Abstract

Essential tremor is the most common of the movement disorders, being 20 times more common than Parkinson’s Disease. It is characterised by postural and kinetic tremor which maximally affects the hands. It can be assessed by physiological techniques, subjective clinical methods, objective clinical methods and handicap/disability scales. Accelerometry, spirography and handwriting assessment, volumetry and handicap/disability questionnaires are commonly used methods. Primidone and propranolol are the first-line drugs. Several second-line drugs have been identified. Surgical techniques include lesioning or stimulation of the ventral lateral thalamus. Alcohol and botulinum toxin A are found to reduce tremor amplitude as well.

INTRODUCTION

Tremor is defined as an involuntary, rhythmic oscillation of a functional body part, produced by alternating or synchronous contractions of reciprocally innervated agonistic and antagonistic muscles. Tremors can be classified as rest or action, and essential tremor is the most important type of action tremor.

Essential tremor (ET) is the most common movement disorder, being twenty times more prevalent than Parkinson’s disease. The overall prevalence is 0.4-6% and increases with age; 1-22% of elderly population suffers from ET. It is found in all ethnic groups.

CLINICAL FEATURES

Inspite of high prevalence of ET, accurate diagnosis has been hampered by the lack of a consensus diagnostic criteria and specific disease marker. It is termed ‘essential’ as there is no underlying cause. Though it is a monosymptomatic illness and has been considered as ‘benign’, it may produce significant functional and social disabilities. Onset is bimodally distributed at the 2nd and 6th decade. Its amplitude increases with age, but frequency may decrease with age. There is no gender predilection. It has an insidious onset with variable progression. Initially there may be a ‘shaky’ feeling inside for several months followed by a stage of intermittently occurring tremor during periods of excitement and fatigue, and ultimately tremor becomes permanent. Exacerbating factors include hunger, fatigue and extremes of temperature; it disappears during sleep. It has both postural and kinetic components; however, in severe essential tremor, rest tremor may also be seen. Movement is distal and flexion-extension. Hands are most commonly affected followed by legs, head, voice, tongue, face and jaw. In the head, ‘no-no’ (tremblement negatif) movement is more commonly seen than ‘yes-yes’ (tremblement affirmatif) movement. Mild asymmetry is the rule. ET is a heterogeneous disease and may be (i) early or late onset, (ii) sporadic or familial and (iii) with or without head tremor. The early onset (beginning < 30 years) form is associated with more hand involvement, associated dystonias, better response to alcohol and more rapid progression. If there is concomitant head tremor, progression of hand tremor is usually slower.

A practical approach to the diagnosis has been recently put forward based on various criteria in the past. A genetic basis has always been suspected as 17.4-100% patients have positive family history. In the familial types, autosomal dominant inheritance is seen and complete penetrance occurs by age sixty five. Recently it has been linked to chromosome 3q13 (the FET1 or ETM1 gene) and chromosome 2p22-25 (the EMT2 gene). Anticipation has been demonstrated in kindreds with the latter gene and analysis indicates that the gene may be a triplicate repeat.

TREMOR ASSESSMENT

Assessment of tremor can be broadly divided into four categories: 1. Physiological techniques, 2. Subjective clinical methods, 3. Objective functional performance tests and 4. Disability, handicap and quality of life assessment scales (Table 1).

Accelerometry

A linear tri-axial accelerometer measures frequency and
During each turn. Handwriting can also be assessed and has depending on the degree of perpendicular displacement from spiral grows. Severity of the tremor is rated from 0 to 10, tendency with the tremor becoming more prominent as the forearm supported on the table. Spirals show a centrifugal out with at least five turns. Pen is held in the normal way and has been rated from 0 to 10. Though tremor is more obvious in spirals than in handwriting specimens, the latter is included as it is readily available in the patient’s medical records, old letters and other personal writings. Assessments of spirometry and handwriting impairment are highly correlated with one another and with disability as well as with right upper limb postural tremor ratings. Spirometry can provide a quick and practical way of reassessing patients by postal survey, which more likely reflects the day to day state of tremor.

### Volumetry

A 100 mL polystyrene beaker of water is held between the thumb and fingers. It is held with arm resting on the table to assess rest tremor and then held near the mouth with shoulder abducted and elbow flexed to 90 degrees for one minute to assess postural tremor. Volume of water remaining in the cup after 60 seconds is denoted as $X_{60}$. Volume of water spilt is indicated by $100-X_{60}$ and correlates well with tremor severity. It also indicates the patient’s capacity to suppress tremor amplitude. Time to first spill water indicates tremor suppressibility. Volumetry is an objective, simple and inexpensive technique to assess tremor and also, it reflects real life situations. However it is insensitive for fine tremors and has a ceiling effect.

