A study of tremor in multiple sclerosis

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Summary
One hundred patients with definite multiple sclerosis, who were randomly selected from a multiple sclerosis unit in London, were examined in order to study the prevalence, subtypes, clinical features and associated disability of tremor in this population. There were 35 males and 65 females with an average age of 47 years and an average disease duration of 18.8 years. The mean tremor duration was 13 years, with a median latency of 11 years from disease onset to appearance of tremor. Tremor was reported in 37 patients but was detected in 58. Tremor affected the arms (56%), legs (10%), head (9%) and trunk (7%). There were no examples of face, tongue or jaw tremor. All the patients had action tremor, either postural or kinetic (including intention). Rest, Holmes' ('rubral') and primary orthostatic tremors were not encountered. Tremor severity ranged from minimal in 27%, to mild in 16% and moderate or severe in 15% of cases. Tremor severity correlated with the degree of dysarthria, dysmetria and dysdiadochokinesia but not with grip strength. In order to determine the clinical characteristics of these tremors, the action tremors of the upper limbs were subclassified according to the predominant site and state of tremulous activity. Of the 50 patients with tremor in the right arm, 32% had distal postural tremor, 36% had distal postural and kinetic tremor, 16% had proximal postural and kinetic tremor; 4% had proximal and distal postural and kinetic tremor and 12% isolated intention tremor. Twenty-seven percent of the overall study population had tremor-related disability and 10% had incapacitating tremor. Patients with abnormal tremor (severity grade >1/10) were more likely than those without tremor to be wheelchair dependent and have a worse Expanded Disability Systems Score, but Barthel activities of daily living indices and cognitive scores were comparable in the two groups.

Keywords: multiple sclerosis; tremor; disability

Abbreviations: ADL = activities of daily living; EDSS = Expanded Disability Status Score

Introduction
The purpose of this study was to find out more about the tremors that can afflict patients with multiple sclerosis, as there is a dearth of information concerning this topic. This project was part of a wider probe into multiple sclerosis tremor that included analysis of the applicability of various tremor assessment techniques, stereotactic surgical interventions (Alusi et al., 2000a, b) and physiological studies (Spyers-Ashby et al., 1999).

Weinshenker and colleagues found that functionally relevant cerebellar deficits occurred in one-third of 259 multiple sclerosis patients who were followed-up for 3 years (Weinshenker et al., 1996) and a similar figure (32%) was noted by Ruitiainen (Ruitiainen, 1997). The severity of ataxia has been shown to correlate with the level of disability and dependence caused by multiple sclerosis (Weinshenker et al., 1991) and inversely with basal pulmonary function (Grasso et al., 2000). Furthermore, the presence of severe cerebellar signs was demonstrated to be associated with a poorer prognosis and a very high risk of respiratory impairment (Weinshenker et al., 1991; Grasso et al., 2000).

The incidence and prevalence of tremor in multiple sclerosis is difficult to establish, partly because the neurological signs occurring during the relapsing and remitting phase of the disease are transient, which contributes to sampling error and also because dissecting intention tremor from serial dysmetria and postural tremor from other postural instabilities is difficult (Sabra and Hallett, 1984). In addition, the Kurtzke functional systems subscale part B (cerebellar function) does not isolate tremor (Kurtzke, 1955), making it impossible to establish in retrospect the proportion of tremulous patients in a study that used this rating scale. Moreover, there are no published quantitative studies that provide information about the contribution of tremor to the disabilities and handicap caused by multiple sclerosis.
However, one study reported tremor of moderate or severe magnitude in 23% and 6% of the patients, respectively (Bauer and Hanefeld, 1993).

Two specific issues, which we have touched on in a previous review (Alusi et al., 1999), concern the occurrence or otherwise of true rest tremor and Holmes’ (‘rubral’) tremor in patients with multiple sclerosis. Charcot noted that rest tremor was not a sign of multiple sclerosis (Charcot, 1875). However, in some neurosurgical papers, apparent ‘rest’ tremor has been described in multiple sclerosis patients (Goldman and Kelly, 1995; Haddow et al., 1997), but these descriptions do not fulfill the current criteria defining rest tremor (Deuschl et al., 1998).

Severe Holmes’ (previously termed ‘rubral’ or ‘midbrain’) tremor is conventionally considered by many neurologists to be the characteristic type of severe tremor found in patients with multiple sclerosis (Bain, 1993; Hopfensperger et al., 1995; Hooper and Whittle, 1998). However, once again, there are no publications that adequately describe this form of tremor in this disease.

Thus this study was designed to obtain answers to the following simple questions. What is the approximate proportion of a hospital out-patient multiple sclerosis population afflicted by tremor? What parts of the body are affected by multiple sclerosis tremor? What are the clinical characteristics of these tremors? Do rest or Holmes (‘rubral’) tremors occur in multiple sclerosis? What are the patterns of disease or the accompanying clinical features associated with multiple sclerosis tremor? How mild or severe are the tremors of multiple sclerosis and what contribution does tremor make to the disability and handicap produced by the disease? Answering these questions is important because multiple sclerosis tremor may, in appropriately selected patients, respond to medical or (stereotactic) surgical interventions (Speelman et al., 1984; Hallett et al., 1985).

