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My hands shake

Classification and treatment of tremor

Background

Tremor is the most common movement disorder in the community and is defined as a rhythmic oscillatory movement of a body part. Classification of tremors is helpful for accurate diagnosis, prognosis and treatment. Most tremors can be separated according to the state in which they occur, that is, during rest or action. Other clinical features, including frequency, amplitude and associated neurological signs, further define tremor.

Objective

This article describes some of the important clinical clues that reliably separate tremors, including the rest tremors of Parkinson disease and vascular midbrain lesions, or the action tremors of enhanced physiological tremor, essential tremor and dystonic tremor.

Discussion

Numerous treatment strategies exist for tremor, but focused, selective use of appropriate medications requires accurate clinical diagnosis. Diagnostic certainty is essential as functional neurosurgery (deep brain stimulation) offers a realistic treatment option for many patients with severe tremor.

■ **Tremor describes an oscillatory, rhythmic involuntary movement of a body part and is the most common movement disorder in the community.¹⁻⁴ Although tremor can involve any part of the body, hands are the most common site. In general, tremor is a descriptive term, but the underlying cause and classification of tremor can usually be determined based on history and observation and aided by investigations when indicated.**

Classification

The phenomenological classification of tremor is helpful in diagnosing the cause of these involuntary movements. The different characteristics of tremor are:

- type of tremor (rest, action or both)
- frequency of tremor
- axis of tremor, and
- associated symptoms (*Table 1*).

Accurate clinical assessment can clarify most of these factors and inform the differential diagnosis. It is encouraging that clinical classification is accepted widely as the gold standard, so special investigations are usually not required for accurate diagnosis.¹

Tremors are separated according to the position in which they are most obvious:

- rest, or
- action.

Action tremor is further separated into postural, isometric and kinetic tremor, where intention tremor is included under kinetic tremor. Rest tremor occurs when the body part is not voluntarily activated and completely supported against gravity (hands rested on the laps). This tremor often augments with mental stress (eg. counting backward) and attenuates with goal directed movements.

Action tremor is any tremor that emerges during voluntary contraction of muscles. Postural tremor is present while voluntarily maintaining a position against gravity as with extending arms in front of the body. Isometric tremor occurs as a result of muscle contraction against rigid stationary object (squeezing the examiner's



Table 1. Characteristics of different tremors

Type of tremor	Frequency (Hz)	Amplitude	Occurrence	Associations
Rest	Low to medium (3–6)	High (reduced with target directed movements)	Limb supported against gravity with muscles not activated	Parkinson disease, drug induced, vascular midbrain lesions, less commonly atypical parkinsonism (eg. multiple system atrophy and progressive supranuclear palsy)
Action			Voluntary muscle contraction	
Postural	Medium to high (4–12)	Low, increases with voluntary movements	Limbs maintains position against gravity	Physiological, essential tremor, thyrotoxicosis, hypoglycemia, Cushing syndrome, alcohol withdrawal, neuropathy and drugs
Simple kinetic	Variable (3–10)	Does not change with target directed movements	Simple movements of the limb	Essential tremor, dystonic tremor, enhanced physiological tremor
Intention	Low (<5)	Increases with target directed movements	Target directed movements	Cerebellar lesions (multiple sclerosis, stroke, mass lesion), drugs, chronic alcoholism
Isometric	Medium	Variable	Muscle contraction against stationary object	Essential tremor, enhanced physiological tremor, dystonic tremor, Parkinson disease
Task specific	Variable (4–10)	Variable	Specific tasks	Dystonic tremor (eg. primary writing tremor, musician's tremor)

fingers). Kinetic tremor occurs during any voluntary movement and is simple when it occurs during nontarget directed movements (flexion/extension, pronation/supination at wrist), and intention when it is target directed, as in the finger-nose test. Kinetic tremor could be task specific when it appears or augments during specific tasks, such as writing.^{1–6}

Evaluation of the patient with tremor

Nothing can substitute a good history in evaluating a patient with tremor. Onset, relieving and exacerbating factors, family history and recent medications are essential. The initial assessment should also include functional limitations caused by tremor, including during activities of daily living, occupation, and social and recreational activities.