### Others

The nine-hole pegboard test assesses upper limb tremor. Gibson maze test is a quantifiable spiral whereby assessment is made based on the number of times a patient’s drawn line crosses the boundaries of a printed spiral.

Activities of daily living and handicaps are assessed by questionnaires and for each situation, a score of 0 to 3 is given depending upon the degree of impairment. The scores are summed and converted into a percentage.

Advantages and disadvantages of the commonly used techniques are given in Table 2.

### Treatment

Therapeutics of essential tremor is essentially medical or surgical. If there is no functional or social disability, reassurance is sufficient. If the tremor is intermittent and predictable, intermittent prophylactic therapy with propranolol can be advised. Physical modifications include biofeedback and application of weights to the wrist during activities so as to steady the hand. Lifestyle modification includes avoiding caffeine.

### Pharmacotherapy

Table 3 enlists the drugs reported to be effective in essential tremor.

#### Pramidone

O’Brien et al first showed the utility of primidone in essential tremor. A review of 8 double-blind placebo-controlled trials and 13 open-label trials has shown primidone to be effective. They have shown 40-50% effectiveness in reducing tremor as well as functional improvement. It reduces

### Table 1: Tremor assessment

<table>
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<th>A. Physiological techniques</th>
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<td>2. Electrophysiologic indices of tremor magnitude: Accelerometry, EMG, Gyroscopic techniques</td>
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<td>3. Computer tracking tasks</td>
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<td>4. Graphic digitizing tablets</td>
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<td>5. Infrared sensor systems</td>
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<td>B. Subjective clinical methods</td>
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<tr>
<td>1. Tremor rating scales</td>
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<td>2. Archimedes spiral drawing</td>
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<tr>
<td>3. Handwriting</td>
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<tr>
<td>C. Objective functional performance tests</td>
</tr>
<tr>
<td>1. Volumetry</td>
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<tr>
<td>2. Nine hole pegboard test</td>
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<td>3. Gibson maze test</td>
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<td>----------------------------</td>
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<tr>
<td>D. Disability, handicap and quality of life assessment</td>
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## Table 3

<table>
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<tr>
<th>Drug</th>
<th>Effectiveness</th>
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<tr>
<td>Pramidone</td>
<td>40-50%</td>
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<tr>
<td>Primidone</td>
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tremor amplitude but not frequency. Its role in essential head tremor and voice tremor is minimal. It has a central action and the action is mainly through primidone and an unrecognised metabolite. Acute side effects can occur such as vertigo, nausea and ataxia and are due to lack of hepatic enzyme induction. They can be minimised by pretreatment with phenobarbitone or by starting with very low doses and gradually increasing. It is started at the dose of 12.5 or 25 mg at night; increase to 250 mg/day.

**Beta blockers**

A review of 16 placebo-controlled trials has shown beta blockers to be effective in the management of ET. Propranolol is the most studied drug. Long acting preparations have been shown to be as effective as short acting ones and are associated with better compliance. Timolol and sotalol are effective while metaprolol and atenolol are less effective, as the mechanism of action is through the peripheral beta-2 receptors. 45-75% of patients experience reduction in tremor and functional improvement has also been proven. Like primidone, it reduces tremor amplitude but not the frequency. It is most effective for high amplitude low frequency tremors. It is more effective than primidone in essential head tremor and voice tremor. However hand tremors are better controlled than head or voice tremor. Tolerance is less likely compared to primidone. Starting dose is 40 mg/day and increased to 120 mg/day; maximum dose tried is 320 mg/day. Side effects such as bronchospasm and heart block must be assessed during follow up. When 750 mg primidone was compared to 120 mg propranolol, efficacy was found to be same. While short term adverse effects were more for primidone, long term adverse effects were more for propranolol and at the end of a study, most patients preferred to continue with primidone rather than propranolol.

**Others**

Benzodiazepines such as alprazolam and clonazepam, topiramate and clozapine have been found to be effective. Phenobarbitone was found to be as effective as propranolol. As the GABA-ergic system is disturbed in essential tremor, gabapentin at a dose of 1200 mg/day has been found to be effective. Interestingly, theophylline has been found to enhance the sensitivity to GABA and one trial has shown its chronic use to reduce the amplitude of tremor. Other drugs found to have some role include methazolamide, flunarizine, clonidine and mirtazapine. There is no role for anti-parkinson's drugs.

