Chapter 20
Tremor

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Clinical Pearls

- Rest tremor is most commonly associated with parkinsonism
- Action tremor occurs in postural and kinetic types
- Essential tremor is typically very slowly progressive over many years

Introduction

Tremor is an involuntary oscillatory movement of a body part. Tremor is a very common neurologic sign that is produced by many neurologic and systemic diseases. It is therefore important to perform a careful history and physical examination, looking for other signs and symptoms that lead to a specific diagnosis.

Patients should be characterized in terms of medical history (age of onset, family history, temporal evolution, exposure to drugs and toxins), tremor characteristics (anatomical distribution, activation condition, tremor frequency) and associated systemic and neurologic signs. Tremor is then broadly classified as isolated tremor (tremor is the only physical abnormality) or combined tremor (tremor occurs in combination with other neurologic or systemic signs).

The anatomical distribution of tremor should be carefully documented. Tremor can be focal (only one body region is affected, such as the voice, head, jaw, or limb), segmental (two or more contiguous body parts in the upper or lower body are affected, such as head and arm tremor, or when tremor is bi-brachial or bi-crural), hemi-tremor (when one side of the body is affected), and generalized (when tremor affects the upper and lower body, bilaterally).

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The identification of activation conditions is critical. Rest tremor occurs in a body part that is not voluntarily activated. It is present when a patient makes an effort to relax and is given ample opportunity to relax the affected body part. Rest tremor should be assessed when the body part is completely supported against gravity. In Parkinson disease, rest tremor amplitude almost always diminishes, at least transiently, during purposeful movements, and tremor amplitude typically increases during mental stress (e.g., mental status testing) and while walking or performing voluntary movements with another body part. Rest tremor may occur in advanced essential tremor and dystonic tremor, but these tremors do not subside during voluntary movements.

Action tremor occurs while voluntarily maintaining a posture against gravity (postural tremor) or while performing a voluntary movement (kinetic tremor). Intention tremor occurs when patients perform a precise movement toward a visual target (e.g., finger-nose-finger testing). There is typically little tremor during the initial movement toward the target, but there is a crescendo tremor as the target is approached. This type of tremor is a sign of dysfunction in the cerebellothalamic pathway. It usually occurs in association with other brainstem or cerebellar signs.

Other forms of action tremor are position-specific tremor during the performance of a specific position or posture, task-specific tremor during specific activities (e.g., writing), and isometric tremor during isometric muscle contraction against a rigid stationary object. Re-emergent tremor refers to a rest tremor that subsides for several seconds and then re-emerges when an upper limb is voluntarily moved from a resting pose to an active posture [1]. Re-emergent tremor is common in Parkinson disease.

Most pathologic tremors have a frequency range of 4–8 Hz, so tremor frequency is usually not helpful diagnostically. There are exceptions to this rule. Myorhythmia and palatal tremor are rare forms of tremor at 1–4 Hz, and primary orthostatic tremor typically has a frequency of 13–18 Hz. Tremor frequency may vary among affected body parts, and it is difficult to estimate without accelerometry or electromyography. A smartphone can be used to measure the frequency of head and extremity tremors.[1]

Acute and Subacute Tremor Disorders

When tremor develops acutely or subacutely (hours, days or weeks), it is usually due to a drug, toxin or acute medical illness, producing an encephalopathy or focal brain lesion (Fig. 20.1). Consequently, there are nearly always other diagnostic signs. Four tremor syndromes are most common: (1) whole body tremulousness with myoclonus, (2) isolated bi-brachial tremor, (3) rest tremor with parkinsonism, and (4) focal or unilateral tremor with associated focal signs. Psychogenic (a.k.a., functional) tremor is also a consideration when tremor begins acutely and there are no other neurologic signs. Beware that tremor due to neurodegenerative disease

