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 EDITORIAL
 

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## Tremor in multiple sclerosis

Tremor, which is an involuntary rhythmic oscillatory movement of a body part, is estimated to occur in 75% of patients diagnosed as having multiple sclerosis.<sup>1,2</sup> It can be severely disabling and is extremely difficult to treat.<sup>3–23</sup> The tremor of multiple sclerosis is frequently embedded in a complex movement disorder, which often includes dysmetria and other ataxic features.<sup>8</sup> There is considerable controversy surrounding the precise definition and identification of the different components of this movement (tremor, dysmetria, and other ataxic features).<sup>1,24–26</sup> Resolution of this controversy is critical to treatment because these separate components respond differently to various interventions.<sup>7,8,17,19,21</sup>

### Incidence and prevalence

The incidence and prevalence of tremor in multiple sclerosis is difficult to estimate accurately, although tremor of moderate and severe magnitudes were found in 32% and 6% respectively of patients in one study.<sup>22</sup> In part this is because of the problem of distinguishing intention tremor from serial dysmetria, which is the result of the voluntary sequential correction of movement errors, and some types of postural tremor from other postural instabilities.<sup>27</sup> In addition, the natural history of multiple sclerosis and in particular the transience of the neurological signs during the relapsing and remitting phase make prevalence studies difficult. This problem is compounded by the structure of the Kurtzke functional systems deployed for the assessment of patients with multiple sclerosis, because subscale part B (cerebellar function) does not isolate tremor.<sup>28</sup> In a 3 year follow up study of multiple sclerosis, cerebellar deficits of functional importance were found to occur in 33% of 259 patients and to be predictive of a worse prognosis.<sup>29,30</sup> A similar proportion was found to have ataxic symptoms in an extensive epidemiological survey undertaken in the United Kingdom and involving over 300 patients with multiple sclerosis.<sup>26</sup> There are no published quantitative studies of the contribution of tremor to the disabilities and handicaps caused by the disease.

### Types of tremor

Tremor of the head, neck, vocal cords, trunk and limbs have all been described in association with multiple sclerosis, but there have been no reports of tremor of the palate, tongue or jaw.<sup>7,8,10–15,16,19,20,31–35</sup>

In the past there have been some confusion and disagreement about the nomenclature for the various types of tremor found in multiple sclerosis, although a working consensus has recently been reached on the classification and definition of tremor in general, which will be adopted here.<sup>1,27,36</sup> In multiple sclerosis true rest tremor (tremor

which is present in a body part that is not voluntarily activated and that is completely supported against gravity) is not seen; a point appreciated by Charcot in 1875.<sup>1,27,37</sup> However, apparent “rest” tremor—for example, shoulder tremor when a patient is sitting upright—has been inaccurately termed rest tremor in some previous surgical papers.<sup>22,38</sup> Furthermore, not one example of rest or “rubral” tremor was encountered in a recent study of 100 patients with clinically definite multiple sclerosis.<sup>39</sup>

Various forms of action tremor have been found in multiple sclerosis.

### POSTURAL TREMOR

Postural tremor can affect the head, neck, trunk, and limbs.<sup>1</sup> Head tremor (titubation) can be in any or all directions. It may persist on lying because of continuing tonic contractions of neck and trunk muscles.<sup>36</sup> A large amplitude “wing beating” postural tremor that increases progressively on maintained posture is well described.<sup>7–9,27</sup> In the legs postural tremors are encountered but primary orthostatic (14–18 Hz) tremor is not, although spastic ataxia can be mistaken for orthostatic tremor.<sup>3,40</sup> Leg clonus can also be misinterpreted as tremor but the first is increased by applying passive stretch to the muscles whereas the second is not.<sup>1</sup>

### KINETIC TREMOR

At least two forms of kinetic tremor occur in multiple sclerosis. Firstly, intention tremor is seen when tremor amplitude increases during visually guided movements towards a target. This tremor has a tendency to worsen with increasing precision requirements and is influenced by non-rhythmic disorders of movement and hypotonia.<sup>36,27</sup> Secondly, it is common to find an action tremor that is seen as a rhythmic oscillation around the movement trajectory. This form of action tremor has two components—a terminal kinetic tremor and a postural tremor of the shoulder girdle—which variably interact and has been termed “hyperkinetic” tremor.<sup>3,41</sup>

Simple kinetic tremor that occurs during voluntary non-target directed actions—for example, opening and closing a fist—is characteristic of essential tremor and has also been described in parkinsonism but not multiple sclerosis.<sup>1,36</sup> Similarly, task specific tremors (for example, primary writing tremor) have not been documented in multiple sclerosis.