Botulinum toxin A infiltrated in the intrinsic muscles of the tremor dominant hand produced improvement in tremor, though there was no substantial improvement in functional scores.

Alcohol has been observed to improve essential tremor. 50-90% of patients are alcohol responsive and small amounts produce dramatic response. Action starts within 10-15 minutes and lasts for 3 hours. However rebound tremor may occur after the effect wears off. The risk of chronic alcoholism is low. Mechanism of action is not known but alcohol has been shown to attenuate the increased blood flow in cerebellum that is seen in essential tremor. It may be used judiciously before meals or at social events.

**Surgery**

Fifty percent of patients have disabling tremor even with optimal medical therapy. Lesioning and stimulation procedures target the ventral lateral thalamus, especially the ventral intermedius nucleus (VIM) or ventral oralis posterior nucleus, where fibres from contralateral dentate nucleus relay and pass to area 4 of the motor cortex. Thalamotomy has been shown to have some role include methazolamide, flunarizine, clonidine and mirtazapine.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Accelerometry and electromyography</td>
<td>Objective measure of frequency and amplitude</td>
<td>Expensive, complex, functional disabilities not assessed</td>
</tr>
<tr>
<td>Tremor rating scales</td>
<td>Simple, cheap, reliable</td>
<td>Tremor pattern not documented</td>
</tr>
<tr>
<td>Volumetry</td>
<td>Simple, cheap, reliable</td>
<td>Tremor pattern not documented</td>
</tr>
<tr>
<td>Spirography/handwriting</td>
<td>Simple, cheap, reliable, reflects real life situations, can be serially documented for follow up</td>
<td>Tremor pattern not documented</td>
</tr>
<tr>
<td>ADL/handicap questionnaire</td>
<td>Simple, cheap, reliable, reflects real life situations</td>
<td>Tremor pattern not documented</td>
</tr>
</tbody>
</table>

**Table 2 : Tremor assessment : advantages and disadvantages**

**Table 3 : Drugs useful in essential tremor**

- Primidone: start with 12.5 or 25 mg at night; increase to 250 mg/day
- Beta blockers such as propranolol: start with 40 mg/day; increase to 120 mg/day
- Benzodiazepines such as alprazolam (0.25-3 mg/day), clonazepam (0.5-4 mg/day)
- Topiramate
- Clozapine: 6-75 mg/day
- Phenobarbitone
- Gabapentin: up to 1200 mg/day
- Theophylline: up to 120-300 mg/day
- Methazolamide: 50-300 mg/day
- Flunarizine (up to 10 mg/day), clonidine and mirtazapine (30 mg/day)
been shown to be effective in the short term and long term follow up after surgery in the form of improvement in tremor scores, activities of daily living, writing and pouring activity.\textsuperscript{3} Complications include dysarthria, ataxia, motor weakness, paraesthesias and mild cognitive deficit.\textsuperscript{2,3,5} However bilateral thalamotomy has been associated with severe dysarthria and anarthria and memory impairment and hence is not advocated.\textsuperscript{2,3,19}

In thalamic stimulation, deep brain stimulation (DBS) lead is connected to an implantable pulse generator (IPG) and the intracranial end is implanted in the VIM nucleus. Postural tremor is more effectively controlled than kinetic tremor.\textsuperscript{3} Complications include microhematomas, contralateral paraesthesias, limb dystonia, dysarthria and dysequilibrium. Tolerance may occur, especially for action tremor. Significant improvement in tremor and activities of daily living has been proven.\textsuperscript{3} Bilateral staged thalamic DBS is associated with mild and modifiable complications such as dysarthria and dysequilibrium.\textsuperscript{2,3,19} It has been shown to be as effective as thalamotomy for reducing tremor amplitude. However DBS is associated with better functional outcome and less adverse effects.\textsuperscript{20} Its advantages include reversibility, adaptability and the possibility of bilateral staged procedure. But it is expensive, involves leaving behind a foreign body, batteries must be replaced regularly and time and effort is required for optimising the stimulus variable.\textsuperscript{1}

**CONCLUSION**

Essential tremor is the most common movement disorder. Diagnosis is based on clinical features supplemented by various tremor assessment techniques. Management is essentially medical and primidone and propranolol are the preferred drugs. Surgery is indicated where medicines fail to give adequate response and deep brain stimulation has shown the best results.

**REFERENCES**