Tremor – Easily Seen but Difficult to Describe and Treat

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ABSTRACT: Tremor is a common movement disorder yet many physicians struggle with its terminology as well as with its treatment. Attempts have been made to develop standard terminology and criteria for tremors but this process continues to evolve. In this review, a summary of the currently-proposed phenomenology and syndromic classification of all types of tremor is presented. The diagnosis and management of essential tremor is presented in more detail, as it is the most commonly encountered tremor.

RÉSUMÉ: Le tremblement – Facile à constater mais difficile à décrire et à traiter. Le tremblement est un désordre du mouvement fréquent qui, pour plusieurs médecins, comporte des difficultés terminologiques et thérapeutiques. On a tenté de développer une terminologie et des critères standard pour les tremblements, mais ce processus est en constante évolution. Dans cette revue, nous présentons un sommaire de la phénoménologie actuelle et une classification syndromique de tous les types de tremblement. Comme le tremblement essentiel est le tremblement le plus fréquemment rencontré, son diagnostic et sa prise en charge sont présentés en détail.


Tremor is the rhythmical, involuntary oscillatory movement of a body part. The terminology for describing tremor is often confusing, with authors using different terminology to describe the same tremor. Below is a summary of the phenomenology and a syndromic classification of tremor from a consensus statement from the Movement Disorder Society published in 1998. Modifications of this approach will occur but it does provide a framework from which to build.

PHENOMENOLOGY

1. Rest tremor – tremor that occurs in a body part that is not voluntarily activated and is completely supported against gravity.

2. Action tremor – any tremor that is produced by voluntary contraction of muscle, including postural, isometric, and kinetic tremor. The latter includes intention tremor.
   a. Postural tremor – tremor present while voluntarily maintaining a position against gravity.
      i) Simple kinetic tremor – non target-directed tremor.
      ii) Intention tremor – tremor that increases in amplitude during visually guided movements toward a target at the termination of the movement. The possibility of a position-specific tremor or a postural tremor produced at the beginning or end of a movement needs to be excluded.
      iii) Task-specific kinetic tremor – tremor that appears or becomes exacerbated during specific activities, e.g. primary writing or occupational tremors.
   iv) Isometric tremor – tremor occurring as a result of muscle contraction against a rigid stationary object (for example, while making a fist or squeezing the examiner’s fingers).

SYNDROMIC CLASSIFICATION OF TREMOR

The phenomenology of tremor can be combined into some specific syndromes that are useful to help determine the underlying etiology and guide treatment.

1. Physiologic tremor syndrome
   This tends to be of high frequency (7–12 Hz) and low amplitude. In normal individuals, a distal finger tremor can often just be seen with the naked eye.

2. Enhanced physiologic tremor syndrome
   The tremor is easily visible, mainly postural and of high frequency (7–12 Hz). There is no evidence of an underlying neurologic disease and it is normally reversible. It is typically

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caused by endogenous or exogenous factors such as hyperthyroidism, hypoglycemia, caffeine, smoking, or drugs (e.g. beta-adrenergic agonists, lithium, valproic acid, steroids).

3. Essential tremor (ET) syndromes

a. Classic essential tremor

See next section for detailed discussion and treatment.

b. Undetermined tremors

Patients with this condition satisfy the criteria for classic ET but exhibit other neurologic signs of uncertain significance, not sufficient to make the diagnosis of a recognizable neurologic disorder. For example, distinguishing between early parkinsonism, ET and dystonic tremor can be impossible early on in the disease process and becomes more clear only over time.

c. Orthostatic tremor

This is a unique syndrome characterized by: 1) a subjective feeling of unsteadiness during standing and in severe cases with walking; 2) a visible and, occasionally, only palpable, fine amplitude rippling/tremor of the legs when standing; 3) EMG recording of a 13-18Hz tremor during tonic activation of a muscle. This tremor tends to respond well to clonazepam.2

d. Task and position specific tremors

Primary writing tremor is the most frequent example of this but other examples include specific tremors in musicians.3 It is unknown whether these task-specific tremors represent a type of ET, a variant of dystonia, or a distinct entity. In primary writing tremor, the tremor is only (or predominantly) present during writing and not during other tasks. Another example is an isolated voice tremor. It is present if an individuals voice is tremulous but no other parts of the body show tremor. It is often considered a form of dystonia or a variant of ET. Dystonic voice tremor is the more likely diagnosis if the tremor ceases during emotional speech production (geste maneuvers), singing, or changes in pitch.