**Methods**

**Patients**

Two hundred and twenty patients were randomly selected from the 365 patients on the Multiple Sclerosis Unit register at the Central Middlesex Hospital using computer-generated random numbers. From this group, a total of 148 patients were selected who met the following criteria: (i) a definite diagnosis of multiple sclerosis with reference to the Poser criteria (Poser et al., 1983); (ii) aged between 18 and 70 years; and (iii) no other neurological disease. This group was invited by postal request to participate in the study. There was a 62% response rate (92 patients agreed to participate, 36 refused and the remainder did not respond). The non-responders were contacted again and, although nine agreed to take part (giving a total of 101 patients), we omitted the last responder to facilitate analysis. Thus the study population consisted of 100 patients. All patients voluntarily gave their informed consent to be studied and the study had local ethical committee approval.

**Tremor definitions and assessments**

The following definitions published in a Consensus Statement of the Movement Disorder Society (Deuschl et al., 1998) were used to describe the various tremor components detected in the patients.

**Rest tremor**

Rest tremor is a tremor present in a body part that is not voluntarily activated and is completely supported against gravity (ideally resting on a couch).

**Action tremor**

Action tremor is any tremor that is produced by voluntary contraction of a muscle, including postural, isometric, kinetic and intention tremor.

**Postural tremor**

Postural tremor is present whilst voluntarily maintaining a position against gravity.

**Kinetic tremor**

Kinetic tremor is tremor occurring during any voluntary movement.

**Isometric tremor**

Isometric tremor is tremor occurring as a result of muscle contraction against a rigid stationary object.

**Intention tremor**

Intention tremor or tremor during target-directed movement is present when tremor amplitude increases during visually guided movements towards a target at the termination of movement and the possibility of position-specific tremor or postural tremor produced at the beginning and end of a movement is excluded.

**Holmes’ tremor**

The following criteria apply to this tremor: (i) rest and intention tremor with irregular presentation (in many patients, postural tremor is also present; the tremor is often not as rhythmic as other tremors); (ii) slow frequency, usually less than 4.5 Hz; and (iii) if the time when a lesion occurred can be identified (for example a stroke), a variable delay (typically 4 weeks to 2 years) between that lesion and the first appearance of tremor is typical of this tremor type. It has been labelled in the past under different names including rubral tremor, midbrain tremor, thalamic tremor, myorhythmia and Benedikt’s syndrome.

**Gestes antagonistes**

These are sensory tricks in which tactile or proprioceptive stimuli applied to a part of the body (typically the head or neck) modify the tremor or dystonia. In practice, the most commonly used geste is placing a finger or hand on the
face in order to suppress spasmodic torticollis temporarily (Anderson, 1995).

Examinations
The patients were interviewed and a standard full general neurological examination was carried out, including eye movements, by one of the authors (S.H.A.) to establish their Functional Status Score (Kurtzke, 1955) and Expanded Disability Status Scores (EDSS) (Kurtzke, 1983). In addition, the following assessments were performed on all 100 cases: (i) 0–4 ataxia clinical scale for dysmetria, dysdiadochokinesia, dysarthria and gait ataxia (Appendix I); (ii) Barthel activities of daily living (ADL) index (Collin et al., 1988); (iii) the Mini-Mental State Examination (Folstein et al., 1975); (iv) a timed walking test over either 20 or 50 metres for all ambulatory patients (the shorter distance was used for those unable to walk 50 m); (v) grip strength—quantified using the Jaymar (Jackson, Mich., USA) hand-held dynamometer; and (vi) the presence or absence of nystagmus was recorded.

A tremor history was obtained from each patient, including details of the onset and spread of tremor. The presence or absence of tremor in the head, face, tongue, trunk and upper and lower limbs was recorded for all patients. Tremor was assessed in three states of muscle activity: rest, posture and movement. In the arms, tremor was assessed at rest and in two postures: with the arms held outstretched and with arms in the ‘bat-wing position’ (flexed at the elbows and the forearms pronated with the fingers held near the nose). Upper limb kinetic tremor was assessed during a finger–nose–finger test. The upper limb tremors were classified as proximal, distal or both, either visually or in more complex cases by claspings patients’ arms either at the wrist or above the elbow, thus isolating the movements of the distal part of the limb.

Tremor severity was rated in each of these situations on a 0–10 scale (Bain and Findley, 1993; Bain et al., 1993a, b; Alusi et al., 2000a). Tremors with a severity of more than grade 1 were termed ‘definitely abnormal’ tremors. A score of 0.5 was given to a tremor if its severity varied between grades 0 and 1. Patients’ head and trunk tremors were scored during posture and whilst resting on a couch. If the motion of the head was independent of the trunk, it was classified as a head tremor. Leg tremor was rated at rest and on posture, with each leg held outstretched whilst sitting.