### Features associated with tremor in multiple sclerosis

The tremor of multiple sclerosis should be considered in the context of ataxia, which literally means disorder or

confusion.<sup>42</sup> However, in practice the term ataxia is used loosely to describe irregularities in voluntary movement.<sup>43</sup> In 1917 Holmes drew attention to the fact that in cerebellar disorders there are, in addition to tremor, decomposition of voluntary movement, asynergia (failure of smooth fusion of the movement's component parts), rebound phenomena, and dysdiadochokinesia. He also noted that at times the active muscles involved in a movement are initially harmonious but after a time develop phase errors that cause further irregularity of movement.<sup>43</sup>

Goal directed movements illustrate the interplay between ataxia and tremor. There are several problems that can induce an oscillation in the terminal component of such movements—namely, true intention tremor, serial dysmetria, low frequency sway movements resulting from proximal postural instability, and postural tremor that has been inhibited by motion.<sup>27 43 44</sup>

### Pathophysiology

In multiple sclerosis the mechanisms of production of tremor are poorly understood because of the presence of multiple CNS lesions, which prevent precise neuroanatomical correlation of structure to function. Lesions from various causes involving the cerebellum, its connections, and the midbrain have all been documented to cause action tremors.<sup>31 37 44 45</sup> There are no postmortem studies in multiple sclerosis linking tremor to a discrete lesion. However, one patient who presented with an isolated severe action tremor affecting the arms was found at postmortem examination to have plaques in the periventricular regions, pons, optic chiasm, superior and middle cerebellar peduncles, cerebellar white matter, and around the dentate nuclei but notably not the red nucleus.<sup>46</sup> In addition, a single case study using MRI showed that a plaque in the superior cerebellar peduncle resulted in severe postural tremor with alternating activation of the agonist-antagonist muscles.<sup>31</sup> This causal relation is supported by primate experiments in which tremor was produced by section of the superior cerebellar peduncle.<sup>47</sup> There are no data available from PET studies of tremulous patients with multiple sclerosis.

Struppler *et al* considered that cerebellar lesions caused postural and intention tremor but not simple kinetic tremor; attributing intention tremor, hypotonia, and dysnergia to neocerebellar disturbances and postural tremor to both archicerebellar and neocerebellar pathology.<sup>36</sup> Lesions of the archicerebellum result in a 3–5 Hz postural tremor of the trunk and limb girdle, whereas lesions of the neocerebellum produce an intention tremor of the limb, which varies in frequency (according to the intended accuracy), in addition to the postural component.<sup>36</sup>

### EMG studies of multiple sclerosis tremor

It is established that action tremors are caused by segregation of EMG activity, or more accurately the insertion of silent epochs into what would have been continuous activity in an active muscle.<sup>48</sup> This segregation of EMG activity in tremulous patients with multiple sclerosis was shown by Altenburger in 1930, and has subsequently been corroborated.<sup>44</sup> In a study of 11 patients with multiple sclerosis with alternating EMG pattern in the agonist-antagonist pairs, the oscillatory movements were subdivided into two groups physiologically: The first had low amplitude tremor, with frequencies between 5–8 Hz with 75–100 ms burst duration, that was only apparent on goal directed movement. The second had disabling wide amplitude tremor, with lower frequencies of 2.5–4 Hz and longer (125–250 ms) burst duration on postural activity which persisted or worsened on intention. Both types of tremor were accompanied by dysmetria.<sup>27</sup>

### CAN TREMOR BE DISTINGUISHED FROM OTHER COMPONENTS OF ATAXIA?

A crucial question is whether or not tremor can be distinguished from the other components of ataxia by physiological means. This problem is complicated by the finding that the manifestations of ataxia differ according to the complexity of movement. Nevertheless, analysis of simple voluntary movements may provide a way of distinguishing these movement disorders.

