Tremor associated with benign IgM paraproteinaemic neuropathy


1 MRC Human Movement and Balance Unit, The Institute of Neurology, 2 The Institute of Neurology and the 3 MRC Cyclotron Unit, Hammersmith Hospital, London UK

Correspondence to: Dr P. G. Bain, Academic Unit of Neuroscience, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, UK

Summary
The clinical and neurophysiological features of six patients with action tremor of the upper limbs associated with IgM paraproteinaemic neuropathy are described. Symptomatic tremor was confined to the upper limbs and was broadly symmetrical. The frequency of associated rhythmic muscle activity ranged from 2.8 to 5.5 Hz in abductor pollicis brevis and from 3.7 to 5.5 Hz in the forearm flexor muscles. Magnetic brain stimulation, somatosensory evoked potentials (SEPs) and stretch reflex studies did not provide evidence for delayed conduction within central pathways. There was marked slowing of the maximum motor conduction velocities in peripheral nerves. Forearm stretch reflexes were present but their latencies were prolonged. Somatosensory evoked potentials were obtained in the majority of patients, but were delayed. Wrist tremor could be modulated by mechanical perturbations or median nerve electrical shocks. Simple voluntary wrist movements were of normal duration and peak velocity, but the kinematic profile was asymmetric. Each movement was associated with a triphasic EMG pattern in agonist-antagonist-agonist muscles but the durations of the bursts were prolonged and the onset of the second agonist was delayed. These results support the hypothesis that distorted, mistimed peripheral inputs reach a central processor (probably the cerebellum) which although intact is misled into producing tremor in certain parts of the body.

Keywords: tremor; paraprotein; neuropathy

Abbreviations: MEP = motor evoked potential; SEP = somatosensory evoked potential

Introduction
Upper limb tremor is present in up to 90% of patients with benign IgM demyelinating paraproteinaemic neuropathy (Smith et al., 1983, 1984; Dalakas et al., 1984; Yeung et al., 1991; Leger et al., 1992; Smith 1994, 1995). It is usually an action or postural tremor predominantly affecting distal rather than proximal muscles and is often irregular and variable in amplitude (Smith et al., 1983, 1984). The occurrence of an intention tremor in patients with IgM paraproteinaemic neuropathy is controversial (Dalakas et al., 1984; Smith et al., 1984; Yeung et al., 1991; Leger et al., 1992; Smith 1994, 1995). It was noted that the two patients with the lowest motor conduction velocities (3.5 and 7 ms⁻¹) did not have tremor but were severely ataxic and that those with the most severe tremors had velocities of between 12 and 22 ms⁻¹ (Smith et al., 1983). A correlation between the frequencies of tremor in the thumb and the ulnar nerve conduction velocities in the forearm of nine patients has been reported (Smith et al., 1984; Smith, 1989).

The consensus of opinion amongst previous investigators was that the appearance of tremor in IgM paraproteinaemic neuropathy bore no relationship to the severity of motor or sensory signs (Dalakas et al., 1984; Smith et al., 1984; Leger et al., 1992; Smith, 1994, 1995). In one report, however, it was noted that the two patients with the lowest motor conduction velocities (3.5 and 7 ms⁻¹) did not have tremor but were severely ataxic and that those with the most severe tremors had velocities of between 12 and 22 ms⁻¹ (Smith et al., 1983). A correlation between the frequencies of tremor in the thumb and the ulnar nerve conduction velocities in the forearms of nine patients has been reported (Smith et al., 1984; Smith, 1989).

Leger et al. (1992) described 12 cases of benign IgM
to varying extents. In two patients (Patients 3 and 4) there
disrupting handwriting and spirometry disability in every case. Tremor in the upper limbs was most
kinetic components were ubiquitous and caused significant
complaint. Tremor was not found at rest but postural and
years. However, in two patients, tremor was the initial
sensory disturbance which preceded tremor by as much as 8
were studied. The age at symptom onset ranged from 51 to
of the clinical features of this rare type of tremor and to
changes could be seen in control subjects and were a function
central conduction latencies (8.8-10.5 ms) and five had serum
neuropathy and found areas of white matter signal intensity
in six cases, but considered that only one patient had evidence
of CNS demyelination when strict diagnostic criteria were
applied. They concluded that in most cases the white matter
changes could be seen in control subjects and were a function
of the patients’ ages.

The aim of this study was to provide an accurate description of the clinical features of this rare type of tremor and to probe with neurophysiological techniques into the mechanism of tremor genesis.