4. Dystonic tremor syndrome

Many different definitions have been proposed but the Consensus Statement1 suggested the following subtypes:

a. Dystonic tremor

Tremor in an extremity or body part that is affected by dystonia. This tremor is usually irregular in amplitude and frequency, and not normally seen during complete rest. The most common example would be that of a dystonic head tremor in an individual with cervical dystonia.

b. Tremor associated with dystonia

This tremor occurs in a body part not affected by dystonia, but the patient has dystonia elsewhere. An example would be the postural and kinetic tremor of the upper limbs indistinguishable from essential tremor in patients with cervical dystonia.

c. Dystonia gene-associated tremor

The patient has only tremor but another individual in the same family has dystonia.

5. Parkinsonian tremor syndromes

This is any form of tremor in a patient diagnosed with Parkinson’s disease (PD). This would include the postural and kinetic tremors that are commonly seen in PD patients. The classic tremor that is part of the diagnostic criteria for PD is a rest tremor. This tremor is typically more than 4 Hz and can be up to 9 Hz especially early on in the disease process.

6. Cerebellar tremor syndromes

These types of tremors have a pure or dominant intention component, are unilateral or bilateral and typically have a frequency below 5 Hz. A postural component may be present but rest tremor is absent. This type of tremor is often used synonymously with an intention tremor. Other findings of cerebellar dysfunction (dysmetria, hypotonia, dyssynergia) should be present before this term is used. Titubation is a slow-frequency oscillation or tremor that is dependant on postural innervation that is probably the result of cerebellar dysfunction or its connections.

7. Holme’s tremor

Many different terms have been used to describe this unique form of tremor. These include “rubral tremor”,4 “midbrain tremor”,5 “thalamic tremor”,6 and “myorhythmia”.7 Because the lesion that causes this type of tremor can arise from many different locations it was decided to avoid a topographic descriptive name and to use the author’s name who gave the first clear description of it.8 This tremor tends to be less rhythmic and is a combination of a rest, intention and postural tremor that is of low frequency (< 4.5Hz). It is the result of a lesion(s) in the central nervous system, typically in the red nucleus, midbrain or thalamus. There is normally a delay of four weeks to two years from onset of the lesion (if this can be determined) and the onset of the tremor.

8. Palatal tremor

This was previously described as palatal myoclonus. However, it was reclassified as a tremor disorder because of pathophysiologic and pathoanatomic data. Two forms are recognized:

a. Symptomatic

Rhythmic movements of the soft palate (levator veli palatini) and often other brainstem-innervated or extremity muscles. There is a preceding brainstem and/or cerebellar lesion with subsequent olivary hypertrophy that can be seen on an MRI scan.

b. Essential

Rhythmic movements of the soft palate (tensor veli palatini) without involvement of other brainstem-innervated or extremity muscles. There is no associated preceding lesion and there is no olivary hypertrophy. Patients normally have an ear click, absent in the symptomatic form.

9. Drug-induced and toxic tremor syndromes

Drug-induced tremors can be of any type with the presentation depending on the drug and the patient. Types include the enhanced physiologic tremor seen with sympathomimetic drugs, and the classic rest tremor seen from dopamine-receptor blocking drugs. To diagnose toxic tremors, other clinical signs of central nervous system intoxication should be seen.
10. Tremor syndromes in peripheral neuropathy
These are normally postural and kinetic tremors. Many different neuropathies have been associated with tremor but the demyelinating neuropathies are more frequently the culprit.

11. Psychogenic tremor
The following criteria have been suggested.
 i. Sudden onset, remissions or both.
 ii. Unusual clinical combinations of rest and postural/intention tremor.
 iii. Decrease of tremor amplitude during distraction.
 iv. Variation of tremor frequency during distraction or during voluntary movements of the contralateral hand.
 v. Coactivation sign. This is observed when testing a trembling limb for rigidity and there is resistance to the passive movement. Two additional features should be present: 1) the tremor is dependent on there being an increase in tone (i.e. the examiner feels the patient “fighting” against him or her); and 2) the tremor disappears when the voluntary increase in tone disappears.
 vi. Somatization in the past history.
 vii. Appearance of additional and unrelated neurologic signs.

12. Unclassified
If a tremor does not fit into one the above categories, it should be described in terms of its phenomenology (i.e. rest, postural or kinetic) and then labeled as unclassified.