The following tests, which previously have been shown to be reliable and valid ways of measuring tremor in patients with multiple sclerosis (Alusi et al., 2000a), were also performed only on the tremulous patients: (i) a finger tapping test (Worthington et al., 1989; Alusi et al., 2000a); (ii) a nine-hole peg test (Mathiowetz et al., 1985; Alusi et al., 2000a); (iii) samples of the patients’ drawing of an Archimedes spiral were obtained and scored on a 0–10 clinical rating scale (Bain and Findley, 1993; Bain et al., 1993b; Alusi et al., 2000a); and (iv) tremor-related disability and handicap [using Tremor Disability and Handicap Questionnaires (Bain and Findley, 1993; Bain et al., 1993b; Alusi et al., 2000a)—see Appendices II and III].

If tremor was visible, the peak amplitude and frequency of postural tremor were recorded using EGAX-5/L2M/ MiM miniature accelerometers, using a technique previously described (Bain et al., 1993a, b). The accelerometers were attached to the nose for recording head tremor, on the dorsal aspect of the hand between the first and second metacarpals for upper limb tremor and over the patella for leg tremor.

Statistical analysis
The significance of differences in the mean age and disease duration of the ‘definite tremor’ group and non-tremor groups was tested using unpaired t tests; disease pattern, handedness and male to female ratio using χ² tests; and for clinical features and measures of overall disability, the Mann–Whitney U test was deployed.

In the tremor group, the association between tremor severity [the maximum (0–10) value obtained on testing the two different postures or kinetic tremor in both arms] and demographic details, tremor-related disability, the associated clinical features, hand function tests and EDSS and Barthel ADL scores were tested using the Spearman rank correlation coefficient. The association between tremor-related disability and disease duration was also tested with the Spearman rank correlation coefficient. The correlation between the maximum tremor severity in the right and left arms was tested using the Spearman rank correlation coefficient.

Results
The study population characteristics
There were 100 patients in the study, of which 35 were males and 65 were females, with a male to female ratio of 1 : 1.8. Eighty-six patients were right handed and 14 left handed. The average age was 47.2 years (SD = 10.3) and the average disease duration, taken as the period from the date of the first symptom to the date of assessment, was 18.8 years (SD = 11.2). At the time of study, the median EDSS was 6.0 (range 0–9). The disease was classified as primary progressive in 22 patients, relapsing–remitting in 15 and secondary progressive with or without relapses in 63 patients.

Prevalence of tremor
Fifty-eight patients had tremor, although it was asymptomatic in 20 patients. The body parts affected were: the arms in 56, legs in 10, head in nine and trunk in seven patients. No tremors of the jaw, tongue or face were detected.

Tremor natural history
In 28 of the 38 patients in whom tremor was symptomatic, it was noticed in either or both arms first. One patient noticed
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Tremor in the head before it involved the arms and the remaining nine patients were unable to recall the sequence of tremor spread. If tremor involved an arm at onset, it spread to affect the other arm, before other body parts and, once started, persisted or progressed over time.

A family history of tremor was given by 7% of the study patients regardless of whether or not they were tremulous. Tremor was exacerbated by anxiety in 19 of the 58 tremulous patients (32.7%), taking a hot bath in four (6.9%) and physical exertion in 13 patients (22.4%). Alcohol was reported to improve tremor in six patients (10.3%) and worsened the tremor of one patient.

In the 31 patients who definitely had abnormal tremor (i.e. tremor severity grade >1), the average latency from the first symptom of multiple sclerosis to the onset of tremor was 13.5 years (SD 10.5) and the median duration of tremor was 3.25 years (Figs 1 and 2). None of the patients reported spontaneous remission of an episode of tremor.

Tremor subtypes and severity

The body parts affected by tremor varied amongst the patients, with the most common pattern being bilateral arm involvement (36 patients) followed by unilateral arm tremor (nine patients) and tremor of the head and arms (five patients). Less frequently, tremor affected all four limbs but spared the head (four patients), the head and four limbs (one patient), the head and three limbs (two patients) or the head and lower limbs (one patient).

Tremor was associated with jerky movements of the arms in three patients. In every case, tremor was of an action type (postural, kinetic or both). True rest tremor, as defined by Deuschl and colleagues (Deuschl et al., 1999), was not encountered. There were no examples of Holmes’ (‘rubral’), primary orthostatic or task-specific tremors.

Tremor was just detectable (grade 0.5–1) in 27 patients, mild (grade 1–3) in 16 and moderate–severe (grade 3–10) in 15 patients (Fig. 3). There was a good correlation between the maximum severities of the tremors present in each arm (Spearman’s ρ = 0.68, P < 0.005).