Good clinical observation is the most important aspect of physical examination and should aim at demonstrating the various aspects of tremor phenomenology described earlier. Arms resting on the lap, extending in front of the body, and finger-nose test are some essential manoeuvres. Holding a cup and drawing a spiral are also useful in diagnosis as well as in determining functional limitations.

The physician should be able to describe tremor in terms of:

- body part (arms, head and neck)
- activation condition (when it is actually present or becomes worse)
- frequency (fast >6 Hz or slow <6 Hz)
- regularity (regular or jerky), and
- amplitude (fine or coarse).

When encountered with a rest tremor it is essential to check for associated rigidity and bradykinesia, suggesting Parkinson disease

(PD). Both the tremor and rigidity may get worse when performing voluntary movements with the opposite limb. Gait is an essential part of assessment, which can demonstrate difficulty in gait initiation, reduced arm swinging and freezing. If PD is suspected, a trial of levodopa is appropriate. Referral to a neurologist is important if features are atypical or fail to respond to medication.

In assessing patients with intention tremor, associated symptoms such as imbalance, dysarthria and ataxia should be inquired and investigated. Stroke causes acute onset symptoms, whereas multiple sclerosis may cause a relapsing course together with visual disturbance and diverse neurological features. Chronic alcoholism is an important cause that needs to be excluded with relevant examination and blood tests.

Thyrotoxicosis is a common presentation of postural tremor that needs exclusion by relevant clinical examination (rapid pulse, eye signs, goitre) and thyroid function tests. Anxiety and panic attacks are commonly associated with postural tremor and relevant features such as palpitations, chest discomfort and a feeling of suffocation should be asked for, particularly in younger patients. Medication overuse and withdrawal are important other causes of postural tremor. Essential tremor should be suspected if the clinical examination is otherwise normal, and especially when there is a positive family history and improvement with alcohol.

Physiologic tremor

All people exhibit physiologic tremor – a benign high frequency, low amplitude, postural tremor. This may be demonstrated when holding a piece of paper on the outstretched hand after exercise or when



anxious. Exaggerated physiologic tremor is visible and occurs in the absence of neurological disease.¹ When encountered, associations such as thyrotoxicosis, Cushing syndrome, hypoglycaemia, alcohol withdrawal and use of certain drugs (eg. beta agonists, corticosteroids) should be excluded. Propranolol may be used for symptomatic relief but alleviation of the cause usually relieves the tremor.^{1,2}

Essential tremor

Essential tremor is the most common adult onset movement disorder with a prevalence of 4–39 cases per 1000 and increasing to 51 per 1000 in those over 60 years of age.⁸ It is usually bilateral, largely symmetrical postural, or kinetic involving hands and forearms. Other features that aid diagnosis are gradual and progressive onset with increase in amplitude of tremor over time, and spread to the neck (titubation) and voice (vocal tremor) in the absence of abnormal posturing (dystonia). A positive family history and acute reduction of tremor amplitude in response to alcohol is typical in essential tremor.^{1–4,9–12}

If the tremor is disabling and intrusive enough to merit treatment, a nonselective beta blockade with propranolol is the mainstay of treatment. The anticonvulsant primidone is equally effective but may cause severe side effects such as nausea and extreme fatigue. One month of phenobarbitone (30 mg) for hepatic enzyme induction before starting primidone is helpful in minimising side effects (the Wodak protocol).^{11–13} In resistant disabling cases, thalamic deep brain stimulation is particularly useful. Electrode placement and stimulation in the thalamus can provide complete resolution of the tremor. Careful assessment by an experienced functional neurosurgical team, including neuropsychological and psychiatric assessment before surgery, is necessary for best outcomes.

