British Medical Bulletin, 2019, **130**:51–63
doi: 10.1093/bmb/ldz017
Advance Access Publication Date: 14 May 2019

Invited Review

Tremor

Tabish A. Saifee*

UCL Queen Square Institute of Neurology, Queen Square, London WC1N 3BG, UK

*Correspondence address. UCL Queen Square Institute of Neurology, Queen Square, London WC1N 3BG, UK.
E-mail: t.saifee@ucl.ac.uk

Editorial Decision 6 April 2019; Accepted 10 April 2019

Abstract

Introduction or background: Tremor is one of the commonest movement disorders and can be disabling. There are many causes and treatment options include medications, adaptations, botulinum toxin injections and functional neurosurgery.

Sources of data: Pubmed.gov peer-reviewed journal articles and reviews.

Areas of agreement: A new tremor classification has been published. Axis 1 of this classification highlights the clinical characteristics of tremor and axis 2 is dedicated to aetiology. The cerebello-thalamo-cortical network and connections to other brain areas is emerging as pivotal to many types of tremor.

Areas of controversy: There has been ongoing debate around the clinical entity of essential tremor and its pathophysiological basis.

Growing points: Increasing understanding of the pathophysiology underpinning tremor is helping to improve classification and is pushing forward trials of new treatment options, particularly surgical options.

Areas timely for developing research: With deeper phenotyping from the new classification, genetics of common forms of tremor are ripe for discovery. New pharmacological therapeutic options are needed to complement the better understanding of the basis of tremor.

Key words: essential tremor, Parkinson's disease, dystonic tremor, orthostatic tremor, physiological tremor, stereotactic neurosurgery, Holmes tremor

Introduction

Tremor is an involuntary, rhythmic, oscillatory movement of a body part.[1] New consensus criteria for classifying tremor disorders were published in 2018.[2] The aim was to produce a more systematic approach to tremor diagnosis using two axes, one detailing clinical features (axis 1) and the other for aetiological classification (axis 2). It was specifically aimed to deal with some of the ongoing controversy surrounding the entity of essential tremor (ET), for which there has been persistent debate. It seems likely that what we describe as ET is in fact a syndrome composed of a variety of aetiologies, many of which are yet to be unearthed.[3]

Tremor is most often described in the upper limbs but can occur in other body parts such as the head, jaw, face, palate or legs. Tremor is both a symptom and a sign and is often described by patients as 'shaking' but can occasionally be confused by a patient or the observing clinician with an alternative hyperkinetic movement, for example, myoclonus. Tremor is the commonest movement disorder and can occur in isolation, such as in ET or in the context of other movement disorders or neurological/medical signs. It can be a clue to an underlying diagnosis. There are few definitive biomarkers but some targeted tests can be helpful. Treatment options are on the whole disappointing but include physical adaptations, oral therapies, botulinum toxin and stereotactic neurosurgery.

Axis 1—clinical features (see Table 1 for summary)

Age

The age at which tremor first occurs should be established. Parkinson's disease is uncommon under 50 years and rare under the age of 40 years.[4] ET can present throughout life with a bimodal peak of onset,[5] in adolescence/young adulthood and late onset. Young onset tremor should raise consideration of rarer genetic conditions such as Wilson's disease, particularly when associated with other movement and behavioural disorders.

Temporal onset and evolution

Some tremors develop subacutely with a latency, typically of weeks or months, after an insult to the brain. This is the case for both symptomatic palatal tremor and Holmes tremor (HT).[6] A sudden onset of tremor after an injury or other health-related problem can point towards functional (psychogenic) tremor. Sudden or rapid onset tremor may be drug-induced or metabolic. Many other tremor types have a gradual progression. Tremor in Parkinson's disease can progress with the condition but may then be seen to wane with later stages of the disease. Some forms of tremor such as enhanced physiological tremor can fluctuate according to precipitants.

Past medical and drug history

Many drugs can cause tremor,[7] detailed later. The past medical history may reveal relevant precipitants such as multiple sclerosis, where disabling tremor is well recognized. The presence of parkinsonian non-motor symptoms, for example, depression, constipation, olfactory loss and rapid eye movement (REM) sleep behaviour disturbance point towards early Parkinson's disease.[8] Symptoms of thyrotoxicosis may manifest with other systemic features of hyperthyroidism.

