.27 This may similarly be true for patients with inflammatory neuropathy and tremor but we observed that none of our patients reported worsening of tremor associated with improvement in their neuropathy (and strength) after treatment with intravenous immunoglobulins or other immunomodulators. All of the patients examined had been given intravenous immunoglobulins and other immunomodulatory treatments without benefit on tremor in most cases. Although a few appeared to improve with treatment, this was sometimes with substantial immunosuppressive drugs, such as rituximab. Where tremor was specifically treated, in most cases there was a poor response to usual antitremor drugs. The high prevalence of tremor in our cohort, the component of disability potentially attributable to tremor and refractoriness to treatment where tried, frames tremor as a potentially important symptom contributing to untreated disability in patients with inflammatory neuropathies.

**Pathogenesis of tremor**

For most demographic and clinical features, except gender, there was no difference between the tremulous and non-tremulous patient groups or any correlation within the tremulous group.
There were no differences in F wave latency between the tremulous and non-tremulous patients, but there was a strong correlation between tremor severity (assessed by spiral scores) and F wave latencies (see figure 1). However, this should be tempered with the fact that we a priori planned analysis of only median nerve data and added the ulnar F wave correlation post hoc. Nevertheless, the finding of similar F wave latencies between tremulous and non-tremulous patients, yet a strong correlation between delayed F wave latencies and tremor severity points towards F wave delay being an important modulator of tremor in those prone to it, in itself seems insufficient to explain the presence or absence of tremor. This might indicate the importance of an additional variable, such as the ability of a central processor (most likely the cerebellum) to adapt to such dispersion, and prevent tremor from arising. Recent data demonstrating defective cerebellar associative learning in patients with inflammatory neuropathy and tremor, but not those without tremor, supports the hypothesis of cerebellar dysfunction in patients with inflammatory neuropathy and tremor. Activation studies using positron emission tomodraphy demonstrating cerebellar overactivity in patients with IgMMPN and tremor seems concurrent with this possibility. Alternative hypotheses such as that proposed by Smith et al in which tremor was felt to be part dependent on the stretch reflex given the finding of a correlation between ulnar motor conduction velocities and thumb tremor, does not seem consistent with our findings. Bain et al similarly were unable to find such a correlation. Our finding of a tremor frequency that does not vary with weight loading also promotes the hypothesis of an important central mechanism in generating the tremor.

Busby and Donaghy, in their study of 102 patients with chronic disimmune neuropathy, remarked on slowed motor nerve conduction velocities and prolonged distal motor latencies in all patients with tremor but F waves were not commented upon. However, this was based on conduction velocities in only four patients of their series of 102 patients, all of whom had very severe tremor. This indicates selection bias for severe tremor in their calculation and there was no comparison reported between conduction velocities in these patients compared with non-tremulous patients. Thus there is sufficient evidence to conclude that our results differ from theirs. Indeed, other series do not demonstrate a difference in motor conduction velocities in tremulous versus non-tremulous patients. A caveat is that patients here were recruited from those attending hospital regularly for treatment with intravenous immunoglobulin which thus may have biased the sample towards one with greater severity of neuropathy. As such, conclusions drawn here can only be applied to this subgroup of patients.

Limb tremor has rarely been described in patients with MMNCB; three patients in a case series of 59 cases of MMNCB had tremor, all at rest. We have described five of nine MMNCB patients in our study as having tremor. In two of these, the tremor was jerky. In only one of these was tremor present at rest in addition to action tremor. Treatment of inflammatory tremor has previously been reported to be variable (summarised by Smith), with many treatment failures but some treatment successes using immunomodulators for treating the underlying neuropathy and rare success using other medications, such as pregabalin. Here, patients with tremor were refractory to normal oral medications used for treating tremor, including pregabalin. There were a small number of cases that responded to treatment of the underlying inflammatory process with immunomodulators but the numbers were too small to draw clear conclusions.

The presence of tremor in inflammatory neuropathies seems unlikely to represent the coexistence of essential tremor (ET) on epidemiological, clinical and neurophysiological grounds. In our series, the prevalence of tremor was some magnitudes higher than that reported for ET in the general population, even for a population over the age of 40 years. Further, the male predominance in tremulous patients (although not statistically significant), similarly described previously, is atypical of ET, as is the very low rate of a family history of tremor (15% in our cohort, a proportion of which may be attributable to parkinsonism rather than ET) and lack of response to alcohol, as may be expected in ET. There was no evidence on careful clinical examination that these patients had an alternative tremor diagnosis, such as parkinsonism or functional tremor.

Use of spirals for rating neuropathic tremor
The use of spirals for rating tremor and their automated analysis has attracted considerable attention in the literature, particularly for use in clinical trials. Our results suggesting that tremor provides a component of the disability experienced by some patients with inflammatory neuropathy indicates that a simple measure of tremor severity would be of interest for future clinical trials in inflammatory neuropathy. However, the potential for confounding of spiral scores from factors due to the neuropathy itself (weakness, sensory impairment) has not previously been addressed. In our series, although patients without tremor made some errors in spiral drawings, these were not typical for those produced by patients with tremor, lacking periodic oscillation. We therefore suggest that this simple measure could be utilised in future clinical trials.

Tremor in inflammatory neuropathies is common, not just in IgMMPN, but also in CIDP and MMNCB. Tremor appears to cause disability, independent of other factors relating to the neuropathy, and is therefore an important outcome measure in future clinical trials of treatment, with simple spiral assessments offering an easy tool to do so. Outcomes for treatment of tremor are disappointing, except in a small number of cases where tremor improves with immunomodulatory treatment of the neuropathy. F wave latencies correlate strongly with the severity of tremor, but this is insufficient to fully explain the presence of tremor in only a proportion of patients with inflammatory neuropathy. Perhaps, as suggested by Bain et al, the presence of an additional factor such as the inability of a central processor such as the cerebellum to adapt to these mistimed signals is additionally required for patients to develop tremor.

**Contributors**
(1a) substantial contributions to conception and design, (1b) acquisition of data or (1c) analysis and interpretation of the data, (2a) drafting of the article or (2b) revising it critically for important intellectual content; and (3) final approval of the version to be published. TAS—1a, 1b, 1c, 2a, 2b, 3. PS—1a, 1b, 1c, 2b, 3. MM—1a, 1b, 2b, 3. ML—1a, 1b, 2b, 3. BB—1a, 1b, 2b, 3. PK—1a, 1b, 1c, 2b, 3. PK—1a, 1b, 2b, 3. IP—1c, 2a, 2b, 3. HM—1a, 2b, 3, KB—1a, 2b, 3. JC—1a, 1b, 2a, 3. ME—1a, 1b, 1c, 2b, 3.

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