Dystonic tremor

This tremor can occur in any body part affected by dystonia, identified by abnormal posturing with overactivity of agonist and antagonist muscles. Dystonic tremor is often jerky, irregular and variable depending on posture and activity, and may be particularly disabling when the upper limbs are involved. Electrophysiological studies confirm a broad range of tremor frequency in the affected limb, which can often be picked clinically (irregular tremor). Dystonic head tremor is the most common example of this classification of tremor. Dystonic tremor needs to be differentiated from patients who have dystonia, but with tremor that occurs in a body part not affected by dystonia.^{1,13,14} Treatment with anticholinergic medications or clonazepam is usually trialled, but dystonic head tremor is usually treated most effectively with botulinum toxin in the posterior neck muscles. In resistant cases where dystonia is a major cause of disability (as opposed to tremor) deep brain stimulation of the globus pallidus can be useful.

Orthostatic tremor

Orthostatic tremor is an unusual and unique tremor syndrome where sufferers feel unsteadiness during standing rather than

tremor *per se*. Typically patients describe a feeling of unsteadiness when standing still for longer than a few seconds. Although the unsteadiness is often disabling, patients rarely fall. Diagnosis is confirmed by demonstrating a very high frequency (13–18 Hz) tremor on electrophysiological studies.

Parkinsonian tremor

Parkinson disease is less common than essential tremor, but is more likely to progress and cause disability.⁸ About 70 000 Australians suffer from PD and about 70% of these patients will have at least moderate rest tremor. As specific treatment options are available, early diagnosis is mandatory.

Parkinson disease is diagnosed by the presence of bradykinesia and either rest tremor or extrapyramidal rigidity.^{15–17} Tremor may be the presenting feature.

When a patient has any form of pathological tremor together with other diagnostic criteria of PD, they are classified as having ‘parkinsonian tremor syndrome’. The typical PD tremor is a pure rest tremor with low frequency (4–6 Hz). Occasionally a postural or kinetic component can be seen with the same frequency. The postural tremor of PD usually emerges after a latent period following adoption of a new posture. This differentiates it from essential tremor where the tremor emerges immediately on adopting a new posture.¹ At times the tremor may be disabling and can spread to involve the arm, and the head and face in advanced disease.

The tremor of PD usually improves with antiparkinsonian medications, including levodopa, dopamine agonists, anticholinergics and amantadine. The presence of severe tremor not improved with medications may be an indication for deep brain stimulation therapy. Our practice is to target the subthalamic nucleus to treat bradykinesia and rigidity, as well as tremor, but in patients where cognitive problems are present the thalamus appears to be a better target.

Cerebellar tremor

A pure or a dominant intention tremor at a frequency of less than 5 Hz is typical for ‘cerebellar tremor’. Tremor should be absent at rest but may be associated with posture. Tremor could be unilateral or bilateral depending on aetiology. Stroke, multiple sclerosis and tumour may affect the cerebellum and cerebellar pathways causing tremor. Drug toxicity (eg. phenytoin, sodium valproate, amiodarone) is another important cause to exclude. It is essential to identify other cerebellar signs as tremor usually occurs in combination with these in cerebellar lesions.¹⁸ In this context, broad based ataxic gait, incoordination of the limbs (finger-nose and heel-shin testing), nystagmus and cerebellar speech may be obvious. Cerebellar tremor is often irregular and jerky.

Holmes tremor

This rare tremor is characterised by a combination of slow rest and intention tremor and may be confused with parkinsonian tremor. It is



differentiated from PD by the slow frequency, prominent postural component and the presence of cerebellar signs. This is of central origin associated with a lesion in the central nervous system (CNS), particularly the midbrain and thalamus.¹⁹ Vascular lesions mostly commonly cause Holmes tremor and magnetic resonance imaging of the brain should be performed. It is difficult to treat, and a defining clinical feature is resistance to dopaminergic medications (eg. levodopa) and treatments for essential tremor (eg. propranolol, primidone). This tremor is also known as ‘rubral tremor’ or ‘midbrain tremor’.