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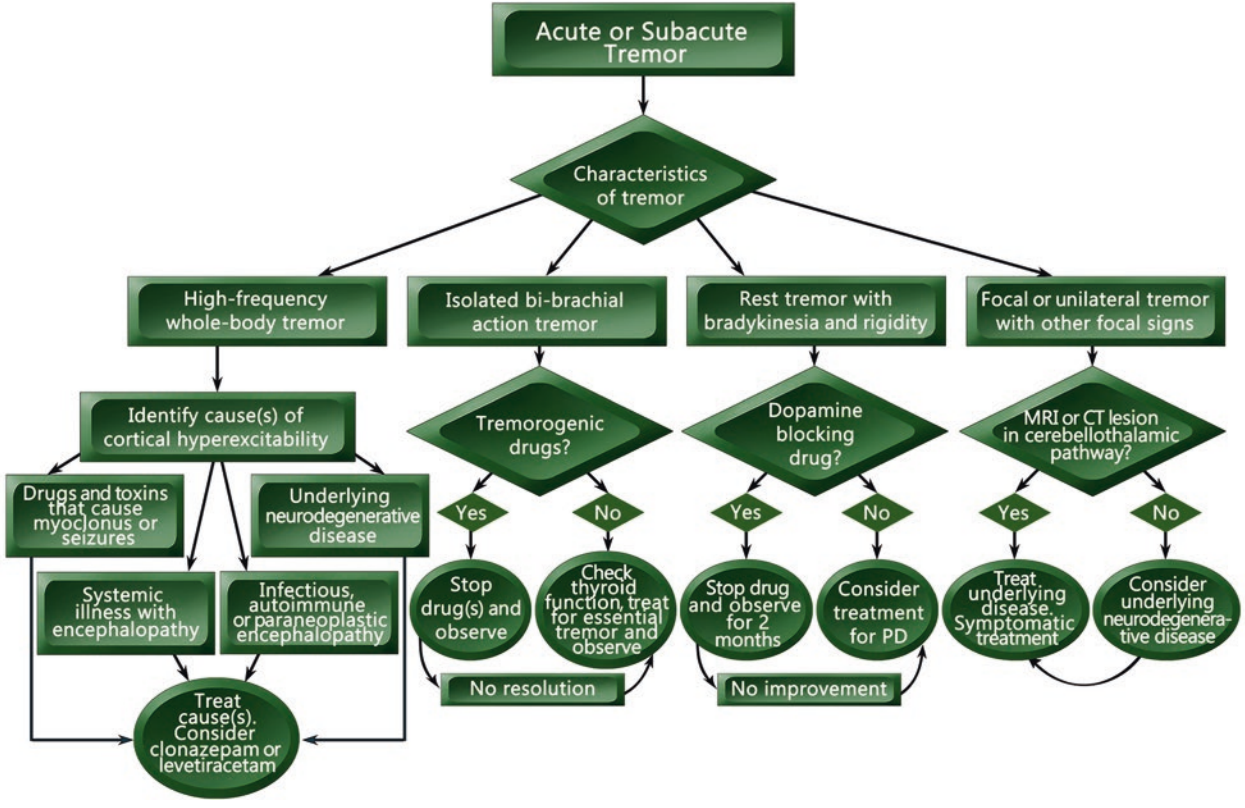

Fig. 20.1 Diagnosis of acute or subacute tremor

(e.g., Parkinson disease) can be recognized suddenly even though it did not begin suddenly. Consequently, a patient's history can be misleading.

Whole Body Tremulousness with Myoclonus

Generalized tremulousness (head-to-toe tremor) is produced by a variety of drugs, toxins, and acute and subacute medical illnesses that increase cerebral cortical excitability [2]. Moreover, chronic neurodegenerative diseases (e.g., Alzheimer disease, Lewy body disease) and hereditary metabolic diseases (e.g., mitochondrial encephalopathies) may cause or predispose one to this type of tremor [3]. The tremor is a rapid 7–20 Hz irregular postural and kinetic tremor that may also occur at rest. This tremulousness is actually rhythmic cortical myoclonus (a.k.a., cortical tremor) and is the most common form of tremulousness in acutely ill inpatients. These patients often exhibit multifocal myoclonic jerks and momentary lapses in limb posture, known as negative myoclonus or asterixis.

When confronted with this syndrome, clinicians should search for systemic illnesses (e.g., liver failure, renal failure, thyrotoxicosis, hypoxia, hypercapnia, sepsis), tremorogenic drugs (lithium, valproate, narcotics, antidepressants, antibiotics), autoimmune and infectious diseases of the central nervous system (e.g., lupus, paraneoplastic disease, ion channel antibodies, HIV encephalopathy) and underlying neurodegenerative disease. Any drug reported to cause tremor, myoclonus or seizures should be regarded as a possible etiology. Treatment is directed at the underlying illness, and benzodiazepines (clonazepam 0.25–1 mg/day) and levetiracetam (250–1000 mg twice daily) are often helpful symptomatically.