Types of tremor seen

Head tremor was of the ‘yes–yes’ type in all nine patients and was accompanied by a dystonic head tilt in four cases. It had a frequency range of 3.7–4.2 Hz and in every case it could be attenuated by a geste. Trunk tremor accompanied head tremor in seven patients. Leg tremor was postural (with a frequency range of 1.3–4.7 Hz) and involved the hip in all 10 of the affected patients. Figures 3 and 4 illustrate the severity and frequency distributions of upper limb tremors, which were classified into five distinct subtypes: (i) distal postural (fine) tremor, which had a small or no kinetic component; (ii) distal postural/kinetic (coarse) tremor; (iii) proximal postural/kinetic tremor; (iv) proximal and distal postural/kinetic tremor; and (v) isolated intention tremor. The clinical features of these five distinct arm tremor subtypes [as detected in the patients’ right arms (n = 50)] are shown in Table 1.

Distal postural (fine) tremor, which had a small or no kinetic component

This tremor was invariably mild (grade 0.5–1) and looked like physiological tremor. However, the frequency was found to be lower (2.6–6 Hz) than that of normal physiological tremor. This tremor was not usually visible on movement. Fifteen of the 20 asymptomatic patients had this form of tremor. It did not cause any disability and there was no associated dysmetria in these patients.
Table 1 Features associated with tremor subtypes present in the patients’ right upper limb (n = 50)

<table>
<thead>
<tr>
<th>Tremor subtype</th>
<th>No. of patients</th>
<th>Tremor frequency</th>
<th>Tremor severity 0–10 (median)</th>
<th>Associated dysmetria 0–4 (median)</th>
<th>No. of patients disabled by tremor</th>
<th>Tremor Disability Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal postural I (fine)</td>
<td>16</td>
<td>2.6–6 Hz</td>
<td>(0.5–1)</td>
<td>0</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Distal postural (coarse)</td>
<td>18</td>
<td>3–7 Hz</td>
<td>(0.5–5.5)</td>
<td>1.0</td>
<td>11</td>
<td>18% (0–77%)</td>
</tr>
<tr>
<td>Proximal postural</td>
<td>8</td>
<td>3.6–4.8 Hz</td>
<td>(1.0–10)</td>
<td>2.5</td>
<td>6</td>
<td>59% (0–95%)</td>
</tr>
<tr>
<td>Distal and proximal postural</td>
<td>2</td>
<td>3.3–5 Hz</td>
<td>(1.0–3.0)</td>
<td>1.5</td>
<td>2</td>
<td>50% (47–53%)</td>
</tr>
<tr>
<td>Intention tremor</td>
<td>6</td>
<td>2.6–3.7 Hz</td>
<td>(0.5–3.0)</td>
<td>0.75</td>
<td>2</td>
<td>14% (0–55%)</td>
</tr>
</tbody>
</table>

*0 = no disability; 100% = max disability.

Fig. 4 Distribution of upper limb tremor frequency (Hz).

Distal postural/kinetic (coarse) tremor
This form of distal action tremor caused flexion–extension movements at the wrist whilst the arms were held outstretched and a horizontal sliding flexion–extension movement at the elbow (‘sliders’) in the ‘bat-wing’ position. A kinetic component was present during the finger–nose test. The severity of this type of tremor (grade 0.5–5.5) was generally greater than that of distal postural tremor, and it had a frequency of between 3 and 7 Hz. It was usually associated with mild dysmetria. Eleven out of 18 patients experienced disability because of this tremor. The extent of tremor-related disability varied from 0 to 77% (mean 18%; see Table 1).

Proximal tremor subtypes: proximal postural/kinetic tremor, and proximal and distal postural/kinetic tremor
These action tremors (proximal postural/kinetic and proximal and distal postural/kinetic) had relatively low frequency bands of 3.6–4.8 Hz and 3.3–5 Hz, respectively. They predominantly affected the shoulder joint causing side-to-side movements of the outstretched arms, and the proximal and distal postural/kinetic tremor subtype also caused flexion–extension tremor at the wrist. Furthermore, these tremors caused an abduction–adduction movement of the upper arm when the arms were in the ‘bat-wing’ posture (‘flappers’). Both tremors could have severe kinetic components that made touching the target in the finger–nose–target test difficult. These tremors caused the greatest tremor-related disability and were associated with marked dysmetria, although proximal postural/kinetic tremor was generally worse than proximal and distal postural/kinetic tremor. Disability was present in six out of eight and two out of two for proximal postural/kinetic and proximal and distal postural/kinetic tremor patients, respectively. The mean severity of the tremor-related disability was 59% for proximal postural/kinetic tremor and 50% for proximal and distal postural/kinetic tremor (Table 1).

Isolated intention tremor
Finally, isolated intention tremor, which was present only during goal-directed movements, was present in only six patients. It was associated with mild dysmetria, had a low frequency band of 3.6–4.8 Hz and was generally mild, causing disability in two cases. The mean tremor-related disability score was 14% and varied from 0 to 55%.

Spiral drawings
Fifty-two of the 56 patients with upper limb tremor had abnormal spirals when drawn with their most tremulous arm. Four of these patients were either unable to hold pen to paper or drew a severely disrupted spiral (grade 10/10) despite relatively good arm strength. The degree of spiral disruption correlated most with the severity of the kinetic component of arm tremor (Table 2).