Patients

The patients’ clinical details are summarized in Table 1. Five men and one woman aged 61–77 years (mean 66.5 years) were studied. The age at symptom onset ranged from 51 to 73 years (mean 58.9 years). Four patients presented with a sensory disturbance which preceded tremor by as much as 8 years. However, in two patients, tremor was the initial complaint. Tremor was not found at rest but postural and kinetic components were ubiquitous and caused significant disability in every case. Tremor in the upper limbs was most marked distally when posture was maintained and during movement (kinetic), disrupting handwriting and spirometry to varying extents. In two patients (Patients 3 and 4) there was notable tremor enhancement towards the end of a goal
directed movement (an intention component). Patient 1 had
initially noticed tremor only whilst writing, but this task
specificity later disappeared. In general the tremor resembled
essential tremor, except that it appeared more irregular. Case
was initially diagnosed as having Parkinson’s disease
because cogwheeling (but not rigidity) was palpable at the
wrists. No tremors of the tongue, jaw or head were seen.
None of the patients had family histories of neuropathy or
tremor with the exception of Patient 5, whose father developed
a mild postural upper limb tremor at about the age of 50
years and lived to 87 years. No tremor was alcohol responsive.
In every case signs of a sensorimotor neuropathy appeared
and all modalities of sensation were affected to some degree
in the feet, although only three patients (3, 5 and 6) made
joint position errors in the fingers. The tendon reflexes were
absent in four patients, but some tendon reflexes could be
obtained in the upper limbs of Patients 2 and 5. Distal muscle
wasting and weakness were ubiquitous, but proximal power
was normal in the arms of every patient and no fasciculations
were seen. All the patients had marked gait ataxia.

Routine investigations

Routine biochemistry, full blood counts, thyroid function
tests, blood glucose, creatine kinase, serum vitamin B\textsubscript{12} and
red cell folate were normal in each patient. Liver function
tests were also normal except for a slightly elevated alanine
aminotransferase at 54 IU l\textsuperscript{-1} (normal <35) in one case. The
erythrocyte sedimentation rate was normal in three patients
but slightly elevated to between 26 and 30 mm h\textsuperscript{-1} in the
first hour in three others. Serum IgA and IgG levels were
normal and Bence Jones protein absent from the urine of
every case. In four patients, CSF protein was elevated
(maximum 1.3 g l\textsuperscript{-1}) but did not contain oligoclonal bands.
CSF cell counts and glucose were normal. Patients 1 and 2
underwent sural nerve biopsies which demonstrated
demyelination and remyelination. In addition, there was
some axonal loss which was respectively mild and severe.
Radiographic skeletal surveys and bone marrow examinations
were normal.

<table>
<thead>
<tr>
<th>Age of onset (years)</th>
<th>Sex</th>
<th>IgM type (conc. g l\textsuperscript{-1})</th>
<th>Sensory modalities affected in the hands</th>
<th>Sensory modalities affected in the feet</th>
<th>Muscle power</th>
<th>Reflexes</th>
<th>Gait ataxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>69</td>
<td>M</td>
<td>(\kappa (2.0))</td>
<td>I</td>
<td>I</td>
<td>5</td>
<td>1</td>
<td>4-</td>
</tr>
<tr>
<td>63</td>
<td>M</td>
<td>(\lambda (9.0))</td>
<td>I</td>
<td>I</td>
<td>5</td>
<td>1</td>
<td>4-</td>
</tr>
<tr>
<td>64</td>
<td>M</td>
<td>(\kappa (2.3))</td>
<td>I</td>
<td>I</td>
<td>5</td>
<td>4-</td>
<td>4+</td>
</tr>
<tr>
<td>65</td>
<td>M</td>
<td>(\kappa (2.5))</td>
<td>I</td>
<td>I</td>
<td>5</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>61</td>
<td>M</td>
<td>(\lambda (7.4))</td>
<td>I</td>
<td>I</td>
<td>5</td>
<td>4-</td>
<td>4</td>
</tr>
<tr>
<td>77</td>
<td>F</td>
<td>(\kappa (4.3))</td>
<td>I</td>
<td>I</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

N = normal; I = impaired; + = present; - = absent. Sensory modalities: To = light touch; P = pin; V = vibration; JPS = joint position sense. Reflexes: L(T+) = left triceps present; b(B+T+) = biceps and triceps present bilaterally. Power: SAB = shoulder abduction; FDI = first dorsal interosseus; APB = abductor pollicis brevis; HFL = hip flexion; ADF = ankle dorsi-flexion.
Tremor in paraproteinaemic neuropathy

Table 2 Somatosensory evoked potentials

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Latencies</th>
<th>Conduction times</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Erb’s point (ms)</td>
<td>Cervical spine (ms)</td>
</tr>
<tr>
<td>1</td>
<td>22.9</td>
<td>26.2</td>
</tr>
<tr>
<td>2</td>
<td>38.0</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>37.0</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>31.2</td>
<td>–</td>
</tr>
</tbody>
</table>

-, Absent.