Isolated Bi-Brachial Tremor

This tremor syndrome is very common in the elderly, and it is often dismissed as essential tremor, as discussed later in this chapter. However, one should always consider the possibilities of hyperthyroidism and of drug-induced tremor, caused by antidepressants, valproate, lithium, amiodarone, bronchodilators, and many other prescription medications [4].

Rest Tremor with Parkinsonism

Rest tremor with parkinsonism (bradykinesia and rigidity) can be produced by any dopamine receptor blocker (e.g., neuroleptics, antiemetics, metoclopramide) [5]. The parkinsonism produced by these drugs is often indistinguishable from early Parkinson disease, and underlying Parkinson disease should always be considered when a patient develops parkinsonism with a modest dose of atypical neuroleptic or metoclopramide. Drug-induced parkinsonism may take 2–6 months to resolve after withdrawal of the offending drug, and patients should be followed for a re-emergence

of signs due to subclinical Parkinson disease. A dopamine transporter scan may be needed in some patients to determine the presence of underlying nigrostriatal degeneration, most commonly Parkinson disease [5].

Acute Focal or Unilateral Tremor

This tremor syndrome is most commonly caused by lesions in the cerebellothalamic pathway: deep cerebellar nuclei, brachium conjunctivum and contralateral ventrolateral thalamus. Stroke, trauma and demyelinating disease are the most common etiologies. Other focal signs are usually present. The tremor is typically an intention tremor or a combination of rest tremor and intention tremor, called Holmes tremor. Holmes tremor was previously called rubral tremor because it is usually produced by lesions in the vicinity of the red nucleus. These tremors may develop within days of the ictus but more commonly develop weeks, months or occasionally years later, suggesting that deleterious neuroplasticity plays an important role in the pathophysiology of these tremors. These tremors are notoriously refractory to medications (e.g., primidone, propranolol and benzodiazepines). Patients with Holmes tremor should be given a trial of dopaminergic therapy (levodopa or a dopaminergic agonist) [6]. Deep brain stimulation (DBS) and thalamotomy have been used in severe refractory cases [7].

Psychogenic Tremor

Psychogenic tremor often begins acutely and commonly fluctuates in frequency, activation characteristics, or location. It may also relapse and remit [8]. An associated psychiatric illness is frequently not evident.

There are two basic types of psychogenic tremor: coherent type and co-contraction type [9]. The coherent type is a conscious or subconscious rhythmic movement of the affected joint(s). The tremor frequency is usually 6 Hz or less because voluntary rhythmic movement at higher frequencies is very difficult and exhausting. The co-contraction type of psychogenic tremor is usually 6–10 Hz and is produced by a conscious or subconscious coactivation of opposing muscles (extensors and flexors) at the affected joint, producing an enhanced physiologic tremor or so-called physiologic clonus.

Electrophysiology is useful in the diagnosis of both types of psychogenic tremor [10], but diagnosis is often evident by physical exam [11]. Psychogenic tremor decreases when the patient is adequately distracted by cognitive tasks or complex motor tasks. It is nearly impossible to move a joint or multiple body parts simultaneously at two different frequencies that are not integer multiples (harmonics). Therefore, people with the coherent form of psychogenic tremor cannot rhythmically move the same or contralateral extremity at a different frequency, except at subharmonics of the psychogenic tremor frequency. The performance of rhythmic voluntary movement at various frequencies will either suppress the psychogenic tremor or cause its frequency to shift to that of the voluntary movement (entrainment). Similarly, very abrupt voluntary movements (e.g., with the opposite hand) transiently suppress the psychogenic tremor.

The dependence of coactivation tremor on voluntary muscle activation is detected during passive manipulation of the wrist. The amplitude of coactivation tremor is generally mild to moderate and is proportional to the degree of coactivation or stiffness. Coactivation tremor stops during interruptions in coactivation, as when patients are distracted.