The tremor population
A comparison between the group of patients with definitely abnormal tremor (i.e. tremor grade >1, n = 31) and the non-tremulous group (n = 42) revealed that the former group were younger on average (t test: t = –2.99, P = 0.005)
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Table 2 Correlation of the tremor severity grades obtained from spirals and clinical examination of two postures (P1 and P2) and during movement (K)

<table>
<thead>
<tr>
<th></th>
<th>Right arm P1</th>
<th>Left arm P1</th>
<th>Right arm P2</th>
<th>Left arm P2</th>
<th>Right arm K</th>
<th>Left arm K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spiral grade</td>
<td>0.25</td>
<td>0.57</td>
<td>0.44</td>
<td>0.56</td>
<td>0.66</td>
<td>0.66</td>
</tr>
<tr>
<td>P value</td>
<td>0.07</td>
<td>&lt;0.005*</td>
<td>&lt;0.005*</td>
<td>&lt;0.005*</td>
<td>&lt;0.005*</td>
<td>&lt;0.005*</td>
</tr>
<tr>
<td>n</td>
<td>50</td>
<td>51</td>
<td>50</td>
<td>51</td>
<td>50</td>
<td>51</td>
</tr>
</tbody>
</table>

P1 = arms outstretched; P2 = arms in ‘bat-wing’ position; K = kinetic tremor. *Statistically significant.

Table 3 A comparison of demographic and clinical features found in the definitely tremulous and non-tremulous patient groups

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Tremor (&gt;1), n = 31</th>
<th>Non tremor, n = 42</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43.7 (SD = 10.4)</td>
<td>50.7 (SD = 9.4)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Female : male</td>
<td>16/15 = 1.1 : 1</td>
<td>30/12 = 2.5 : 1</td>
<td>0.083</td>
</tr>
<tr>
<td>Handedness R : L</td>
<td>26 : 5</td>
<td>36 : 6</td>
<td>1.66</td>
</tr>
<tr>
<td>Disease duration (mean: years)</td>
<td>17.2 (SD = 10.36)</td>
<td>20.7 (SD = 13.10)</td>
<td>0.162</td>
</tr>
<tr>
<td>Disease pattern</td>
<td></td>
<td></td>
<td>0.84</td>
</tr>
<tr>
<td>PP</td>
<td>8</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td>2</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>SP</td>
<td>21</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>EDSS (median)</td>
<td>6</td>
<td>5.5</td>
<td>0.016*</td>
</tr>
<tr>
<td>Barthel ADL index (mean)</td>
<td>14.0</td>
<td>17.7</td>
<td>0.13</td>
</tr>
<tr>
<td>Dysarthria (median)</td>
<td>1</td>
<td>0</td>
<td>0.001*</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>15</td>
<td>12</td>
<td>0.15</td>
</tr>
<tr>
<td>Mini-Mental score (mean)</td>
<td>26.9</td>
<td>28.2</td>
<td>0.27</td>
</tr>
<tr>
<td>Wheelchair dependence</td>
<td>10</td>
<td>2</td>
<td>0.02*</td>
</tr>
<tr>
<td>Walking speed (m/s)</td>
<td>0.72</td>
<td>0.9</td>
<td>0.74</td>
</tr>
<tr>
<td>Grip strength-dominant (kg)</td>
<td>25</td>
<td>27.6</td>
<td>0.39</td>
</tr>
<tr>
<td>Grip strength-non dominant (kg)</td>
<td>24.6</td>
<td>25.3</td>
<td>0.98</td>
</tr>
</tbody>
</table>

R = right; L = left; PP = primary progressive; RR = relapsing–remitting; SP = secondary progressive. *Statistically significant.

(Table 3). There was no significant difference in the male to female ratios between the two groups (χ² independence 3.0, P = 0.08), the average multiple sclerosis disease duration (Z = −2.41, P = 0.16) or the distribution of the multiple sclerosis disease patterns (i.e. primary progressive, relapsing–remitting and secondary progressive) (Table 3). However, there were only two patients with tremor who were still in the relapsing phase of the disease compared with seven in the other group (Table 3). EDSS scores were significantly worse in the tremulous groups (Z = −2.4, P = 0.016), differing by +0.5 EDSS points (Table 3).

The tremulous group scored significantly worse on the 0–4 dysarthria scale [Z = −3.92, P (two-tail) <0.001], but there were no significant differences between the two groups in the incidence of nystagmus [Z = −1.43, P (two-tail) = 0.15], the cognitive test scores using the Mini-Mental State Examination [Z = −1.10, P (two-tail) = 0.27], disability profile using the Barthel ADL index scores [Z = −1.5, P (two-tail) = 0.13] or the average grip strength (irrespective of whether dominant or non-dominant scores were compared) [Z = −0.86, P (two-tail) = 0.39, Z = −0.03, P (two-tail) = 0.98, respectively]. However, tremulous patients were more likely to be wheelchair dependent (χ² independence 5.5, P = 0.02). In patients who were still able to walk, with or without aid, there was no significant difference in average walking speed between the patients with abnormal tremor and those without tremor (P = 0.74) (Table 3).