When rapid simple voluntary movements are performed by healthy subjects there is a symmetric kinematic profile with acceleration and deceleration phases of equal duration. This is accompanied by a triphasic EMG pattern consisting of an agonist burst (initiating motion), an antagonist burst that checks it, and a second agonist burst that makes a terminal adjustment.<sup>49</sup>

In patients with cerebellar deficits there is start delay, a slow and prolonged acceleration phase, and lack of uniform deceleration, causing an asymmetric kinematic profile.<sup>50</sup> Analysis by EMG of fast stereotyped elbow flexion movements in dysmetric patients showed that the duration of the initial biceps or triceps bursts were prolonged, although this was less evident when the same patients performed smooth movements slowly.<sup>51</sup> In some hypermetric patients a delayed first antagonist EMG burst has been reported during simple ballistic movements. However, in fact the antagonist burst may have two components (an initial task invariable and late task dependent component, which varies with movement distance and load), so that an apparent delay may be caused by an absent first component. Furthermore, delay of the second component may contribute to hypermetria.<sup>52</sup> In a compound movement there is the additional problem of positional error when the movement reverses direction, as manifest by dysdiadochokinesia, which is reflected physiologically by the abnormal, late, timing of the antagonist deactivation before initiation of agonist activity.<sup>51</sup>

Studies of voluntary ballistic movements in essential tremor (a pure action tremor) have shown that the second antagonist burst is delayed, a finding that may be relevant to tremor production.<sup>53</sup> Thus it may be possible to distinguish tremor from dysmetria by looking at the timing and size of the EMG bursts accompanying rapid simple movements.

It has also been suggested that in ataxia there is additional adventitious motion resulting from purposeless contractions of other muscle groups.<sup>45</sup>

### Assessment of multiple sclerosis tremor

Conventional tremor rating scales are often chosen for the assessment of tremor severity in multiple sclerosis because the Kurtzke functional systems scale lacks a tremor specific subscale.<sup>28</sup> However, these scales were designed primarily for evaluating rest and postural tremors, whereas the accompanying ataxia makes clinical rating of tremors in multiple sclerosis more difficult.<sup>3</sup> The ferocity of some tremors limits the applicability of quantifying tremor in spirals, maze drawings, handwriting specimens, and measuring the volume of water spilt from a cup to patients with mild action tremors. The same applies to measures of upper limb function such as the nine hole pegboard test and finger tapping. Assessments with EMG, accelerometry, computerised tracking tests, and kinematic studies all have associated difficulties: EMG can only provide a surrogate marker of limb movement; whereas accelerometric signals of intention tremor are inaccurate because the finger-nose-finger test provides a non-stationary signal consisting of at most 10 tremor cycles and both the tremor and intended limb movement frequencies overlap, reducing the signal to noise ratio. Tracking tests can be useful for

quantifying tremor involving a single joint but are unsuitable for the assessment of tremors that appear in free limb movements which involve multiple joints.<sup>54–55</sup> Kinematic studies can circumvent this difficulty but analysis of the derived signal is complex and limits their widespread deployment.<sup>56–57</sup> It is also important to make an overall assessment of patient disability because there can be major interactions between tremor and the other neurological deficits found in multiple sclerosis, and the differential contribution of tremor to the overall disability may influence treatment.

### Treatment

patients with multiple sclerosis adapt to tremor by reaching with both hands, bracing an arm during manual tasks, or restraining it to prevent self injury. As restoration of normal posture and movement is rarely attained, the use of compensatory techniques are encouraged by therapists, although good results are scarce.<sup>44–58</sup> These methods include giving choreographic advice, altering the patient's environment—for example, using a barber's chair for postural head tremor—and weighting a tremulous limb with bracelets and heavy utensils.<sup>59</sup> The second is of limited value to patients with either proximal muscle weakness or savage tremors because relatively high loads (750–1000 g) are required for tremor control, and this can exacerbate fatigue and weakness.<sup>58</sup> Furthermore, Manto *et al* elegantly demonstrated that limb weighting increased hypermetria in patients with cerebellar lesions, but not normal subjects, because in the former the size of the antagonist EMG burst (which checks movement) did not increase.<sup>60</sup> Dynamic systems with multidegree of freedom orthoses and robotic arms based on virtual reality have been developed to assist tremulous patients with multiple sclerosis but are not widely deployed.<sup>61</sup>