To treat psychogenic tremor, one must identify and treat the underlying psychiatric disturbance(s). Unfortunately, the long-term prognosis is frequently poor and depends greatly on the acceptance of diagnosis by the patient and other physicians and therapists. Early diagnosis and therapeutic intervention improve the odds of improvement [12].

Chronic Tremor Disorders

Chronic tremor disorders begin insidiously and are gradually progressive over years. The most common chronic tremor syndromes are essential tremor, rest tremor with parkinsonism (e.g., Parkinson disease), dystonic tremor, and action tremor with ataxia. These four conditions are commonly misdiagnosed due to incorrect characterization of tremor and failure to recognize associated diagnostic signs. It is critically important to distinguish essential tremor and other isolated tremor syndromes (Fig. 20.2) from the combined tremor syndromes (Fig. 20.3).

Essential tremor (ET) is most common. Parkinson disease (PD) occasionally presents with isolated rest or action tremor in the hands or with isolated rest tremor in the lips, tongue, jaw or lower limbs. Electromyography (EMG) is a useful diagnostic test for orthostatic tremor (Fig. 20.3).

Essential Tremor

Essential tremor has not been defined consistently, and this has led to considerable diagnostic confusion in research and clinical practice [13]. Essential tremor is an isolated tremor syndrome of bi-brachial postural or kinetic tremor of at least 3 years duration, with or without head tremor or tremor in other locations, in the absence of other diagnostic neurologic signs, such as dystonia or parkinsonism, and there should be no clinical history of tremorogenic drugs, toxins or hormones. Essential tremor is frequently hereditary, so a family history is common. The required 3 years duration is recommended because this tremor syndrome can be a presenting phenotype of hereditary dystonia and ataxia, and isolated bi-brachial action tremor can be the initial sign or symptom of Parkinson disease. In short, patients may present with bi-brachial tremor that appears to be essential tremor but subsequently develop other signs and symptoms, including parkinsonism, dystonia, ataxia and dementia.

Most patients with essential tremor have mild to moderate tremor that progresses over decades, and a majority of these patients have never seen a physician for their tremor [14]. Nevertheless, some disability from tremor is the rule, and some patients progress to severe disability. Rapid progression over a few years should alert the

clinician to the possibility of a tremorogenic comorbidity such as Parkinson disease or dystonia.

The reported age of onset of essential tremor is usually >40, but this condition develops so insidiously that age of onset is frequently uncertain [15]. Nevertheless, Deuschl and coworkers found that incident hand tremor after age 70 is associated