Family history

A family history of tremor and other movement disorders such as ataxia or dystonia provide a clue to aetiology. ET is commonly seen to run in families, often with an autosomal dominant inheritance pattern. A history of consanguineous marriage raises the prospect of an autosomal recessive condition such as in early onset parkinsonism. Fragile X tremor ataxia syndrome (FXTAS) is one of the most common genetic forms of tremor and has a late onset (mean age 60s) associated with progressive gait ataxia, dementia, neuropathy and dysautonomia.[9]

Alcohol and drug sensitivity

Alcohol sensitivity was previously thought to be diagnostic for essential tremor. However, there

Table 1 Axis 1—clinical features

Axis 1 item	Clinical features
Activation conditions	Action
	Postural (position dependent or position independent)
	Kinetic (simple kinetic, intention, task-specific)
	Isometric
	Rest
Tremor frequency	Low frequency (<4 Hz)
	Medium frequencies (4–8 Hz or 8–12 Hz)
	High frequency (>12 Hz)
Body distribution	Focal: head, face, jaw, lips, tongue, voice, arms, legs
	Segmental: more than one contiguous body part (includes bibrachial)
	Generalized
Age at onset	Infancy (birth to 2 years), childhood (3–12 years), adolescence (13–20 years), early adulthood (21–45 years), middle adulthood (46–60 years) and late adulthood (>60 years)
Past medical history	Relevant illnesses such as thyrotoxicosis, multiple sclerosis
Family history	Suggestive of ET or rarer genetic cause (e.g. FXTAS)
Alcohol and drug sensitivity	Response to alcohol and other pharmacological treatments
Temporal onset and evolution	Sudden (functional or drug/toxic) versus progressive (ET, parkinsonism)
	Stable
	Fluctuating (enhanced physiological tremor)
Other features	Entrainment, distractible, pauses with ballistic contralateral limb movements to target
Other signs	Neurological (e.g. parkinsonism, dystonia, ataxia)
	Systemic signs (e.g. encephalopathy, thyrotoxicosis, liver failure)
Additional laboratory tests	Structural imaging (MRI or CT)
	Receptor imaging (e.g. DAT SPECT)
	Serum/tissue biomarkers
	Electrophysiology (EMG, accelerometry)

ET – essential tremor; FXTAS – fragile-X tremor/ataxia syndrome; DAT SPECT – dopamine transporter single-photon emission computed tomography scan; EMG – electromyography.

is evidence to suggest that the effect of alcohol may be relatively non-specific and common among multiple tremor syndromes. A response to alcohol may suggest a positive response to drugs that affect GABAergic transmission such as primidone or clonazepam. Drug responsiveness may be useful in the context of levodopa for parkinsonian tremor but some patients may not respond to levodopa at all or require higher doses. Neuropathic tremor due to inflammatory neuropathies can in some cases respond to immune-mediated treatments such as intravenous immunoglobulin or rituximab.

Ruling out mimics

A strategic approach to diagnosis is contingent on identifying tremor and distinguishing it from other hyperkinetic movement disorders. Occasionally, 'tremor' can be used by patients or clinicians to describe alternative movements such as myoclonus (rapid brief jerky movements that can be semi-rhythmic) or clonus (upper motor neuron sign associated with the stretch reflex). Epilepsia partialis continua, often seen in the face or hand unilaterally, represents frequent focal partial motor seizures and can be distinguished by the persistence in sleep,

the arrhythmic, unilateral nature of the movement and worsening with touch (tactile stimulus sensitivity). In patients with parkinsonism, a rhythmic movement of the leg akin to tremor can sometimes be seen when the patient is trying to initiate gait.

Anatomical distribution of tremor

Tremor can be focal, affecting a single body part; segmental, affecting two or more contiguous body parts (or bibrachial); hemitremor, affecting one side of the body; and generalized.[2] The presence of tremor in body parts other than upper limbs can be helpful diagnostically and may open an avenue for specific treatment options, for example, botulinum toxin for head tremor. Leg, jaw or chin tremor at rest is sometimes seen in parkinsonism. A tremor in the head can be seen in isolation, in dystonic tremor, tremor arising due to cerebellar disease and essential tremor. On the contrary, the presence of head tremor is a red flag against the diagnosis of Parkinson's disease or neuropathic tremor. Tremor of the legs on standing is orthostatic tremor. Tremor of the voice is most commonly seen in dystonic tremor and can be heard on examination.