Tremor-related disability

Twenty-seven of the 100 patients studied reported tremor-induced disability on the tremor ADL disability score and 10% suffered from incapacitating tremor (tremor disability score >50%). Thirteen patients felt they were handicapped either because of the physical effects of tremor or because they were embarrassed by the tremor, or both. In patients with tremor severity grade >1, tremor-related disability correlated with the maximum tremor severity score (n = 27, Spearman’s ρ = 0.66, P <0.005). Every patient with tremor severity greater than grade 3 reported tremor-related disability (Fig. 5). In those definitely tremulous patients who were able to recall the onset of their symptoms (n = 26), the latency from multiple sclerosis disease onset to the development of tremor did not determine the degree of associated disability (Spearman’s ρ = 0.09, P = 0.65). Furthermore, there was no relationship between the degree of tremor-related disability and multiple sclerosis disease duration. (n = 23, Spearman’s ρ = 0.19, P = 0.39).
Associated clinical features

Upper limb tremor severity was highly correlated with ataxic features [dysarthria (n = 27, Spearman’s $\rho = 0.48$, $P = 0.01$), dysmetria (n = 29, Spearman’s $\rho = 0.51$, $P = 0.004$) and dysdiadochokinesia (n = 29, Spearman’s $\rho = 0.56$, $P = 0.001$)] and also with tests of upper limb function [the finger tapping test and the nine-hole peg test (n = 26, Spearman’s $\rho = -0.45$, $P = 0.022$, and n = 27, Spearman’s $\rho = -0.47$, $P = 0.01$, respectively)]. It also correlated with multiple sclerosis disability (EDSS) (n = 31, Spearman’s $\rho = 0.41$, $P = 0.02$) and the Barthel ADL index (n = 31, Spearman’s $\rho = -0.42$, $P = 0.02$). There was no correlation between upper limb tremor severity and global cognitive function, measured by Mini-Mental Scores (n = 27, Spearman’s $\rho = -0.07$, $P = 0.73$) or with grip strength (n = 27, Spearman’s $\rho = -0.33$, $P = 0.09$).

Discussion

The population sample

This was not a geographically based study as patients were randomly recruited from a multiple sclerosis unit accepting secondary and tertiary referrals from general practitioners or neurologists. This creates bias towards more disabled patients. This phenomenon is well recognized in natural history studies of multiple sclerosis (McAlpine and Compston, 1952; Weinshenker et al., 1989). Furthermore, the exclusion of all probable and possible cases of multiple sclerosis from this study will have skewed the data further towards worse disease. The mean disease duration of our patient population was 18.8 years compared with 12 years in the total population figures from the 1989 Weinshenker study. This explains the high proportion (63%) of our patients with secondary progressive multiple sclerosis (with or without relapses) compared with 33.5% in a general multiple sclerosis population (Weinshenker et al., 1989), as within 6–10 years of disease onset 30–40% of patients with initial relapsing–remitting disease enter the progressive phase (Weinshenker et al., 1989).

Multiple sclerosis tremor

This is the first detailed study of tremor and the prevalence of its subtypes in multiple sclerosis. Abb and Scaltenbrand estimated the prevalence of tremor in multiple sclerosis to be 75% (Abb and Scaltenbrand, 1956), whilst another multiple sclerosis population study in Germany detected tremor of moderate or severe magnitude in 32 and 6% of their patients, respectively (Bauer and Hanefeld, 1993). Fifty-eight per cent of our population had tremor, but it was not reported by 20 of them, even though five had arm tremor worse than grade 1/10 in severity and one patient, with severe cognitive dysfunction, had tremor greater than grade 3/10. In part, this was because 16% had a mild non-disabling symmetrical distal postural upper limb tremor that resembled normal (8–12 Hz) physiological tremor (Shahani and Young, 1976) except that it had a lower frequency (2.6–6 Hz). This under-reporting of symptoms by multiple sclerosis patients has been observed before in studies of other deficits, such as dysarthria (Thomas et al., 1997).

Tremor causing disablement was said by Kandel and Hondcari to occur in one in seven patients (14%) with multiple sclerosis, which is close to our figure (13%) for tremor-related handicap (Kandel and Hondcari, 1985). However, we found that 27% of our patients reported disabling tremor and that 10% were incapacitated by their tremor. It is notable that tremor-related disablement was strongly correlated with upper limb tremor severity, but not with disease or tremor durations. The most severe forms of arm tremor were proximal, causing tremor at the shoulder and were associated with the highest tremor-related disability scores, followed in decreasing order of disability by distal postural/kinetic tremor, isolated intention tremor and finally distal postural tremor, which produced no disability.

The most common tremor subtype was not isolated intention tremor or Holmes’ (‘rubral’) tremor as might have been expected, but was a coarse distal tremor of the arms, which was present in 18% of the population, one notable result of this study being that isolated intention tremor is a relatively uncommon manifestation of multiple sclerosis, occurring in only 6% of the population. Furthermore, not one example of Holmes’ (‘rubral’) tremor was encountered. Indeed we draw attention to the original writings of Holmes (Holmes, 1904), who was the first to describe the characteristics of this tremor in detail and did not refer to demyelinating disease as a cause for it. In addition, true rest tremor was not detected in this population, which is in accordance with Charcot’s observation and our review of the literature (Alusi et al., 1999). Thus we conclude that multiple sclerosis typically causes various forms of upper limb action tremor.