Table 3 Magnetic stimulation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Muscle</th>
<th>Latency</th>
<th>Central motor conduction time (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Scalp (ms)</td>
<td>C7/T1 (ms)</td>
</tr>
<tr>
<td>1</td>
<td>(R) ADM</td>
<td>40.0</td>
<td>34.5</td>
</tr>
<tr>
<td></td>
<td>(L) ADM</td>
<td>38.8</td>
<td>32.7</td>
</tr>
<tr>
<td>2</td>
<td>(R) ADM</td>
<td>34.9</td>
<td>29.0</td>
</tr>
<tr>
<td></td>
<td>(L) ADM</td>
<td>37.6</td>
<td>30.1</td>
</tr>
<tr>
<td>3</td>
<td>(R) FDI</td>
<td>58.9</td>
<td>46.4</td>
</tr>
<tr>
<td></td>
<td>(L) FDI</td>
<td>54.0</td>
<td>45.9</td>
</tr>
<tr>
<td>4</td>
<td>(R) FDI</td>
<td>51.7</td>
<td>47.6</td>
</tr>
<tr>
<td></td>
<td>(L) FDI</td>
<td>48.6</td>
<td>40.4</td>
</tr>
<tr>
<td>5</td>
<td>(R) BIC</td>
<td>26.7</td>
<td>20.6</td>
</tr>
<tr>
<td></td>
<td>(R) FDP</td>
<td>33.7</td>
<td>26.7</td>
</tr>
<tr>
<td>6</td>
<td>(R) ADM</td>
<td>70.8</td>
<td>66.6</td>
</tr>
<tr>
<td></td>
<td>(L) ADM</td>
<td>66.8</td>
<td>57.8</td>
</tr>
</tbody>
</table>

ADM = aductor digiti minimi; FDI = first dorsal interosseous; BIC = biceps; FDP = flexor digitorum profundus.

Treatment

Four of the patients received immunosuppressive therapy in the form of prednisolone (Patients 1, 2, 3 and 5), azathioprine (Patients 3 and 5), melphalan (Patients 1 and 3) and plasma exchange (Patients 2 and 3), but the short term effect of these treatments on the underlying neuropathies was unimpressive and the patients' tremors were not noticeably improved.

Propranolol, in doses varying from 80 to 120 mg per day, was tried in four patients (3-6) and produced some benefit, albeit modest, in two of them. Clonazepam, 0.75 mg day\(^{-1}\), produced a little improvement in the only patient (Patient 2) to receive the drug. Primidone (250 mg day\(^{-1}\)) was administered to two patients (Patients 4 and 6) with limited success.

Methods

Somatosensory evoked potentials

Somatosensory evoked potentials were recorded from electrodes placed over the contralateral scalp, 2 cm posterior to C3 and C4 (international 10/20 system) with reference either to Fz or to linked earlobes, after electrical stimulation of the median nerve at the wrist; stimulus intensity was set at just above motor threshold. Recordings were also made from electrodes placed over Erb’s point and over the neck at the level of C4. In each patient, two series of 400 responses were averaged, with filters 3 dB down at 0.16 Hz and 2.5 kHz. Latencies to the first negative deflection at Erb’s point, cervical cord and cortex were measured.

Magnetic stimulation

Magnetic stimulation of the motor cortex and then cervical spine was performed using a Novametrix Magstim 200 (The Magstim Company, Whitland, Dyfed, UK) with a round coil (external diameter 12 cm). The patients’ muscles were activated and the intensity of stimulation used varied from 70–90% of stimulator output.

Polymyography

Pairs of silver/silver chloride electrodes (diameter 8 mm) were placed 4 cm apart over the biceps, triceps, finger flexors and extensors, abductor pollicis brevis, abductor digitii minimi and first dorsal interosseous muscle bellies of each patient’s more symptomatic arm. The signals were amplified (Digitimer D150, Digitimer Ltd, Welwyn Garden City, Herts, UK), filtered (time constant 3 ms; low pass filter 3 kHz) and recorded on a Gould electronics ES2000 Chart recorder. Tremor frequency was estimated by measuring the average number of EMG bursts in three 10-s epochs of postural tremor recorded whilst the arms were held outstretched.

Stretch reflexes

Stretch reflexes were elicited in the forearm flexor muscles of each patient and eight control subjects (five men; mean age 56.2 years, range 43–67 years). The semipronated forearm rested on a platform above a torque motor (Printed Motors type G12M) with the fingers encased in a rigid splint, attached to the motor, and the wrist aligned with the motor shaft. The forearm was then clamped securely to allow movement only at the wrist joint.

The patients held their wrists in a constant position, with reference to an oscilloscope display, against a steady standing...
torque of 0.38 Nm. Stretches were given by increasing the torque to either 1.52 or 2.28 Nm for 250 ms and were triggered at 5 s intervals in batches of 32 trials. The order of the two magnitudes of torque was randomized. The patients were instructed not to react to the stretch in any way, but to maintain a constant level of muscle activation throughout the experiment.

Joint angular position [from an infinite resolution Bourns (5 cm diameter) servopotentiometer mounted on the motor shaft], joint velocity (by analogue differentiation of the position signal), and rectified EMG (from Ag/AgCl electrodes placed over the forearm flexor muscles) were recorded. The responses were amplified and filtered (time constant 3 ms, low pass filter 1 kHz). Signals were then passed through a CED 1401 laboratory interface (Cambridge Electronic Design, Cambridge, UK) and fed to a personal computer using data collection and averaging programs (sampling rate 2 kHz per channel).