Frequency

The frequency of tremor (the number of times the body part oscillates per second, measured in Hz) is recorded by motion sensors (such as accelerometers) and electromyography. It is not often particularly helpful for the diagnosis of tremor as there is significant overlap among tremor types. However, there are situations in which it can help, particularly with fast or slow tremor frequencies. Orthostatic tremor of the legs on standing is typically associated with a frequency of 13–18 Hz.[10] Parkinson's disease-related tremor is typically described at 4–8 Hz but overlaps significantly with other more 'benign' tremor types such as essential tremor. Myorhythmia describes a slower oscillatory movement, often jerky, and is typically seen at rest in the limbs and cranial muscles at 1–4 Hz. There is some overlap in frequency with palatal, intention and HT. It often has an identifiable underlying aetiology such as a lesion within the brainstem, diencephalon and cerebellum, with associated corresponding signs.

Activation conditions

Tremor should be defined according to the state it is seen in. The two main states are rest and action.[2] Action tremor includes postural tremor (during contraction of muscles) which can either be position independent or position dependent, simple kinetic tremor (during movement), intention tremor (crescendos with limb approaching target), task-specific (e.g. only when writing or playing an instrument) and isometric tremor (when contracting against a stationary rigid object).

Rest tremor occurs when there is no voluntary muscle contraction in a body part. It is enhanced by cognitive tasks (e.g. counting backwards) and movement of another body part (e.g. contralateral arm). In Parkinson's disease, rest tremor is typical, abating with action. Tremor in the hand can also be seen when the patient is walking with the arms assuming their natural 'swing'. Re-emergent tremor, usually associated with Parkinson's disease, can be seen when a patient outstretches their arms and sustains a posture with the emergence of tremor after a short latency.

Tremor severity

The severity of tremor and its impact on functional tasks helps the clinician identify whether specific treatment is necessary and whether successive treatment trials or even surgical options are warranted. Tremor amplitude has a poor correlation with patient-reported disability.

Signs of systemic illness

General medical signs can also be useful, for example, a patient with features of thyrotoxicosis or with encephalopathy in the context of hepatic failure or lithium treatment.

Neurological signs

Other neurological features such as parkinsonism (bradykinesia of rapid movements such as finger tapping, rigidity of the limbs with/without activation of the contralateral limb, gait disorder) is indicative of the cause. Pen and paper tasks such as drawing an Archimedes spiral, a sample of handwriting and line drawing are useful diagnostically. In parkinsonism, small tight, bunched up spirals or writing may be differentiated from dystonic and essential tremor. They are also useful for assessing progression and response to treatment.[11] Dystonic posturing of a body part where tremor is visible helps diagnose dystonic tremor.

Investigations

In a clinical setting, tremor is often diagnosed on the clinical features rather than the results of investigations, although these can prove helpful to exclude other conditions.

Electrophysiological tests

Nerve conduction studies and electromyography (EMG) are very occasionally useful, namely in the context of neuropathic tremor, where a demyelinating neuropathy is often seen. Electrophysiological tremor analysis with EMG and accelerometry is niche and often only available at tertiary neurology centres. It allows confirmation of tremor, consideration of mimics (myoclonus) and Fourier analysis to determine tremor frequency (and effects on frequency of weight loading the limb). Although not routinely performed, coherence studies of homologous limb muscles can provide information on the likelihood of functional or orthostatic tremor, where uniquely high inter-limb coherence is seen. Further, electrophysiological criteria for the diagnosis of functional tremor have been validated.[12]

Imaging

Brain imaging for unilateral tremor, unusual tremor syndromes such as orthostatic tremor and lesional tremor syndromes (e.g. palatal tremor, HT) is employed, most typically with magnetic resonance imaging (MRI). In addition, dopamine transporter (DAT) single-photon emission computed tomography (SPECT), such as ^{123}I-ß-FP-CIT, can effectively distinguish between early PD (abnormal result) and ET (normal result).

Serum biomarkers

Occasionally, genetics can be useful but this is predominantly in the context of tremor associated with other movement disorders such as myoclonus, dystonia or ataxia. Blood tests for thyroid function, copper studies, routine biochemistry and haematology are common screening tests.

Axis 2—aetiology

Axis 2 of the tremor classification simply highlights whether the tremor is acquired, genetically defined or idiopathic (in which case it is coined as familial or sporadic). Deciding on axis 2 often comes from clinical features of the tremor from axis 1.