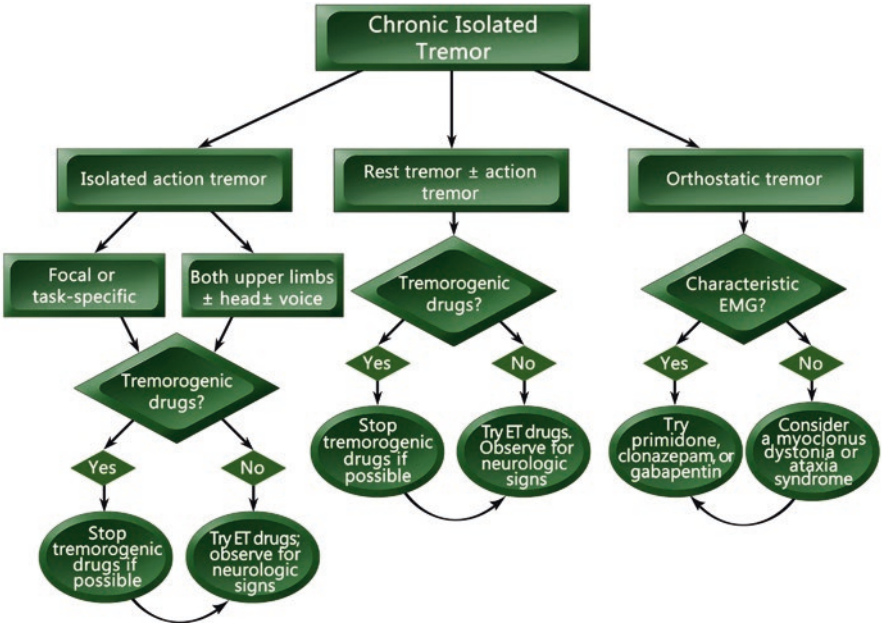

Fig. 20.2 Diagnosis and management of isolated tremor syndromes

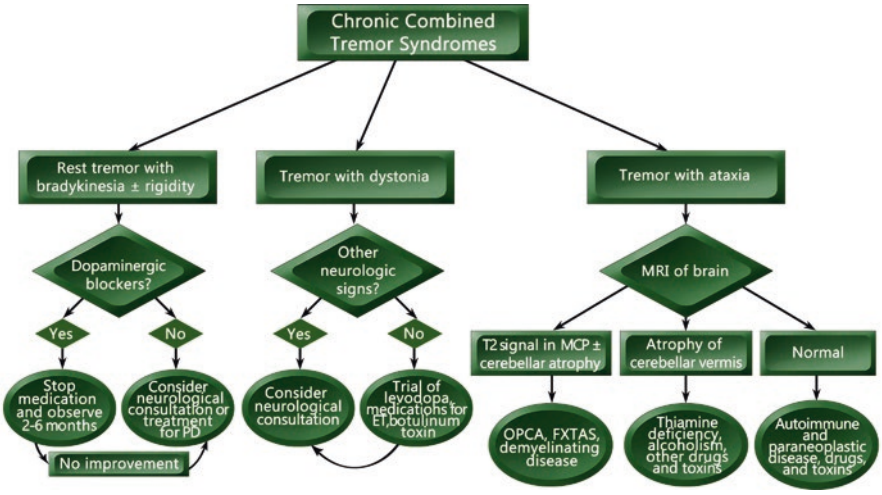

Fig. 20.3 Diagnosis and management of chronic combined tremor

Table 20.1 Drugs for essential tremor and other action tremor syndromes

Drug	Dosage	Common side effects
Propranolol	30–240 mg/day in thrice daily dosing or once daily dosing with extended release	Bradycardia, syncope, erectile dysfunction, fatigue
Primidone	25–300 mg/day in 1–3 divided doses	Nausea, sedation, ataxia, dizziness, and confusion
Topiramate	50–200 mg/day in twice daily dosing or once daily dosing with extended release	Weight loss, anorexia, extremity paresthesias, trouble concentrating, memory loss and nephrolithiasis
Gabapentin	300–2400 mg/day in thrice daily dosing	Dizziness, somnolence, ataxia, nausea

with poor grip strength, cognitive impairment, and increased mortality [16]. There is a small but statistically significant increased risk of dementia in people who develop essential tremor after age 65, and there is also a small increased risk of Parkinson disease (Parkinson disease) in elderly patients with action tremor [17]. Therefore, isolated action tremor in the hands, beginning after age 65, should not be dismissed as essential tremor and instead should be regarded as a possible indication of other age-associated diseases or medication effects.

Treatment should begin with an assessment of the patient's treatment goals and should address comorbidities that affect quality of life, particularly depression. Quality of life scales correlate poorly with essential tremor severity and often reveal a significant psychosocial burden from depression [14]. Counseling may be needed for patients with impaired coping. Self-stabilizing electronic eating utensils are now available (GYENNO, www.gyenno.comand and Liftware, www.liftware.com) for patients with mild to moderate tremor.

The pharmacologic treatment of essential tremor is often unsatisfactory. Propranolol, primidone, topiramate and gabapentin have shown efficacy in controlled studies but are often poorly tolerated by older people (Table 20.1) [18]. Each of these medications should be started at a low dosage (Table 20.1) and slowly titrated each week as tolerated and as needed. None of these drugs has a strong dose-response relationship, so dosing is largely trial-and-error [19]. Many patients stop their medication(s) because of cost, side effects or poor efficacy [20]. Patients frequently report a benefit from ethanol, but objective studies of ethanol have revealed modest benefit in most patients [21]. Furthermore, the benefit is short-lasting, and there is rebound exacerbation of tremor as ethanol is metabolized. Most experts do not recommend ethanol for the treatment of essential tremor, but some patients find it helpful at evening mealtime.

Available drugs, including ethanol, reduce tremor by an average of 50%, notwithstanding an occasional dramatic response. A 50% reduction is adequate for mild-moderate tremor but not for severe tremor. For severe tremor, thalamic deep brain stimulation surgery is an FDA-approved option, and this procedure is capable of reducing tremor by >80% [19]. Unilateral noninvasive thalamotomy with gamma knife radiation [22] is still investigational, but unilateral thalamotomy with high-intensity focused ultrasound [23] was recently approved by the FDA.