Medical treatments for multiple sclerosis tremors, or ataxia, or both are empirical and generally unrewarding, although the following medications have been reported to have some beneficial effect: hyoscine, isoniazid, glutethimide, clonazepam, carbamazepine, primidone, tetrahydrocannabinol, and ondansetron.<sup>3–6–15</sup> However, for this group of patients their benefit to side effect ratio is generally low and most of these studies did not employ double blind controlled protocols. Ethyl alcohol and propranolol, which reduce the magnitude of some other action tremors, for example essential tremor, have not been shown to be effective.<sup>3–6</sup> Extracranial application of brief AC pulsed electromagnetic fields in the pico Tesla range was reported to decrease the amplitude of tremor in three patients with chronic progressive multiple sclerosis, although this promising finding needs further exploration.<sup>2</sup>

In selected patients with multiple sclerosis thalamotomy has been reported to alleviate contralateral limb tremor initially in between 65% and 96% of cases, although in about 20% tremor returns within 12 months and functional improvement of the relevant arm is estimated to occur in only 25% to 70% of patients.<sup>19–20–22–23–62–63</sup> Nevertheless, some patients have regained their capacity to eat and drink independently.<sup>63</sup> Cooper also noted that head tremor was improved by thalamotomy in five out of six patients.<sup>16</sup> Despite the relief of tremor afforded, there are several reservations about this procedure for patients with multiple sclerosis. These include moderation of benefit by the remaining ataxia, immediate postoperative side effects, and a possible negative influence on the rate of progression of the underlying disease.<sup>19</sup> In no prospective study has the influence of thalamotomy on overall disability, handicap, and quality of life of tremulous patients with multiple sclerosis been measured; nor have side effects been quantified. The incidence of reported side effects varies from 0% to

45% of cases in different studies.<sup>16–23–62–63</sup> This probably reflects variation in case selection and improved surgical techniques, which now utilise better imaging and intraoperative electrophysiology. Experience has shown that optimal results are obtained in patients with (a) relatively stable disease, (b) good mobility, (c) minimal overall disability status, and (d) minimal ataxia in the tremulous limb, although the last is difficult to establish preoperatively when it may be submerged by severe tremor.<sup>19–20–22–23</sup>

A recent thalamotomy series involving nine patients and utilising CT/MRI guidance, showed no significant long term complications.<sup>62</sup> It is notable that in this cohort of patients with multiple sclerosis stimulation at the expected coordinate location for the nucleus ventralis lateralis of the thalamus did not elicit the expected responses—a finding that may be related to the focal and diffuse cerebral atrophy caused by multiple sclerosis.<sup>62</sup> Relevantly, other groups have reported that lesions centred on the classic target (lower part of the nucleus ventralis intermedialis) need to be large to alleviate (a) kinetic type tremors, (b) low frequency/high amplitude tremors, and (c) tremor involving proximal or widely distributed muscle groups.<sup>64</sup> As the incapacitating tremors seen in multiple sclerosis usually have these three characteristics a more optimal surgical target may be the nucleus ventralis oralis posterior.<sup>65</sup> The most often reported complications of thalamotomy are worsening of gait, hemiparesis, and dysarthria. In addition, epilepsy, sensory disturbances, dysphagia, and transient bladder disturbance, depression, confusion, lethargy, and somnolence have also been, albeit rarely, described.<sup>16–23–63</sup> Recently three papers, on a total of 23 patients, have shown that thalamic stimulation can also alleviate multiple sclerosis tremor in up to 69% of patients but in one series tremor recurred in 20%.<sup>35–66–67</sup> The relative merits of thalamic stimulation versus lesion placement remain controversial, as there have been no comparative trials of the two techniques. Nevertheless, if a second procedure was contemplated deep brain stimulation may be preferable because some side effects are potentially reversible.<sup>67</sup>

### Conclusion

The action tremors seen in patients with multiple sclerosis can be among the most severely disabling encountered in clinical practice. Alas, the mechanisms producing these tremors are poorly understood. In part this is because they are often embedded within complex movement disorders, which makes them difficult to study. Disabling tremors in multiple sclerosis rarely respond sufficiently to medical treatment. Thus stereotaxic surgery remains the treatment of choice. However, this form of surgery has immediate and potential long term risks. The question of whether thalamic stimulation is preferable to lesioning awaits a definitive answer. In addition the optimal intrathalamic target site requires clarification. Consequently there is a strong case for entering patients with multiple sclerosis who are disabled by their tremor into scrupulous clinical trials, with multidimensional outcome measures. Although inevitably the degree of success will depend on case selection, surgical technique and postoperative physiotherapy, aimed at optimising functional gain.

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