Pathophysiology of tremor

Most forms of tremor are associated with oscillatory activity between various nodes in the brain that includes the cerebellum, thalamus and cortex (cerebello-thalamo-cortical loop). Specific tremor types involve other brain areas linked to this network such as the basal ganglia in parkinsonian[13] and dystonic tremor, the cerebellum and supplementary motor areas of the cortex in orthostatic tremor,[14] the olivary nucleus in palatal tremor[15] and the dependence on the peripheral motor-sensory nervous system for neuropathic tremor.[16] ET has a few competing hypotheses that are not mutually exclusive. This includes a cerebellar neurodegenerative process favoured by a few, a GABAergic hypothesis and a network hypothesis implicating the dominant cerebello-thalamo-cortical network.[17] Functional tremor is rather distinct, pathophysiologically and discussed separately.

Tremor syndromes (summarized in Table 2)

Essential tremor

ET is likely the commonest tremor disorder in clinical practice. ET is a tremor predominantly of the arms, without other neurological signs but may affect other body parts such as the head. It is a bilateral, symmetrical, upper limb action tremor with postural components (e.g. arms outstretched) and a kinetic component (e.g. with finger–nose movements).[2] There may be a bimodal peak with a younger onset (second or third decade), often with a dominant family history and an older onset that some advocate separating in to a distinct diagnostic category.[18]

As with some other tremor types, ET can impair the ability to carry out activities of daily living and often transiently improves with small amounts of alcohol. Tremor or other movement disorders such as dystonia may be present in the family occasionally leading to an axis 2 diagnosis of a dystonic syndrome. The frequency of tremor should be over 4 Hz (slower movements suggest myorhythmia with alternative underlying aetiologies). There has been some debate about whether ET is neurodegenerative but the evidence is not robust and it may well be a non-degenerative, slowly progressive process.[14,19]

Despite the dominant family history and high penetrance, there has been a failure to find a common, ubiquitous genetic cause with a few exceptions in smaller subpopulations. Associations have been found on genome-wide association studies (GWAS).[17] This may relate to the clinically and genetically heterogeneous nature of this condition, particularly with onset in the elderly, where a variety of competing aetiologies should be suspected. It seems likely that ET is a syndromic diagnosis with a large number of underlying specific genetic and environmental aetiologies. Over time, it is likely that these will be increasingly segregated. Nevertheless, it remains a useful clinically diagnostic term for the purposes of patient understanding, therapeutic management and coordinating patient support services.

Enhanced physiological tremor

A 10 Hz physiological tremor can be measured in healthy individuals in an outstretched hand. An enhanced form of this physiological tremor is common and can be seen in some patients in the form of a bilateral upper limb action tremor, particularly associated with high emotion, tiredness or caffeine. It is driven by enhancement of the mechanical reflex and descending high frequency central neurogenic oscillations. The tremor amplitude is typically not large and does not have significant manifestation in other body parts on examination although some patients may feel the tremor elsewhere. ET is the key differential but the reversibility and electrophysiological findings can help distinguish the two. A component of the measured frequency is reduced with weight loading of the limb, not seen with ET.[20]

Other isolated tremor syndromes

Voice or head tremor typically occurs in the context of dystonia or ET but also in an isolated form. Tremor can be associated with the repetitive performance of skilled motor tasks such as writing, playing an instrument or sport.[21] Such task-specific tremors are typically focal, position-specific and can be associated with dystonia or occur in an isolated form. There are other rare focal tremors that may occur in the absence of other neurological signs, such as hereditary geniospasm, which has similarities with brainstem myoclonus and various forms of facial tremor.[22]

Cerebellar tremor

Intention tremor is typical in cerebellar disease. It is a crescendo tremor that increases in amplitude as the tested limb approaches its visual target. It is often confounded with simple kinetic tremor that does not significantly change in amplitude on approach to its target. Intention tremor is rarely an isolated tremor syndrome but rather is typically caused by a lesion in the cerebellothalamic pathway. It is often of a low frequency (<5 Hz) large amplitude tremor affecting