Drug induced tremor

Tremor is considered to be drug induced if it occurs after a reasonable time frame following drug ingestion.¹ Drug induced tremors may demonstrate the entire spectrum of clinical features of tremor, depending on the toxin (*Table 2*). Common syndromes include enhanced physiological tremor seen with sympathomimetics and antidepressants and classic Parkinson rest tremor associated with neuroleptics and dopamine blocking agents.¹ Alcohol withdrawal usually results in enhanced physiological tremor which needs to be differentiated from intention tremor secondary to cerebellar damage in chronic alcoholism. Toxic tremors (occurring in the presence of drug intoxication) are usually associated with other clinical signs of CNS intoxication such as gaze abnormalities and gait disturbance.¹

Tremor syndromes in peripheral neuropathy

Many peripheral neuropathies are associated with tremors, which are predominantly postural and kinetic. These tremors are peripheral in origin and commonly seen with demyelinating neuropathies especially with dysgammaglobulinemias.¹ Treatment of the underlying neuropathy may not be sufficient to resolve the tremor, and often modest doses of propranolol are needed.

Psychogenic tremor

Psychogenic tremor should be included in the initial differential diagnosis of any patient with tremor. In some specialty clinics, psychogenic tremor accounts for more than 10% of cases.^{20,21} Sudden onset and remission with unusual clinical signs in combination with tremor should raise the possibility of a psychogenic aetiology. Disappearance and change in frequency of tremor when co-activating the antagonistic muscles (resistance to passive movements about a joint) in the tremulous limb is a useful sign (the ‘co-activation sign’).²² Distraction typically reduces the amplitude of tremor and often tremor frequency will also vary. These features are less often seen in organic tremor. A past history of somatisation and appearance of additional and unrelated neurological signs are often used as additional evidence.¹

Electrophysiological studies can be helpful, particularly if a broad range of tremor frequencies is recorded (this would be unusual in

Table 2. Common causes of drug induced tremor

Postural	Intention	Rest
<ul style="list-style-type: none"> • Alcohol • Amiodarone • Amphetamines • Beta adrenergic agonists • Caffeine • Cyclosporine • Dopamine • Corticosteroids • Sodium valproate • Theophylline • Thyroid hormones • Tricyclic antidepressants 	<ul style="list-style-type: none"> • Alcohol • Lithium 	<ul style="list-style-type: none"> • Metoclopramide • Prochlorperazine • Neuroleptics (dopamine blockers)

centrally mediated tremors) or if tremor frequency changes with weighting of the limb. The diagnosis of psychogenic tremor is probably best made by a neurologist, as the myriad presentations of this form of tremor can make definitive diagnosis difficult.

Tremor of Wilson disease

This rare and important cause of tremor presents at an early age (4–25 years). Involuntary movements may appear as a flapping, intention tremor, most commonly in ‘wing beating’ posture (arms abducted at the shoulders, elbows bent). Patients will usually have associated dystonia, bradykinesia and rigidity. Abnormal liver function tests and Kayser-Fleischer rings in the eyes are important associations.¹⁶ This rare disease of inborn error of copper metabolism is often fatal if not detected early and copper studies are usually diagnostic (reduce serum ceruloplasmin and copper, increased urinary copper on 24 hour collection).

Investigating a patient with tremor

The diagnosis of tremor is clinical but can be supported and further characterised by electrophysiological studies using surface electromyography (EMG) and accelerometers. An EMG assessment of the tremor is the most reliable method of diagnosing primary orthostatic tremor. Tremor analysis can also be useful in diagnosing dystonic tremor and differentiating difficult to assess tremors and psychogenic tremor. Although not routinely used, clinical rating scales are available for assessing severity of tremor including response to treatment.^{1,21}

Primary care physicians should routinely measure thyroid, renal and liver function in patients with action tremor. Other routine and specific investigations should be ordered depending on the clinical suspicion of aetiology of tremor.

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