In all but one case, tremor commenced in one or both upper limbs. However, in addition to upper limb action tremor, multiple sclerosis causes, in order of decreasing prevalence, postural tremor of the legs, head and trunk. We did not detect tremor of the face, jaw or tongue or task-specific or primary orthostatic tremors.

Head tremor was typically of the ‘yes–yes’ variety and may have a dystonic aetiology, as it could be decreased by a geste and in four cases was associated with a head tilt, observations that have since encouraged us to use botulinum toxin to treat multiple sclerosis patients with intrusive head tremor.

Clinical associations with multiple sclerosis tremor

Our data showed highly significant correlations between the presence of tremor and that of dysarthria (but not nystagmus), and the severity of tremor and the severities of dysarthria,
dysmetria and dysdiadochokinesia. These relationships provide strong circumstantial evidence to support the view that the action tremors of multiple sclerosis are the result of damage to the cerebellum or its connections. The absence of a correlation between the presence or severity of tremor and cognitive function, Barthel disability profile, grip strength or walking speed suggests that there is a specific relationship between multiple sclerosis tremor and defective cerebellar function rather than just with diffuse cerebral damage.

One other intriguing result is the apparently high incidence (7%) of our multiple sclerosis patients (irrespective of whether or not they have tremor) reporting a family history of tremor. This result suggests that the question of whether or not there is an association between multiple sclerosis and a form of familial tremor merits further scrutiny, as studies of essential tremor, the most common tremor encountered in the general population, show a prevalence of 0.3–1.7% (Bain et al., 1994; Findley, 2000). However, we do not know what types of tremor afflict our patients’ kindreds as they were not examined. In this respect, it is perhaps noteworthy that 16% of our multiple sclerosis population had distal postural tremor resembling physiological tremor but with frequencies more typical of (or even lower than) essential tremor (Deuschl et al., 1999), as there is evidence from clinical and positron emission activation studies to suggest that the latter is associated with cerebellar hypermetabolism (Jenkins et al., 1993) or may be a subtle cerebellar disorder (Deuschl and Elble, 2000).

Mechanisms of multiple sclerosis tremor

Our data indicate that multiple sclerosis causes action tremors that are probably the result of damage to the cerebellum or its connections rather than Holmes’ (‘rubral’ or ‘midbrain’) tremor or true rest tremor. The reason for this is not known but may be related to possible sparing of the dopaminergic pathways by the multiple sclerosis disease process. This hypothesis is supported by the conspicuous absence of true rest tremor in our multiple sclerosis patients and those reported in the published literature, as well as by the lack of responsiveness of multiple sclerosis tremor to L-Dopa replacement, which is in contrast to the marked tremor suppression caused by L-Dopa in many, but not all, patients with Holmes’ tremor originating from other aetiologies (Findley and Gresty, 1980; Remy et al., 1995). More importantly, this hypothesis can be tested using PET to measure putaminal and caudate fluorodopa uptake in tremulous multiple sclerosis patients, although we anticipate that the results would be normal.

The most frequent manifestation of tremor found in this study was a broadly symmetrical upper limb action tremor, which indicates that the patho-physiological processes underlying multiple sclerosis tremor involve bilateral mechanisms. It is possible that the presence of bilateral involvement of the cerebellum or its connections by multiple sclerosis lesions is common, but it is difficult to confirm this hypothesis as post-mortem studies involving multiple sclerosis patients with documented tremor are sparse (Fahn, 1986). Furthermore, the multiplicity of lesions in this disease, especially in a disabled tremulous group of patients, also makes it difficult to show direct linkage from a specific lesion to the presence of tremor. An alternative explanation for the broadly symmetrical nature of upper limb tremor in multiple sclerosis is that both sides of the cerebellum incorrectly calibrate for damage to the motor and/or sensory systems involved in movement control, in a similar way to that seen in patients with IgM (immunoglobulin M) paraproteinaemic peripheral demyelinating neuropathy (Bain et al., 1996) and that tremor is the result of this faulty adaptation.

Treatment of multiple sclerosis tremor

Medical treatment of multiple sclerosis tremor is generally unrewarding, although carbamazepine, clonazepam, glutethamide, hyoscine, isoniazid, ondansetron, primidone and tetrahydrocannabinol have been reported to have some beneficial effect (Findley and Gresty, 1981; Sabra et al., 1982; Clifford, 1983; Koller, 1984; Hallett et al., 1985; Morrow et al., 1985; Francis et al., 1986; Sechi et al., 1989; Aisen et al., 1991; Henkin and Herishanu, 1991; Rice et al., 1997). In our (uncontrolled) clinical experience, propranolol, at doses of 160–240 mg/day, can be useful but its efficacy has not been demonstrated in a clinical trial (Koller, 1984) and the benefit appears to be temporary.