Table 2 Summary of commonest tremor types and treatment

	Type of tremor	Body part commonly affected	Frequency	Other features	Treatment
Essential tremor	Action	Bilateral upper limbs	4–12 Hz	Slowly progressive, family history, alcohol response	Propranolol, primidone, topiramate, gabapentin, VIM lesion/DBS
Enhanced physiological tremor	Postural>kinetic	Bilateral upper limbs	8–12 Hz	Fluctuates with precipitants	Trigger avoidance, propranolol
Dystonic tremor	Action, occasionally rest	Asymmetric upper limbs and head	3–5 Hz	Task and position specific, jerky, null point, geste	Trihexyphenidyl, clonazepam, GPi/VIM lesion/DBS
Cerebellar tremor	Intention	Asymmetric or symmetric limbs, head and trunk	<5 Hz	Nystagmus, dysarthria, limb and gait ataxia	Clonazepam, botulinum toxin, VIM DBS
Holmes tremor	Kinetic>rest	Unilateral upper limb	<5 Hz	Ataxia, hemiparesis	Levodopa, thalamotomy
Palatal tremor	Rest	Palate (occulofacial structures if symptomatic)	<3 Hz	Ear clicks (essential), nystagmus, abnormal imaging (including HOD) (symptomatic)	Botulinum toxin, Gabapentin for nystagmus, consider quinine or trihexyphenidyl
Parkinsonian tremor	Rest, re-emergent	Asymmetric upper limbs, legs, jaw	3–6 Hz	Rigidity, bradykinesia	Levodopa, trihexyphenidyl, clozapine, VIM/STN/GPi lesion/DBS
Neuropathic tremor	Action	Bilateral upper limbs	4–8 Hz	Demyelinating neuropathy	Propranolol, pregabalin, IVIg, rituximab, VIM DBS
Orthostatic	Isometric on standing	Bilateral lower limbs	13–18 Hz	Unsteady on standing, EMG confirmation	Gabapentin, clonazepam, VIM DBS
Functional	All states	Upper limbs	3–6 Hz	Entrainment, pauses, variability, coherence	Clear explanation, multidisciplinary therapy, withdraw medications
Drug-induced	Action>rest	Bilateral upper limbs	8–12 Hz	Drug history	Propranolol, acetazolamide, tetrabenazine

VIM – ventral intermediate nucleus; DBS – deep brain stimulation; GPi – globus pallidus internus; HOD – hypertrophic olivary degeneration; STN – subthalamic nucleus; IVIg – intravenous immunoglobulin; EMG – electromyography.

head, limbs and trunk without a rest component.[2] It is caused by lesions in deep cerebellar nuclei, cerebellar outflow tracts or ascending connections to thalamus or cortex. The commonest aetiologies include stroke, drugs (e.g. alcohol, carbamazepine), multiple sclerosis, neurodegenerative diseases (e.g. hereditary ataxias) and posterior fossa tumors. Cerebellar disease can cause other forms of tremor such as HT or palatal tremor.

Dystonic tremor

Dystonia is characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive movements, postures, or both.[23] Dystonic movements are typically patterned, twisting and may be tremulous. Dystonic tremor can occur in any body part but is commonly seen in the neck (cervical dystonia), voice or limb when associated with tremor. Some patients with dystonia have tremor in other body parts not associated with dystonia and the term 'tremor associated dystonia' is used. Features commonly seen in dystonic tremor include geste antagoniste, where the patient's own tactile input (e.g. touching their chin in tremulous cervical dystonia) can subdue the dystonia or tremor. Dystonia can often be task-specific such as in writer's cramp, where tremor may co-exist. Dystonia in one limb may be seen to overflow to neighbouring muscles or be mirrored in the contralateral limb. There can be muscle hypertrophy and associated discomfort, for example in cervical dystonia. A null point for tremor is seen in certain positions, where the tremor is less severe. The tremor is often asymmetrical, jerky and affects one side of the body more than the other.[24]

Wilson's disease

This is a very rare condition but given its morbidity and treatability, is worth mentioning. It may cause a wing-beating upper limb tremor, or any form of tremor including HT, although very rarely as an isolated action tremor.[22] Usually, other features such as liver disease or other movement disorders (e.g. dystonia, dysarthria, parkinsonism), Keiser–Fleischer rings at the corneal–scleral junction or behavioural changes are also seen. It predominantly affects younger people and is rare to present beyond the age of 35 years.[25]

Holmes tremor

HT is described as a rest and intention tremor of slow (low) frequency, typically below 5 Hz. It often has a proximal limb component and there is commonly a postural component, although this is not necessary for diagnosis. Holmes' tremor is almost always attributable to brain lesions within the brainstem, cerebellum or thalamus. As such, this tremor has also been known as rubral, mesencephalic, cerebellar-outflow or thalamic tremor. The most common aetiologies are vascular, for example, ischaemic or haemorrhagic stroke. Other insults such as traumatic brain injury are the next most common group. The tremor develops after a mean latency of two months (with a wide possible range) after insult to the brain.[6] Due to the lesion location, additional signs such as hemiparesis and ataxia are common.