Parkinson Disease

Rest tremor occurs in the limbs, lips, jaw and tongue of patients with Parkinson disease and rarely in patients with other causes of parkinsonism (i.e., bradykinesia and rigidity), such as progressive supranuclear palsy and multiple system atrophy [24]. Rest tremor in the hand typically consists of a complex "pill rolling" movement of the fingers. Rest tremor is suppressed, at least transiently, when a voluntary movement or posture is initiated, and re-emergent tremor is also common. Bradykinesia and rigidity may be difficult or impossible to detect in patients with tremor-predominant Parkinson disease [25]. The presence of micrographia, hypophonia, decrement in repetitive finger and hand movements, and REM sleep behavior are important clues to the diagnosis. Head tremor and voice tremor are not typical of Parkinson disease and are most consistent with essential tremor or dystonic tremor. However, it is not uncommon for essential tremor and Parkinson disease to coexist in a patient because both are common. Dopamine transporter single-photon emission computed tomography (e.g., ioflupane I-123 SPECT or DaTscan™) may be needed in some patients, but this method will not distinguish Parkinson disease from other causes of nigrostriatal degeneration (e.g., multiple system atrophy).

Bradykinesia and rigidity respond more predictably than tremor to levodopa. The response of tremor to levodopa ranges from complete to nil, and the reasons for this variability are unknown. Large daily dosages of levodopa (800–1200 mg) in combination with carbidopa may be necessary, but one should always start with a low dosage (carbidopa-levodopa 25/100 one half tab thrice daily), and increase the dosage every week or two in half-tab increments as tolerated and as needed. Some patients, particularly women, are very sensitive to levodopa. A dopamine agonist (pramipexole, ropinirole or rotigotine) may be efficacious when levodopa is not adequate [26]. Unfortunately, the agonists are often poorly tolerated by older patients due to hallucinations, drowsiness, impulse control disorders and peripheral edema. Anticholinergics are generally avoided because of cognitive side effects. Propranolol (Table 20.1) is worth trying if there are no contraindications. Amantadine 100 mg twice daily is occasionally beneficial but may cause confusion, hallucinations, livedo reticularis and peripheral edema. Unfortunately, refractory tremor is not uncommon and is one of the indications for deep brain stimulation surgery. The subthalamic nucleus is the preferred target because tremor, bradykinesia and rigidity respond to this therapy, and medication requirements are reduced [27]. Most patients undergoing surgery are younger than 70 and do not have dementia [27].

Dystonic Tremor

Dystonic contractions are frequently tremulous, and patients with focal dystonia of the face, voice or neck frequently exhibit action tremor in the upper limbs. Dystonic tremor can be rest tremor or action tremor, and the dystonic contractions are often missed when the tremor is severe [28]. Consequently, patients with dystonia are commonly misdiagnosed as essential tremor. Patients with subtle dystonia

(abnormal posturing) of the face, neck, voice or upper limbs may exhibit action tremor that is indistinguishable from essential tremor, so a careful search for dystonic posturing and voice irregularities is required. Dystonic tremor may respond to so-called sensory tricks (*geste antagoniste*) in which touching an affected body part reduces tremor and dystonic posturing.

Dystonia is a highly heterogeneous disorder with numerous etiologies, and in most cases, the underlying etiology is unknown [29]. Treatment of dystonic tremor is largely a trial-and-error process. A variety of medications are tried, including those used for essential tremor (Table 20.1), but there is no consistent response to any medication. Intramuscular botulinum toxin injections may be helpful. Deep brain stimulation surgery is reserved for severe refractory cases [27, 30].

Action Tremor with Ataxia

Determining the etiology of late-onset ataxia is a diagnostic challenge. Sporadic and hereditary ataxias must be considered, even when there is no family history [31, 32].

Tremor and ataxia are common features of multiple sclerosis [33], and tremor is occasionally very disabling. These patients usually respond poorly to medications (propranolol, primidone, benzodiazepines, gabapentin) and may ultimately undergo stereotactic surgery with mixed success [34].