Stereotactic thalamotomy has been performed for the alleviation of disabling multiple sclerosis tremor since 1960 (Cooper, 1960) and, more recently, thalamic stimulation has been deployed effectively, but the results are critically dependent on careful patient selection (Geny et al., 1996; Haddow et al., 1997; Hooper and Whittle, 1998; Nguyen et al., 1996, 1998; Alusi et al., 2000b). Neurosurgeons have now begun to target the nucleus ventralis oralis posterior rather than nucleus ventralis intermedius of the thalamus to alleviate multiple sclerosis tremor (Alusi et al., 1998), which is surprising because the former is the basal ganglia output nucleus and the latter the cerebellar input nucleus of the thalamus (Alusi et al., 1998, 1999; Stein and Aziz, 1999). One explanation for this paradox may be that cerebellar tremors, like those seen in multiple sclerosis, are actually generated by the basal ganglia (Deuschl et al., 1999). Thus when the cerebellum is malfunctioning, it may be better to eliminate the basal ganglia output to the motor cortex (Stein and Aziz, 1999). This view extends Irving Cooper’s speculation that ‘tremor results from pathological conflict of pallido- and dentato-fugal communication within the motor thalamus’ by supposing that these basal ganglia and cerebellar outflows are usually brought into balance by competition between them. Thus stereotactic surgery may alleviate multiple sclerosis tremor by restoring this balance after the disease has damaged the cerebellum or its connections. However, the optimum site within the thalamus for relieving
tremor in multiple sclerosis is still controversial and may vary according to tremor subtype.

**Conclusion**
This is the first detailed study of the prevalence and clinical characteristics of the tremors caused by multiple sclerosis in which the extent and magnitude of tremor and its related disability have been evaluated. We provide data demonstrating that multiple sclerosis causes various types of action tremor that vary from mild to one of the most severe forms of tremor encountered in clinical practice. Rest and Holmes’ (‘rubral’) tremors were not encountered. Furthermore, our data support the view that multiple sclerosis tremors are usually the result of cerebellar dysfunction.

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**References**


Speelman JD, Van Manen J. Stereotactic thalamotomy for the relief of intention tremor of multiple sclerosis. J Neurol Neurosurg Psychiatry 1984; 47: 596–.


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Appendix I
Ataxia scale

Dysarthria
0 No impairment
1 Mild dysarthria but comprehensible
2 Moderate dysarthria with interruption in flow
3 Severe dysarthria and incomprehensible, very difficult to understand
4 Completely unintelligible

Dysdiadochokinesis
0 No problem
1 Mild but detectable clumsiness and slowing of pronation–supination rate
2 Moderate clumsiness and slowing of pronation–supination rate
3 Severe clumsiness and slowing of pronation–supination rate
4 Unable to perform repetitive sequential movements

Dysmetria
0 No impairment
1 Mild dysmetria but reaches the target
2 Moderate dysmetria, reaches target after several attempts
3 Severe dysmetria, short of target after many attempts
4 Cannot use hands

Gait
0 Normal
1 Stance width increased, mildly unstable gait but can walk without support
2 Moderately unstable gait and needs support for walking (stick)
3 Unable to walk, needs the assistance of two persons
4 Wheelchair bound

Appendix II
Tremor activities of daily living questionnaire
(Please read carefully. For each item circle the number which best describes how easy or difficult it is for you to perform the activity)
1. Able to do the activity without difficulty.
2. Able to do the activity with little effort.
3. Able to do the activity with a lot of effort.
4. Cannot do the activity by yourself.

How well are you able to . . . . . . . . . . . . . . . . . . . ?
1. Cut food with a knife and fork
2. Use a spoon to drink soup
3. Hold a cup of tea
4. Pour milk from a cup or carton
5. Wash and dry dishes
6. Brush your teeth
7. Use a handkerchief to blow your nose
8. Have a bath
9. Use the lavatory
10. Wash your face and hands
11. Tie up your shoe laces
12. Do up buttons
13. Do up a zip
14. Write a letter
15. Put a letter in an envelope
16. Hold and read a newspaper
17. Dial a telephone
18. Make yourself understood on the phone
19. Watch the television
20. Pick up your change in a shop
21. Insert an electric plug into a socket
22. Unlock your front door with the key
23. Walk up and down the stairs
24. Get up out of an armchair
25. Carry a full shopping bag

Appendix III
Assessment of tremor-related handicap questionnaire
The patient is asked to answer the following questions by putting a circle around the appropriate letter.

Has your tremor stopped you:
1. Working?
2. Applying for a job or promotion?
3. Shopping by yourself?
4. Doing a favourite hobby or sport?
5. Travelling by public transport?
6. Driving a car?
7. Eating out?
8. Going on holiday?
9. Accepting a party invitation?

Key:
A no
B yes because you are embarrassed by the tremor
C yes because of the physical difficulties produced by the tremor
D yes because of BOTH the physical difficulties and the embarrassment produced by the tremor.