Essential tremor
Essential tremor (ET) is probably the most common movement disorder whose etiology and pathogenesis are unknown. Previously, the prefix “benign” had been used but, as individuals can be totally disabled, use of this term is now discouraged. The prevalence of ET ranges from 0.4 to 22% (best estimate ~4%) in the elderly population. This wide range is, in part, dependent on the criteria used for diagnosis and only recently have attempts been made to establish more universally accepted ones.1,10 Most studies have shown that ETs much more prevalent than PD (up to 20X difference).9,11 It is frequently familial with 17 to 100%12,13 of patients having a positive family history. A recent twin study confirmed a genetic cause of ET is likely but also suggested that environmental factors play a role.14 Two different chromosomal regions have been linked to familial ET, one on chromosome 3q1315 and another on chromosome 2p22-25.16 No specific gene mutations have been found to date.

The underlying pathophysiologic cause of ET is unknown17 with no abnormalities having been identified in autopsies of ET patients.18,19 Electrophysiologic studies are consistent with a central source of oscillation with the inferior olive and cerebellum implicated by positron emission tomography,20 and animal studies.21 The inferior olivary neurons have rhythmic properties and interconnections that are conducive to the production of tremor. Lesions in the cerebellum and thalamus reduce ET, an observation suggesting that the abnormal oscillation is transmitted to the motor cortex through the cerebellum and its projection to the ventrolateral thalamus.17

Many different diagnostic criteria have been proposed for ET.1,10,22-24 Each has its specific advantages and disadvantages. The definition and classification of ET are still based on clinical phenomena with none of the clinical features being entirely specific or sensitive. Whether the action tremor is predominantly kinetic or postural has been debated, however, more recent evidence suggests that the kinetic tremor tends to be more severe.25 Patients with a severe action tremor may also have a mild resting tremor that is often confused with PD. Typically, in patients with ET, there is no pause in the tremor when the arm is brought from a rest to outstretched posture. This is in contrast to patients with PD where there is typically a pause or “reset” of the tremor when the limb is extended from a resting state. Although tremor in the arms should be bilateral, it is important to remember that it is most often asymmetric.26 Core and secondary criteria have been proposed by Bain et al27 based on the Tremor Investigation Group Criteria and the Consensus Statement of the Movement Disorder Society. The core criteria include: 1) bilateral action tremor of the hands and forearms (but not rest tremor); 2) absence of other neurologic signs, with the exception of the cogwheel phenomenon; and 3) may have isolated head tremor with no signs of dystonia. Secondary criteria include: 1) long duration (>3 years); 2) positive family history; and 3) beneficial response to alcohol. The core criteria must be fulfilled for the diagnosis and the secondary criteria are present in more than half of patients and support the diagnosis. These criteria are simple and easy to remember for clinical use but would not be specific enough for research purposes. Findings that suggest a diagnosis other than ET include: unilateral tremor, leg tremor, rigidity, bradykinesia, rest tremor (PD); gait disturbance (PD, cerebellar tremor); focal tremor (dystonic tremor); isolated head tremor with abnormal posture (dystonic tremor); sudden or rapid onset (psychogenic tremor, toxic tremor).

Treatment of essential tremor
Most individuals diagnosed as having ET only require assurance that they do not have any other neurologic disease, especially PD. The progression is very slow but it can cause disability that interferes with function and gainful employment.9 More severely affected individuals must weigh the potential side effects of the treatment against the modest benefits that are seen from most of the current treatment options.

Alcohol transiently improves tremor in 60-90% of ET patients.27,28 Its mechanism of action is poorly understood but is felt to be a central rather than peripheral effect.29 Although there has been concern that the use of alcohol may lead to an increased risk of alcoholism, this does not seem to be the case.30 Alcohol use in moderation before meals or at social events to ameliorate tremor is a reasonable treatment approach.

The lack of understanding of both the underlying physiology and pharmacology has resulted in a lack of truly effective therapies. A long list of potential medications has been reported to improve ET, however most of them arise from small, uncontrolled case series. Once better-designed trials are performed this initial benefit is frequently not seen. Only two medications have consistently shown to be helpful – the “two Ps” – propranolol and primidone.