Gait ataxia and mild-moderate action tremor in the upper limbs is a classic syndrome of thiamine deficiency in alcoholics, but this syndrome also occurs in chronically ill people that are malnourished (e.g., cancer patients). Atrophy of the cerebellar vermis is seen with magnetic resonance imaging (MRI) or computed tomography (CT scan). When in doubt, give the patient thiamine! In addition, a careful consideration of drugs (phenytoin, lithium, amiodarone, 5-fluorouracil, cytosine arabinoside) and environmental toxins is needed when confronted with this syndrome. This syndrome can evolve subacutely over a few months and may then be associated with no diagnostic clues on MRI. Early diagnosis and treatment are critical.

Paraneoplastic and other autoimmune cerebellar degenerations (e.g., systemic lupus and steroid-responsive encephalopathy associated with autoimmune thyroiditis) also evolve subacutely. The MRI is initially normal, and the syndrome is associated with several autoantibodies [31].

Olivopontocerebellar atrophy is a form of multiple system atrophy (MSA-Cerebellar) that produces action tremor with other signs of ataxia in 25% of patients [35]. Atrophy of the pons and cerebellum may be seen on MRI, often with abnormal T2 signal in the cerebellar peduncles and pons (hot cross bun sign). Intention tremor is also a feature of some autosomal dominant spinocerebellar ataxias (SCA), especially SCA2, SCA8 and SCA12 [32]. The drugs used for essential tremor are often tried but with little or no success. Thalamic deep brain stimulation has been used in a few cases of SCA with mixed success.

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disorder that occurs in older men (age > 50) and rarely women with premutations (55–200 CGG repeats) in the fragile X mental retardation 1 gene [36]. The core features of this syndrome are gait ataxia and action tremor. Associated features may include cognitive impairment, disinhibited behavior, mood disturbance, peripheral neuropathy, parkinsonism, and dysautonomia, producing impotence and urinary and bowel incontinence. Patients may have grandchildren with fragile X mental retardation. MRI usually reveals cerebral and cerebellar atrophy with abnormal T2 signal in the middle cerebellar peduncles (MCP). Genetic testing is diagnostic. The tremor and ataxia are refractory to pharmacotherapy. Thalamic deep brain stimulation has been effective in reducing tremor, but the other aspects of ataxia may be exacerbated by surgery [37].

Uncommon Isolated Tremor Syndromes

Orthostatic Tremor

Primary orthostatic tremor is a generalized 13–18 Hz tremor that occurs when patients stand [38]. The tremor is very rhythmic and uniquely coherent or synchronous throughout the body. Thus, this form of tremor and psychogenic tremor are the only forms of tremor with a diagnostic electrophysiologic test. The tremor may not be visible. However, the tremulous muscle contraction is often palpable, and auscultation of the tremulous muscle contraction reveals a characteristic rhythmic sound similar to a helicopter. This "helicopter sign" is more easily heard on the speakers of an EMG machine during muscle recording with skin electrodes.

The chief complaint is usually unsteadiness while standing, associated with tremulousness in the lower limbs. This unsteadiness is relieved by sitting or walking. Gait and tandem gait are usually normal. Other forms of orthostatic tremor [39] and myoclonus [40] may occur or increase while standing but do not have the characteristic electrophysiologic findings of primary orthostatic tremor. Primidone, clonazepam and gabapentin are often of modest benefit. A handful of severe cases have undergone ventrolateral thalamic DBS with variable success [41].

Focal and Task-Specific Tremors

Tremor occasionally is limited to one body part (e.g., head, chin, voice, limb) or to one specific activity (e.g., writing or playing a musical instrument), and there may be no other neurological signs or symptoms. There is growing evidence that these focal and task-specific tremors are forms of focal dystonia. The treatment approach is the same as for dystonic tremor [30].