The onset latencies and durations of the stretch reflexes were measured by inspection of the averaged rectified EMG signals on a computer screen. The size of each stretch reflex was calculated by integrating the rectified EMG over the duration of the response and expressed as a percentage over the rectified EMG activity measured during the 100 ms period preceding the torque pulse.

**Resetting studies**

Studies were performed to establish whether mechanical wrist perturbations or median nerve stimulation could influence tremor phase. For mechanical wrist perturbations, the apparatus and torque settings, including the standing torque, were identical to those used to measure the stretch reflexes. Torque pulses were given every 5–8 s at random times with respect to the ongoing tremor. Wrist position, angular velocity and forearm flexor and extensor EMGs were recorded from 2 s before to 2 s after the stretch. Forty trials were collected for each size of torque pulse and then averaged. The latency and duration of the response were measured. The duration of the first agonist burst and the latencies and durations of the antagonist and second agonist bursts were measured by inspection of the traces using a cursor. The size of each burst was calculated by integration of the rectified EMG.

**Results**

**Peripheral nerve conduction and EMG studies**

The median and ulnar nerve maximum motor conduction velocities for the above elbow to wrist segments ranged from 9 to 27 and 11 to 28 m s⁻², respectively. Focal conduction block was detected in these nerves in two cases (Patients 2 and 3). F-waves could not be obtained after stimulation of the median nerve at the wrist, except in Patients 3 and 4 in whom F-wave latencies were 63 and 79.6 ms, respectively. Sural sensory nerve action potentials were invariably absent and EMG evidence of denervation was detected in the intrinsic hand muscles of every patient.

**Somatosensory evoked potentials**

The results are shown in Table 2. In five of the six patients cortical SEPs were obtained, but were significantly delayed. In Patients 1 and 2 the central sensory conduction times from cervical cord to cortex were normal. In Patients 3, 4 and 6 the cervical cord potential was not recordable, although the conduction time from Erb’s point to cortex suggested that the central sensory conduction time was likely to be normal.

**Magnetic stimulation**

The results are shown in Table 3. The upper limit of the normal range for the central motor conduction time calculated as the difference in latencies following magnetic stimulation over the motor cortex and over the cervical cord is ~9 ms (Rothwell et al., 1991). Most of the results fall within this limit. However, Patient 3 had values that were asymmetric and marginally prolonged.

**Polymyography of tremor**

In every patient rhythmic EMG activity occurred when a posture was maintained and during movement, but disappeared when the arm was fully relaxed. Rhythmic
Tremor in paraproteinaemic neuropathy

Fig. 1 Polymyograms recorded while the arms were outstretched (A) and pronated (B) from two patients (Patients 6 and 2, respectively) with tremor and benign IgM paraproteinaemic neuropathy. The top four traces in each frame show EMG recordings from biceps (Bic), forearm extensor (FE), first dorsal interosseous (FDI) and abductor pollicis brevis (APB) muscles. The bottom trace in each frame is the signal from an accelerometer (Accel) attached to the dorsum of the hand between the distal ends of the second and third metacarpal bones. Tremor is associated with rhythmic EMG activity at a frequency of ~5 Hz in the biceps, whilst the frequency of EMG activity in intrinsic hand muscles is ~3 Hz.

activity was usually most apparent in hand and forearm muscles, although rhythmic activity was also frequently present in biceps and triceps muscles (Fig. 1). In four patients an alternating pattern of EMG activation was visible in the forearm flexor/extensor pairs, but in two cases there was no clear pattern. The frequency of rhythmic activity in intrinsic hand muscles (abductor pollicis brevis, 2.5-5.5 Hz) was generally lower than that in arm and forearm muscles (forearm flexors, 3.7-5.5 Hz). For much of the recording therefore, different frequencies of rhythmic activity were present within proximal and distal muscles of the same limb. Moreover, these frequencies were not simple harmonics of each other as can be seen in Fig. 1.

At times, the faster frequency of the upper arm and forearm muscles predominated, with the intrinsic hand muscles seemingly being driven at the same rate. However, when rhythmic activity in the upper arm muscles became less apparent the forearm muscles generally adopted the same frequency as that in the intrinsic hand muscles.

Fig. 2 Reflex responses to muscle stretch could be obtained in all patients with tremor and benign IgM paraproteinaemic neuropathy despite the general absence of tendon reflexes on clinical examination. Results are shown from all patients (1–6) as well as a normal subject for comparison. The upper trace of each pair of records shows average wrist position, while the lower trace is the average rectified EMG signal from the forearm flexor muscles. All patients had reflex responses to muscle stretch. However, the reflex responses occurred later than the normal stretch reflex (see bottom records). The duration of the reflex responses in Patients 1, 2 and 4 is comparable to normal, while the reflex responses in the other patients are more dispersed: dispersion was associated with on-going tremor preceding muscle stretch. Note that it is not possible to identify different components of the patients' reflex responses (in contrast to the identifiable early and late components of the normal stretch reflex).