Propranolol has been the best studied but other β-adrenergic blockers have been shown to be effective. Surprisingly, the sample size for most of the controlled studies has been very small (average 15–25 patients).31 Approximately 40-50% of
patients will experience symptomatic benefit, with a smaller percentage having a dramatic improvement. These agents are less effective for voice and head tremor. β-adrenergic blockers reduce the amplitude but not the frequency of the tremor. For propranolol, the usual starting dose is 40-80 mg per day with dose response studies suggesting 240-360 mg/day as the optimal dose range. Doses of more than 360 mg/day usually conferred no additional benefit. Patients often prefer the ease of long-acting propranolol or other longer acting β-adrenergic blockers like nadolol and these agents have been shown to be just as effective. The mechanism of the beneficial action of β-adrenergic agonists is not known with certainty. Drugs that act through a peripheral β₂ mechanism confer the most benefit. β-blockers that act selectively through a β₁ mechanism (e.g. atenolol) do not seem to have any benefit. Common potential adverse reactions include orthostatic lightheadedness, fatigue, nausea, diarrhea, rash, impotence, and depression. Patient monitoring of pulse rate and blood pressure are recommended. Relative contraindications for β-adrenergic blockers include: heart failure, especially when it is poorly controlled, second or third-degree atrioventricular block, asthma, and diabetes in which the symptoms of hypoglycemia may be masked. Side effects observed with one β-adrenergic blocker may not be seen with another and therefore trying an alternative one is worthwhile.

Primidone – the efficacy of primidone has been demonstrated in many small case-controlled, as well as double-blind, placebo-controlled trials. The degree of improvement is highly variable with some patients having almost complete resolution while others having none. Overall the effectiveness of reducing tremor amplitude is approximately 40-50%. As with propranolol, there is no effect on tremor frequency and a poor response to head and vocal tremors. The long-term efficacy of primidone has not been proven but two studies have demonstrated that efficacy is maintained at one-year follow-up. The usual starting dose is half of a 125 mg tablet at bedtime. The optimum dose is not clear, with some patients having an adequate response on very low doses (62.5mg/day) while others requiring > 250 mg/day. In one study, the maximal effect was at 250 mg/day with no additional benefit seen at doses up to 1,000 mg/day.

The mechanism of action of primidone’s anti-tremor effect is unknown. Phenoobarbital is one of primidone’s active metabolites but it has little, if any, anti-tremor effect on its own. Acute side effects of vertigo, nausea and unsteadiness occur in 20-30% of patients. These are usually temporary and resolve with continued use. Starting with a small bedtime dose (62.5mg qhs) can partially help some patients overcome these side effects. Informing patients of these early potential side effects and stressing that they are normally only transient will help with compliance. Initiating therapy at very low doses (25mg/day) of liquid suspension has been advocated to improve patient compliance but this strategy has not been shown to be effective in a randomized double-blind trial. Long-term side effects are uncommon with doses of less than 250mg/day and usually consist of mild daytime sedation. There have been direct comparative trials between primidone and propranolol suggesting that primidone may be better tolerated and more effective. Combination therapy of primidone and propranolol may be effective when monotherapy with either drug is not successful.

Other medical treatments

Benzodiazepines appear to have limited efficacy in treating ET, yet continue to be used frequently. Specifically, clonazepam has been found to have no beneficial effect in typical ET. Alprazolam, in one double-blind, placebo-controlled trial of 24 patients, showed substantial improvement in 50% of patients. Sedation is a common and dose-limiting adverse effect that restricts chronic use. Gabapentin is one of the latest medications to be studied for its anti-tremor effect. Two small case series demonstrated tremor reduction, however a larger double-blind controlled study failed to confirm any benefit over placebo. Another anticonvulsant, topiramate has been suggested to have efficacy in one small placebo-controlled crossover study but this will require confirmation in a larger trial. Clozapine, an atypical neuroleptic has been suggested to control tremor. Its expense and rare incidence of agranulocytosis necessitating frequent blood work, limit it as a potential treatment option. Methazolamide, calcium channel blockers (funaridine, nimodipine, nifedipine), clonidine, trazadone, pregabide (a GABA agonist) have all failed to demonstrate any benefit in double-blind controlled trials.

Botulinum toxin A injections into hand flexors and extensors have been used in an effort to suppress the limb tremor in ET patients. One randomized, double-blind, placebo-controlled study reported a 75% improvement compared to 27% for placebo. Improvement was of a mild to moderate degree using tremor scales and accelerometry. However, no substantial functional improvement was noted and all patients experienced some degree of finger weakness. A larger trial also did not demonstrate any improvement in functional outcome. For patients with a marked head or vocal tremor, botulinum toxin A has been shown to be helpful.

SURGICAL TREATMENT

As will be discussed in detail by Abosch and Lozano in this issue, both thalamotomy and deep brain stimulation of the thalamus are highly effective treatments for drug resistant tremor.

REFERENCES