Palatal tremor

Palatal tremor is often a slow frequency tremor and has previously been referred to as palatal myoclonus. The palate rhythmically or semi-rhythmically, rises up and down, seen on mouth opening. It can be isolated, often with ear-clicking, where it is usually unaccompanied by other signs and some suggest a considerable proportion of such cases are functional (psychogenic) in origin.[26] Symptomatic palatal tremor is usually caused by an identifiable lesion, for example, a stroke in the posterior fossa in an area known as the Guillain–Mollaret triangle (cerebellar dentate nucleus, red nucleus, inferior olive). In such situations, the inferior olive is deafferented by fibres from the dentate and over a period of time, typically weeks or months after the insult (e.g. stroke), the inferior olives are seen to become bright and swollen on T2-weighted MRI, known as hypertrophic olivary degeneration. There are known rare causes of this such as 'progressive ataxia and palatal tremor', caused by genetic mutations.

Parkinsonian tremor

Tremor occurs frequently in Parkinson's disease and can take the form of rest tremor, postural tremor, kinetic tremor and orthostatic tremor. The classical 'pill-rolling' rest tremor of 4–6 Hz occurs less commonly in atypical parkinsonian conditions. It usually develops asymmetrically at onset but can develop to affect both hands, yet may wane later in the disease. Other body parts can be affected such as the jaw, lips, tongue or legs at rest and it tends to worsen with stress or concentration. Establishing other motor features such as bradykinesia and rigidity are often important in distinguishing parkinsonian tremor form other differentials such as ET. Re-emergent tremor in the outstretched arms can be seen after a short latency (rather than immediately as with typical postural tremor). Hand or finger tremor seen when observing gait is typical for Parkinson's disease. An internal or 'invisible' tremor is more often described by patients with Parkinson's disease than those with other types of tremor such as ET. Involvement of the head is rather unusual in Parkinson's disease and would suggest consideration of alternative types of tremor such as dystonic tremor.

Neuropathic tremor

Neuropathic tremor occurs in select patients with hereditary or inflammatory neuropathies.[27,28] Of the chronic inflammatory neuropathies, anti-MAG neuropathy (a distal sensory neuropathy with the associated anti-MAG antibody) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) are among the most typically associated with limb tremor. Roussy–Levy syndrome was the initial term coined for patients with Charcot–Marie–Tooth disease and tremor or ataxia, now known to associate with a variety of genotypes. The pathophysiology of tremor in inflammatory neuropathies is likely due to maladaptive central networks such as the cerebello-thalamo-cortical network, associated with antibodies targeted to the cerebellum[29] and triggered by impairment in peripheral nerve conduction.[16,30] A recent antibody, neurofascin-155, that targets the cerebellum, has been described in a very small subgroup of patients with CIDP and ataxia or tremor. It is likely that there is a different mechanism at play when tremor occurs in hereditary neuropathies. Tremor is usually that of an action tremor in the limbs and does not typically affect the head, face or voice. Nerve conduction studies demonstrate delayed distal motor latencies, prolonged conduction velocities and prolonged and dispersed F-waves, compatible with demyelination.

Orthostatic tremor

Orthostatic tremor is a disabling rare tremor disorder causing an insidious onset of difficulty with standing due to a feeling of unsteadiness. Patients do not often complain of tremor as their primary concern. There is usually a short latency (seconds) on standing before the onset of an unsteady feeling. This latency shortens as the disease progresses, over years.[31] After the latency, patients seek postural support to remain standing or else sit down or start walking. Although falling is feared, it is uncommon.[10] Tremor on standing is not usually visible but a fine rhythmic movement can often be palpated from leg muscles. Auscultating the thigh muscles produces a thudding sound, known as the 'helicopter sign'. Diagnosis can benefit from EMG to confirm the typical high-frequency tremor (13–18 Hz) in leg muscles and helps rule out mimics such as orthostatic tremor with a slower frequency (pseudo-orthostatic tremor) and orthostatic myoclonus (both of which have higher rates of identifiable causes).[32] Nevertheless, the diagnosis is quite characteristic from the clinical findings and a pragmatic approach could be to bypass this test. The pathophysiology is uncertain but seems to involve a cerebello-thalamo-cortical network with other nodes that may include the pons and supplementary motor area.[33]

Functional tremor

Functional (psychogenic) tremor is a movement disorder reported by the patient as involuntary,

yet has properties similar to a voluntarily generated movement. There seems to be an abnormal expectation and sense of agency for self-generated movements.[34] A 'precipitating factor' is identifiable to occur in a majority of cases, prior to tremor onset.[35] Such triggers include infection, injury, migraine, surgery, high emotion and syncope, leading to a movement without a subjective, normal sense of voluntary movement. Psychiatric disorders appear more prevalent but are not requisite and should not form the foundation of this diagnosis.