**Stretch reflexes**

Reflex responses in forearm flexor muscles following stretch could be obtained in all cases, despite the general absence of tendon reflexes on clinical examination (Fig. 2). Reflex responses were more clearly seen in those patients who were able to hold their wrists still against the background torque. Reflex responses could also be seen in those with marked tremor, although their responses tended to be more dispersed. The onset latencies of the reflex responses, which ranged from 77.6 to 113.4 ms (Table 4), were all considerably longer than that of the normal short latency reflex (mean
Table 4  Stretch reflexes

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Latency (ms)</th>
<th>Duration (ms)</th>
<th>Size (% increase)</th>
<th>Estimate of cortical loop time (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>104.0</td>
<td>48.0</td>
<td>280</td>
<td>65.2</td>
</tr>
<tr>
<td>2</td>
<td>84.0</td>
<td>97.0</td>
<td>280</td>
<td>63.3</td>
</tr>
<tr>
<td>3</td>
<td>91.0</td>
<td>98.2</td>
<td>145</td>
<td>69.7</td>
</tr>
<tr>
<td>4</td>
<td>113.4</td>
<td>44.4</td>
<td>270</td>
<td>78.4</td>
</tr>
<tr>
<td>5</td>
<td>88.0</td>
<td>123.0</td>
<td>151</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>77.6</td>
<td>100.4</td>
<td>46</td>
<td>82.5</td>
</tr>
<tr>
<td>Average</td>
<td>93.0</td>
<td>85.2</td>
<td>195</td>
<td>71.8</td>
</tr>
<tr>
<td>Controls</td>
<td>28.9</td>
<td>72.6</td>
<td>840</td>
<td>36</td>
</tr>
</tbody>
</table>

Latency is the onset latency of the first response after the stretch; for controls this corresponds to the onset of the short latency reflex. For comparison, the mean onset latency of the long latency reflex in controls was 54.6 ms. Duration is the total duration of the reflex response and in controls is the time from the beginning of the short latency reflex to the end of the long latency reflex. Size is expressed as percentage increase in EMG over background levels. Estimated cortical loop time was obtained by combining the N1 of the SEP from wrist with latency of motor evoked potential in forearm muscles (NB The forearm motor evoked potential latencies were sometimes considerably shorter than the hand muscle latencies given in Table 3.) Lack of a clear SEP in Patient 5 made it impossible to estimate cortical loop time.

The onset latencies were also longer than that of the normal long latency reflex (mean 54.6 ms).

It was difficult to determine whether the reflex responses obtained in our patients corresponded to the short or long latency components of the normal stretch reflex (or a combination of both components). Latency criteria could not be used because of the marked slowing in conduction along peripheral pathways. Nor could the responses be separated into early and late components on the basis of configuration (see Fig. 2).

Since the long latency component of the stretch reflex is believed to use a motor cortical loop, we estimated the loop time from forearm to motor cortex and back in each patient using the N1 of the SEP (for the afferent pathway) and motor evoked potential to forearm flexor muscles (for the efferent pathway). By comparing the onset latencies of the reflex responses and the estimated cortical loop times (Table 4), it is apparent that the entire reflex response to stretch could have been subserved by a cortical loop in all patients other than Patient 6. Even in this latter patient, the majority of the reflex responses could have used a cortical loop.

The average onset latency of the reflex responses in patients was 93 ms compared with an average cortical loop time of 69.9 ms. The difference, of 23.1 ms, is similar to the difference of 19.6 ms between the latency of the normal long latency reflex (54.6 ms) and the cortical loop time in normal subjects (36 ms). This suggests that the reflex responses seen in patients and the long latency reflexes in normals may have a similar physiological basis.

The onset latencies of the reflex responses did not correlate with period of tremor.

The timing of rhythmic forearm flexor muscle activity could be clearly altered by brief mechanical perturbations of the wrist in three (Patients 1, 4 and 6) out of four patients (Fig. 3A). Individual trials were collected in Patients 4 and 6 and the resetting indices were 0.9 and 0.6, respectively. In Patient 3, who had a larger amplitude wrist tremor, the resetting index was only 0.4. The known relationship between the resetting index and tremor amplitude/perturbation size (Britton et al., 1992) may explain the rather limited effect of brief mechanical perturbations in the patient with a larger amplitude tremor: the resetting index increases with larger...
Table 5  Ballistic wrist movements

<table>
<thead>
<tr>
<th>Movement profile</th>
<th>Patients (n = 4)</th>
<th>Controls (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle (°)</td>
<td>n.s.</td>
<td>42.4±1.8</td>
</tr>
<tr>
<td>Velocity (deg s⁻¹)</td>
<td>n.s.</td>
<td>607±56</td>
</tr>
<tr>
<td>Duration (ms)</td>
<td>n.s.</td>
<td>142±12.8</td>
</tr>
<tr>
<td>Ratio T₁:T₂</td>
<td>P&lt;0.001</td>
<td>1.65±0.09</td>
</tr>
<tr>
<td>First agonist burst</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration (ms)</td>
<td>P&lt;0.05</td>
<td>99.7±8.7</td>
</tr>
<tr>
<td>Size (mVs)</td>
<td>n.s.</td>
<td>11.9±4.7</td>
</tr>
<tr>
<td>Antagonist burst</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency (ms)</td>
<td>n.s.</td>
<td>81.5±6.8</td>
</tr>
<tr>
<td>Duration (ms)</td>
<td>P&lt;0.005</td>
<td>119.5±8.5</td>
</tr>
<tr>
<td>Size (mVs)</td>
<td>n.s.</td>
<td>14.1±5.9</td>
</tr>
<tr>
<td>Second agonist burst</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency (ms)</td>
<td>P&lt;0.001</td>
<td>198±10.4</td>
</tr>
<tr>
<td>Duration (ms)</td>
<td>P&lt;0.005</td>
<td>115±6.6</td>
</tr>
<tr>
<td>Size of 2nd/1st agonist bursts</td>
<td>n.s.</td>
<td>1.1±0.06</td>
</tr>
</tbody>
</table>