Uncommon Combined Tremor Syndromes

Rest Tremor Without Evidence of Dopaminergic Deficit

Fluorodopa PET (positron emission tomography) and dopamine transporter SPECT imaging of the dopaminergic nerve terminals in the striatum are used clinically and experimentally to assess the health of the nigrostriatal pathway in Parkinson disease and other forms of parkinsonism. With the advent of these methods, it was soon discovered that 4–20% of patients enrolled in Parkinson disease research studies did not have abnormal scans [42]. These patients were labeled with the acronym SWEDD (scan without evidence of dopaminergic deficit), and most of them exhibited asymmetric rest and postural tremor. Subsequent studies suggest that a small percentage of these patients do indeed have Parkinson disease (false negative scans), but most have a variety of other conditions including essential tremor, dystonia, fragile X-associated tremor/ataxia syndrome, progressive supranuclear palsy, multiple system atrophy, and psychogenic tremor [43]. The bottom line is that not all rest tremor is Parkinson disease. Re-emergent rest tremor, micrographia, relatively little action tremor, fatiguing or decrement in rapid repetitive hand movements, and a good response to levodopa favor the diagnosis of Parkinson disease, but the diagnosis is difficult, even for experienced specialists [25, 44, 45].

Myorhythmia and Palatal Tremor

Myorhythmia is an unusually slow 1- to 4-Hz tremor that affects various combinations of the face, jaw, throat, tongue, head, eyes, torso and extremities [46, 47]. Virtually all patients have pathology in the brainstem or cerebellum. Stroke is the most common etiology, but demyelinating disease, Whipple disease, celiac disease, Hashimoto encephalopathy, paraneoplastic disease, Wernicke disease, olivopontocerebellar degeneration, viral encephalitis, and collagen vascular disease have all been described. When the etiology is stroke, myorhythmia typically begins weeks to months after the ictus, suggesting that secondary neuroplastic changes release or produce abnormal rhythmic brainstem and bulbospinal activity. Myorhythmia is rare, but it is important to recognize because the underlying etiologies are often treatable. The symptomatic treatment of myorhythmia is generally unsuccessful [46]. Olivary hypertrophy (seen with MRI) and 1–3 Hz palatal tremor (a.k.a., palatal myoclonus) often occur when the cerebello-olivary pathway is affected [48]. This tremor is asymptomatic and is generally one of multiple signs of brainstem or cerebellar pathology.

Oculomasticatory myorhythmia and oculofacioskeletal myorhythmia are classic signs of Whipple disease affecting the central nervous system [49]. There is a characteristic pendular convergent-divergent movement of the eyes that is synchronous with movements of the face [46]. The classic clinical triad of Whipple disease is the combination of gastrointestinal malabsorption, supranuclear gaze palsy, and oculomasticatory myorhythmia, but isolated central nervous system signs and symptoms

may occur. Whipple disease is treatable with trimethoprim-sulfamethoxazole or with ceftriaxone in patients allergic to sulfa, so the presence of myorhythmia should alert clinicians to the possibility of this rare treatable disease.

Wilson Disease

About 50% of patients with Wilson disease present with neurologic or neuropsychiatric signs and symptoms, and tremor occurs in more than half of these patients [50, 51]. Wilson disease is often considered in the differential diagnosis of tremor, but neurologic Wilson disease rarely if ever starts after age 55. There are no reports of Wilson disease presenting as an isolated tremor syndrome. Signs of dystonia, ataxia or parkinsonism are always present in combination with asymmetric rest, postural or intention tremor in the upper limbs and frequently elsewhere [51].

Tremor Associated with Peripheral Neuropathy

Upper extremity action tremor often occurs in patients with acquired and hereditary (Charcot-Marie-Tooth) demyelinating polyneuropathies [52]. Medications for essential tremor are often tried with little success, and rare cases have undergone stereotactic surgery with mixed success.

Future Therapies

All forms of tremor are relatively refractory to pharmacotherapy. Virtually all forms of tremor emerge from oscillation in the corticobulbocerebellothalamocortical loop, and the ventrolateral thalamic nucleus (ventralis intermedius) appears to be an effective target for any tremor treated with stereotactic surgery [7]. From the standpoint of new drug development, additional understanding of the pathophysiology of tremorogenic oscillation in the corticobulbocerebellothalamocortical loop, particularly the ventrolateral thalamus, is needed to identify targets for drug development. Aside from Parkinson disease, all drugs for tremor were discovered serendipitously or by trial and error.

Many elderly patients do not qualify for DBS surgery due to comorbidities, or they are simply averse to the risks of invasive surgery. Unilateral high-intensity transcranial focused ultrasound is an option for these patients [23].

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