The tremor often varies and is distractible, often more severe with attention to the tremulous body part such as during examination.[36] Rhythmic tapping of the patient's contralateral limb to a dictated rhythm is effortful for the patient, requiring undue attention and seems to 'entrain' the rhythm of the tremulous limb or body part to that of the tapping limb. This may be a partial shift in the frequency of the tremulous limb rather than complete entrainment. Brief pauses in the tremor can be attained when a brief goal-directed movement is made on command in the contralateral limb.[37] Tremor may be seen at rest, posture and with movement (often of similar amplitude across states) and can vary significantly in frequency. Disability can be selective and tremor amplitude can worsen with weight loading of the limb and improve or alter with placebo interventions such as applying a tuning fork to the tremulous limb. Electrophysiological tests based on these clinical features have been described[38] and validated[12] to confirm and reinforce the diagnosis but are often only available in very few neurological centres.

Drug-induced tremor

Pharmacotherapies are a common cause of tremor and multifocal myoclonus (often confounded with tremor). There are a range of underlying aetiological mechanisms. This can include tremor due an idiosyncratic effect of the medications, a toxic-overdose phenomenon, a drug-induced parkinsonism and as part of a tardive disorder. There are a few medications that have a strong association with tremor and a high index of suspicion should be held, particularly, if there appears to be a chronological link to the onset of tremor and worsening tremor with dose escalation. The most important causes of drug-induced tremor include valproate, lithium (where levels can be normal and tremor or myoclonus can manifest after years of treatment yet be refractory to medication withdrawal), amiodarone, thyroxine overdose and anti-rejection drugs (e.g. tacrolimus). There are a variety of other causes for multifocal myoclonus and tremor including drugs of abuse, selective serotonin reuptake inhibitors, tricyclic antidepressants, antibiotics, anti-epileptics, beta-2 agonists and steroids.[7]

Tardive movement disorders occur after a latency of months or years of dopamine-blocking drugs and are commonly seen in mental health treatment settings. They typically present as an orolingual chorea but also can manifest as other movement disorders including tremor. They are induced by use of dopamine receptor-blocking drugs over years (or occasionally months) and often do not remit, potentially even worsening, when the drug is stopped.[39] In this clinical context, one should establish the impairment/disability caused by the tremor and measure this against the need for ongoing treatment, in discussion with the prescribing psychiatrist.

Treatments for tremor

Unfortunately, apart from invasive neurosurgical options for a few tremors, treatment for tremor is disappointing. It is uncommon to completely alleviate most tremors with oral treatments and so setting realistic expectations is important. Modest tremor reduction might be achievable, particularly with low amplitude tremor. Side effects are common from the medications available, especially in the elderly population. Reassurance can be sufficient for some patients when the tremor is mild and the aetiology is not lesional or degenerative. The amplitude or objective severity of tremor is a weak predictor of patient-led demand for treatment. Other factors such as patient perception of severity and effect on activities of daily living should be considered when approaching treatment.

Non-pharmacological approaches

There are increasing numbers of wearables and appliances available to patients. Technology, such as voice recognition software can help. An experienced occupational therapist may be able to provide guidance regards weighted appliances and limb weights. For patients with orthostatic tremor, portable seating such as a tripod can be of functional benefit.

In the case of functional tremor, a multidisciplinary approach with therapists experienced with these disorders is the key.[40,41] Making a rapid, positive diagnosis (rather than purely one of exclusion) and being open with the patient (using of clinical signs to reinforce diagnosis)[42] and provision of adequate explanatory information (e.g. patient-facing websites such as www.neurosymptoms.org) is often a key component to successful future management. It is important to identify and manage any precipitating factor (e.g. alleviating pain with analgesics) and coexisting mental health problem, although avoiding relying on the latter for a diagnosis. Avoid drug treatments and aim to wean unnecessary medications.