The values given are mean±SEM. T₁:T₂ is the ratio of the acceleration time to the time from peak velocity to next zero velocity. Student's t test used for statistical comparison: significance taken at 5% level.

The performance by patients of self-paced, self-terminated rapid movements of the wrist over 30 degrees was in several respects remarkably normal (Table 5; Fig. 4). Movement duration, size of movement and peak velocity were all within the normal range, despite the distal weakness and sensory loss in the patients.

Other kinematic parameters, however, were not normal. The velocity profile of the wrist movement was asymmetric: the ratio of T₁:T₂ (see Methods for definition of T₁ and T₂) was significantly greater in patients (1.65) than in normal controls (1.21; P<0.001). In addition, each of the patients' movements was followed by oscillations of the wrist (tremor) about the end position (Fig. 4).

Each ballistic wrist movement was associated with a triphasic pattern of activity in agonist–antagonist–agonist muscles similar to that seen in normal subjects. The onset latency of the antagonist burst (measured from the onset of the first agonist burst) was normal but the onset latency of the second agonist was significantly prolonged (198 ms versus 122 ms in normals; P<0.001). In addition, the second agonist burst was of longer duration (P<0.005).

Discussion

Tremor is reported to occur in ~40–90% of patients with IgM paraproteinaemic neuropathy (Smith et al., 1983; Dalakas et al., 1984; Yeung et al., 1991; Leger et al., 1992; Smith, 1994). A critical question is whether the neuropathy in patients with IgM paraproteinaemia induces tremor, and if so, how?

Relationship between tremor and neuropathy in patients with IgM paraproteinaemia

In the patients presented in this report, tremor appeared at a mean of 3 years after the development of the neuropathy and in two patients tremor appeared a few months before a sensory disturbance. The close temporal association between
the onset of the neuropathy and the appearance of tremor is most easily explicable on the basis of a common link between the two conditions.

The alternative explanation, that patients with IgM paraproteinaemic neuropathy develop a coincidental tremulous condition, is unlikely on epidemiological, clinical and neurophysiological grounds. The percentage of patients with IgM paraproteinaemic neuropathy that have tremor, up to 90% in some reports (see Introduction), is between 10 and 200 times greater than the prevalence of essential tremor in the whole population, and ~10 times that in the population of people over 70 years old (Rautakorpi et al., 1984). Furthermore, the clinical features of the tremor associated with IgM paraproteinaemic neuropathy are not those of hereditary essential tremor. The male preponderance, the typically negative family history and the mean age at onset of 59 years in patients with tremor and IgM paraproteinaemic neuropathy contrast with the equal sex incidence, positive family history and a median age of onset in the second decade in patients with hereditary essential tremor, although in the latter condition the age of onset has a bimodal distribution with a second lesser peak in the fifth decade (Bain et al., 1994). Lastly, the polymyographic findings in patients with IgM paraproteinaemic neuropathy differ from those obtained in patients with essential or parkinsonian tremor. In two of our patients, the frequency of rhythmic (tremorgenic) activity in the intrinsic hand muscles was lower than that in more proximal muscle groups of the same arm (Fig. 1). Such a difference in the frequencies of rhythmic activity in proximal and distal muscles of the same arm is not seen in patients with essential or parkinsonian tremors.

What is the nature of the link between tremor and the demyelinating neuropathy associated with IgM paraproteinaemia? (i) The tremor could be directly caused by the neuropathy: in other words, the neuropathy might, by itself, be the critical factor that leads to instability (tremor) in the nervous system of patients with IgM paraproteinaemia. (ii) Alternatively, the tremor and the neuropathy may depend on a third factor: for instance a paraprotein (either the IgM paraprotein or one related to it) which might act upon the PNS to produce a demyelinating neuropathy and upon some other part of the nervous system (e.g. cerebellum) to produce tremor. (iii) The physiological abnormalities produced by the peripheral neuropathy might lead in some patients to an adjustment or resetting of a central parameter that incites tremor.

We found no evidence of lesions within the CNS in the patients described in this report. Magnetic brain stimulation revealed normal conduction along corticospinal pathways in all but one patient. In this latter patient, the borderline increase in the central motor conduction times observed could be accounted for by demyelination of the proximal portion of the nerve roots. The prolonged 'central conduction times' reported by Leger et al. (1992) can be explained on the same basis. Magnetic stimulation over the cervical region excites the motor roots ~4 cm distal to the anterior horn cell body (Boniface and Mills, 1992) and central motor conduction times (calculated as the difference in onset latencies following magnetic stimulation over the cortex and over the neck) therefore includes a period for conduction over the most proximal portions of the PNS (Rothwell et al., 1991). Conduction along central sensory pathways assessed by somatosensory evoked potentials was also essentially normal. Furthermore, our six patients showed no clinical evidence of brain or spinal cord disease. In the absence of identifiable lesions within the CNS, it seems reasonable to suggest that the neuropathy is, by itself, critical to the development of tremor in patients with IgM paraproteinaemia.

If the neuropathy itself is indeed critical to the development of tremor in patients with IgM paraproteinaemia, one might ask whether it is the absence or distortion of sensory input that causes the nervous system to become unstable. We suggest here that the latter is the more important mechanism. The clinical and neurophysiological evidence indicates that sensory inputs potentially reach all levels of the CNS, despite the markedly reduced maximum motor conduction velocities in the peripheral nerves. Clinical evidence of proprioceptive loss is not required for the development of tremor as three of our patients with upper limb tremor had normal joint position sense in the distal inter-phalangeal joints of the fingers. In the majority of patients a cortical SEP could be obtained following stimulation of the median nerve at the wrist, albeit greatly delayed compared with normal. The fact that any cortical SEPs could be recorded in our patients is itself remarkable given the delay and dispersion that must occur in the afferent volley as it traverses the PNS. Indeed, it suggests the existence of some mechanism that 'tightens up' the dispersed afferent volley and so allows the cortical responses to be recorded.

Stretch reflexes could be obtained in all patients, although the response latencies were again very prolonged compared with normal. In contrast to the prolonged latencies, the response durations were nearly normal, especially in those patients who did not have large amplitude on-going tremor (e.g. Patients 1, 4 and 5). The near-normal duration of the reflex responses is again remarkable, given the delay and dispersion in nerve impulse conduction that must occur in the periphery. We do not know whether the reflex responses obtained in our patients were equivalent to the short or long latency components (or both) of the normal stretch reflex. On the basis of latency, it is possible that our patients' reflex responses represented only the long latency component of the normal stretch reflex, which is believed to employ a motor cortical loop. Certainly, the general absence of (spinal) tendon reflexes on clinical examination in our patients might lead one to suspect that the short latency component of the stretch forearm flexor stretch reflex would be small or absent. If this reasoning is correct, it implies either that the long latency component of the stretch reflex is not as dependent as the short latency component on a highly synchronized afferent volley from the muscle spindles or that some...
mechanism at a supra-segmental level tightens up the sensory volley.

The results of this study have shown that in our patients, the sensory cortex and presumably other parts of the brain, far from being deprived of sensory input, receive a remarkable amount of sensory information, despite the severe neuropathy. The findings are consistent with the idea that instability in the nervous system (tremor) in patients with IgM paraproteinaemic neuropathy is due to distortion rather than absence of sensory input.

A corollary would be that tremor should not occur in the absence of sensory input. This may explain the absence of symptomatic leg tremor in our patients who all had impaired joint position sense in the toes (Table 1), alternatively information from the legs may be processed centrally in a different way to that received from the arms.

In our patients with IgM paraproteinaemic neuropathy, the most obvious distortion of sensory input was the delay in sensory information from the periphery reaching the CNS because of the reduction in maximal conduction velocities in peripheral nerves. The results of a previous study showed a correlation between tremor frequency in the thumb and ulnar nerve maximum motor conduction velocities (Smith et al., 1984). We were unable to confirm this correlation, but the number of patients in our study may have been too small.

**Mechanisms responsible for tremor**

Some insight into how distorted sensory inputs might lead to tremor can be gained by analysing the performance of ballistic wrist movements by patients with IgM paraproteinaemic neuropathies. The patients' movements were in many respects normal, despite their neuropathy and distal (but not proximal) weakness and wasting. Movement sizes, peak velocities and durations were the same as those of control subjects.

However, the patients' movements were not entirely normal since they had markedly asymmetric velocity profiles and the ratio of the acceleration period ($T_1$) to the deceleration period (from the point of maximum velocity to next zero velocity ($T_2$)) was significantly greater than that for controls. Patients' movements had shorter $T_2$ deceleration phases relative to their acceleration phases ($T_1$). In addition, their movements were followed by underdamped oscillations of the wrist about the target position. Each patient's ballistic wrist movements were accompanied by a triphasic pattern of activity in agonist–antagonist–agonist muscles similar to normal (Wachholder and Altenburger, 1926), but the durations of the bursts were prolonged.

Furthermore, the timing of the second agonist burst (relative to the onset of the first agonist) was significantly delayed. The delayed second agonist burst allowed the unopposed action of the antagonist muscle to decelerate the wrist back past the target position.