Oral agents

Small doses, titrated slowly and according to side-effects is a generic treatment approach. Propranolol is often used in many tremor types including ET, taking care with asthma, heart failure and diabetes. The long-acting formulation has better compliance and a dose between 240–320 mg/day may be most effective. Primidone, an anticonvulsant, is one of the most effective treatment options for ET, particularly at higher doses up to 750 mg/day but is often poorly tolerated. It needs to be titrated very slowly from 25 mg (half of a 50 mg tablet). Topiramate has been shown to be effective as well as gabapentin and alprazolam.[34,35] Judicious use of small quantities of alcohol or oral treatments such as clonazepam/propranolol/primidone on an adhoc basis prior to social gatherings is used by some patients as a practical option. Dystonic tremor can be treated with clonazepam or trihexyphenidyl.

Levodopa, although helpful for rigidity and bradykinesia in Parkinson's disease, is less reliably effective for tremor and higher doses of levodopa may be needed. An alternative oral agent includes clozapine, although this is rarely used for this indication given the monitoring requirements. Trihexyphenidyl should be avoided due to likely side effects. As with many of the low-frequency tremors (intention, palatal, myorhythmia), HT is difficult to treat. However, some patients seem to respond to levodopa therapy that should be trialled.[6]

For palatal tremor, gabapentin could be used for the ocular component if present. There are no good controlled trials for the treatment of neuropathic tremor. However, oral agents similar to those used for the treatment of ET could be considered as well as treating the underlying inflammatory neuropathy.

For drug-induced tremor, if there is uncertainty regards the trigger, a trial of drug reduction and withdrawal may be considered depending on the necessity of the drug.

Botulinum toxin

Intramuscular injections of botulinum toxin into upper limb muscles rarely have systemic side effects. Focal weakness that can result, is reversible over a few weeks or months. In turn, if beneficial, such injections would require repeating regularly for persisting symptomatic benefit. Toxin injections are not ubiquitously used as treatment for tremor but are increasingly recognized by some to be an option in otherwise refractory cases, particularly those not suitable or amenable to surgical intervention.[43,44]

Functional neurosurgery

Deep brain lesions such as strokes involving the thalamus have been known to ablate tremor. Interfering with this node in the cerebello-thalamo-cortical oscillatory loop, surgically, has been proven to be very effective for the treatment of tremor. This can be achieved with either radiofrequency ablation using an implanted electrode into the brain, stereotactic radiosurgery (SRS) with gamma knife (multiple focused beams of radiation to create

a brain lesion), MR-guided focused ultrasound (MRgFUS) (multiple focused beams of ultrasound) or implantation electrodes for deep brain stimulation (DBS). The preferred target for most tremor types is the ventral intermediate nucleus of the thalamus (VIM) and nearby structures. Although invasive, they are capable of reducing ET by more than 80% in the short-term, far more effective than pharmacological approaches. Decisions between these approaches are made on availability, expense, safety and long-term efficacy.[45]

MRgFUS in particular, has received a lot of attention in the press recently due to its non-incisional approach (similarly to SRS) and as such may in future be worth considering in suitable patients,[46,47] not conducive to DBS. However, MRgFUS is currently only available in one centre in the UK at the time of writing and data on longer-term durability is lacking. Benefits of DBS and MRgFUS over SRS are the immediate improvement in tremor as compared with the delayed response (months) with SRS. Although large trials supporting functional neurosurgery are generally lacking for these other forms of tremor such as dystonic tremor, orthostatic tremor, HT and neuropathic tremor, there has been improvement in case series.

Conclusion

Tremor is one of the commonest movement disorders. Recognizing the different tremor syndromes can help guide diagnosis and specific treatments. Investigations are not often critical to diagnosis yet structural brain imaging and functional imaging for dopamine transport are important in a few syndromes. While not widely available, electrophysiological measurements with EMG and accelerometry can be valuable in the characterization of tremors and are crucial in select cases. Deeper phenotyping of tremor syndromes will allow better discovery of underlying causes such as genetics.[3] Oral pharmacological therapies have a modest overall benefit. Newer options will be based on our better understanding of tremor. Alternative treatments such as lifestyle adaptations, non-pharmacological therapy for functional tremor and botulinum toxin in refractory organic tremor cases can be considered. Surgical therapies in the form of DBS or stereotactic brain lesioning are among the most overall effective treatments for tremor but naturally are invasive.

Conflict of interest statement

I have received travel assistance for conferences from Allergan and Ipsen.

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