These kinematic and EMG abnormalities are similar to those that have previously been reported in hereditary essential tremor (Britton et al., 1994) and cerebellar disease (Hallett et al., 1991; Hore et al., 1991). Both essential tremor and cerebellar disease are associated with asymmetric velocity profiles and underdamped oscillations of the wrist at the end of each movement, although in the latter condition movements are also performed more slowly than normal. The timing of the second agonist burst is delayed in essential tremor, while the durations of the agonist and antagonist bursts are prolonged in cerebellar disease.

It has previously been argued that the mechanisms responsible for the timing of the second agonist burst in a ballistic movement play a critical role in the generation of tremor in patients with hereditary essential tremor, not least because the latency of the second agonist burst was found to correlate significantly with the period of tremor (Britton et al., 1994). That the second agonist burst also occurs late in patients who have tremor associated with an IgM paraproteinaemic neuropathy further supports a link between tremor and the mechanisms responsible for the timing of the second agonist burst. Both peripheral and central mechanisms seem to be responsible for the timing of the second agonist burst in a normal ballistic movement. Peripheral inputs can modulate the second agonist burst (Hallett et al., 1991), but they are not essential to its generation, since the second agonist burst may be seen in completely deafferented patients (Rothwell et al., 1982); whilst the cerebellum is thought to be responsible for producing bursts of muscle activity that provide dynamic stability to a limb (Vilis and Hore, 1980).

We suggest that patients with IgM paraproteinaemic neuropathy have a specific cerebellar functional disturbance caused by the delayed and distorted afferent input. As a result of the delayed and distorted input from the periphery, the cerebellum, although intact, resets to produce a mistimed, delayed second agonist burst that allows the antagonist muscle to act unopposed and results in the abnormal limb kinematics. The resulting error in limb position and velocity are then fed back (via demyelinated peripheral nerves) to the cerebellum which perpetuates the error. In contrast, the abnormal timing of muscle activity in hereditary essential tremor is thought to arise as a direct consequence of an abnormality in the CNS. Nevertheless, the tremors resulting from both neuropathic and hereditary essential tremor have two important similarities. (i) PET activation studies have shown that in both conditions the cerebellar hemispheres are hyperactive bilaterally, both during tremor and at rest (Colebatch et al., 1990; Brooks et al., 1992; Jenkins et al., 1993). The bilateral cerebellar activation is thought to be abnormal because passive wrist oscillation in the patient groups (neuropathic and essential tremor) produced only ipsilateral cerebellar activity (Brooks et al., 1992; Jenkins et al., 1993; D. J. Brooks and I. H. Jenkins, personal communication). (ii) Both tremors have a common physiological abnormality, namely a delayed second agonist burst.

The prolonged latency of the second agonist burst (which was measured from the first agonist burst) cannot be
accounted for by prolonged efferent conduction time in either the central or peripheral nerves of our patients with neuropathic tremor, because any delay would affect the latency of the first agonist burst equally. However, efferent delay may account for some of the phenomenological differences between essential and neuropathic tremor.

The proposed model neatly explains two additional findings of the present study. (i) The modulation of tremor by mechanical perturbations and median nerve shocks in patients with IgM paraproteinaemic neuropathy is consistent with peripheral inputs having an important role in the generation and maintenance of tremor. Peripheral inputs cannot only reach the oscillatory mechanisms responsible for tremor (again demonstrating that sensory input is not absent despite the severe neuropathy) but can also influence those oscillatory mechanisms. (ii) The slower frequency of tremor in distal limb muscles could be explained by the increasing absolute delay incurred by afferent inputs from more distal parts of the limb. Furthermore, the model would predict the previously reported link between tremor frequency and peripheral nerve conduction velocity in these patients (Smith et al., 1984).

A final problem remains as to why only a proportion of patients with IgM paraproteinaemic neuropathy develop tremor. Delay in the afferent conduction pathway cannot be the sole reason, since some patients with severe slowing never develop tremor. We can only speculate on the reasons for this. One possibility is that the precise nature of the conduction deficit is important; perhaps gross dispersion of the sensory input is less effective in producing tremor than pure slowing. Alternatively, perhaps the capacity of the cerebellum (or other CNS structures) to reset a critical control parameter in the presence of delayed afferent input varies between patients.

In conclusion, the data from SEPs, resetting studies and forearm stretch reflexes support the hypothesis that distorted, mistimed, peripheral inputs reach a central processor which, although intact, is misled or reset into producing a delayed second agonist burst and thus tremor in certain parts of the body. Unfortunately, treatment of the underlying neuropathy with immunosuppressive drugs, or the tremor with alcohol, clonazepam, primidone or beta-blockers has yielded rather disappointing results, but, as yet, there have been no controlled therapeutic trials for this rare condition.

Acknowledgements
We wish to thank Dr R. Ross Russell and Professor R. A. C. Hughes for referring patients under their care and Mr R. Bedlington and Mr P. Asselman for their excellent technical support. P.G.B. was supported by a grant from the Wellcome Trust.

References


Rautakorpi I, Marttila RJ, Rinne UK. Epidemiology of essential


