Tremor: Phenomenology, Etiology, Diagnosis, and Treatment

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Tremor is an involuntary rhythmic, oscillatory movement produced by synchronous or alternating contractions of antagonist muscles. Tremor is one of the most common movement disorders and also one of the most common neurological symptoms. A wide variety of etiologies can cause tremor, with essential tremor being the most common. Parkinson's disease, multiple sclerosis, and drug-induced tremors are other etiologies commonly seen in clinical practice. Diagnosis of the specific etiology of tremor is based on the clinical characteristics of the tremor as well as associated symptoms. The phenomenology of tremor including whether the tremor is present at rest, with posture or with action, allows classification of tremor. Imaging studies, while not in themselves diagnostic, can help rule out structural etiologies. Dopamine transporter imaging is a recent modality that can help distinguish essential tremor from parkinsonism. The treatment of tremor is based on etiology and, where possible, treatment of the underlying disease state. Deep brain stimulation of the thalamus can be an effective treatment modality in cases of medication-resistant tremor.

29.1 Phenomenology of Tremor

Tremor is one of the most common movement disorders and essential tremor is the most prevalent pathological tremor in adults [1, 2]. Tremor is defined as an involuntary rhythmic, oscillatory movement produced by synchronous or alternating contractions of reciprocally innervated antagonist muscles [3, 4]. The hands are most commonly involved although the legs, voice and head may also be affected. Tremors can be classified by their distribution and frequency, as well as by the "state of activity." The state of activity refers to whether the tremor occurs at rest or with action [3, 5, 6]. The following definitions are often applied:

1. *Rest tremor* is observed when the affected body part is supported against gravity and is not voluntarily activated.

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2. *Action tremor* is observed during voluntary contraction of muscles and has the following subtypes:
   (a) *Postural tremor* occurs during voluntary maintenance of a position against gravity (e.g., holding hands outstretched in front of the body).
   (b) *Kinetic tremor* occurs during any aspect of voluntary movement. It can be present when the movement begins, during the course of movement, and as the target is reached (intention tremor).
   (c) *Task-specific tremor* is a type of kinetic tremor that occurs primarily during the execution of a specific task, such as writing or singing.
   (d) *Isometric tremor* is present during muscle contraction that is not accompanied by a change in position of body part (such as maintenance of tightly squeezed fist).

Tremor subtypes and common etiologies are listed in Table 29.1.

29.2 Etiology of Tremor

Essential tremor (ET), Parkinson's disease (PD), multiple sclerosis (MS), and medications are common causes of tremor in clinical practice. However, just as the phenomenology of tremor is varied, the possible etiologies for tremor are numerous, and careful attention to the history and details of the examination are required to ascertain the specific cause.

29.3 Physiological Tremor

A fine action tremor is seen in the majority of people under certain circumstances and is called a physiological tremor [7]. It is a low-amplitude, high-frequency tremor that is often not symptomatic. Enhanced physiological tremor (EPT) refers to a state where the baseline tremor is exacerbated by anxiety, exercise, metabolic disorders such as hyperthyroidism, and drugs including amphetamines, anticonvulsants, antidepressants, beta-receptor agonists, and caffeine [3]. The frequency of EPT ranges from 8 to 12 Hz and is affected by the mechanical properties of the oscillating limb. Unlike ET, the frequency of EPT can be reduced by mass loading, for example, with a lead-weighted wristband.

29.4 Essential Tremor

ET is by far the most common pathological tremor. The term (*tremor semplice essenziale*) was coined by Burressi to describe an isolated action tremor in the absence of other neurological signs [8]. Critchley wrote the first detailed review of ET and considered it to be heredofamilial [9]. Recent observations have raised the issue that it may be a neurodegenerative process with additional symptoms developing over time and with specific genetic etiologies in some cases [2, 10]. Therefore, ET may present in a variety of clinical forms with differing pathological substrates [11, 12]. Video 29.1 demonstrates the postural and intention tremor seen in ET.

ET can be either hereditary or sporadic. The prevalence of ET (0.9 %) is comparable to that of epilepsy (0.7 %). The prevalence increases with age, and ET affects about 4–6 % of people aged 65 years or older [13, 14]. ET presents as a postural and kinetic action tremor, typically bilateral, involving the arms and, in some cases, the head. The voice may also be affected. The tremor may spread to involve the legs, chin, and trunk [15, 16]. Tremor frequency is between 4 and 12 Hz and is inversely related to age with older patients having a lower frequency [15, 17]. Isolated head tremor may also occur, and in such cases cervical dystonia (CD) is a diagnostic consideration, particularly if there is a directional component [6]. Asymmetric hypertrophy of the cervical muscles, especially the sternocleidomastoid, may be observed in CD but is very unusual in ET [18]. CD can coexist with ET and was present in nearly one-third of the ET families in a genetics study, including 10.7 % of ET probands. The dystonic component is often undiagnosed in these individuals [19]. Video 29.2 demonstrates the combination of ET with cervical dystonia. Rest tremor may be seen in the elderly with long-standing

Table 29.1 Tremor diagnosis based on state of activity

	Rest tremor	Postural tremor	Kinetic tremor	Associated symptoms	Common etiologies
Essential tremor	+/–	+++	++	Usually none, occasional difficulty with tandem gait, cognitive changes	ET, FXTAS
Parkinsonian tremor	++	+/–	+/–	Bradykinesia, rigidity, gait, and posture changes	PD, MSA, PSP, DLBD
Cerebellar tremor	+/–	++	++	Based on etiology, for example, optic neuritis in MS, Kaiser-Fleisher rings in Wilson's disease	MS, trauma, Wilson's disease, phenytoin toxicity, alcohol intoxication
Midbrain tremor	+	++	+++	Holmes (rubral) tremor with rest < postural < kinetic tremor	Stroke, midbrain tumor, intracranial hemorrhage

DLBD diffuse Lewy body disease, *ET* essential tremor, *FXTAS* fragile X-associated tremor/ataxia syndrome, *MSA* multiple system atrophy, *PD* Parkinson's disease, *PSP* progressive supranuclear palsy
+++ required feature for diagnosis
++ usually present
+ may be present
+/– may or may not be present, not diagnostic

ET. However, the superimposition of PD or other forms of parkinsonism can also be a possibility [20, 21].

The understanding of the pathological processes underlying ET is limited with inconsistent findings. In one autopsy study, two broad categories of pathology were observed [22]. Prominent cerebellar changes were seen in about 75 %, which included a significant decline in the number of Purkinje cells and a marked increase in the number of swollen Purkinje cell axons called torpedoes. The remaining 25 % of brains showed Lewy bodies confined, for the most part, to the locus coeruleus. Other brain stem structures that show Lewy bodies in PD including the substantia nigra and dorsal vagal nucleus were minimally affected. The authors suggested that the two pathological subtypes were mutually exclusive with the former called cerebellar ET and the latter the Lewy body variant of ET [2]. In contrast, other studies failed to show an increase in Lewy bodies in ET autopsied cases compared to controls [23]. In addition, it is reported that 30 % of persons over the age of 65 years have Lewy bodies at autopsy, raising the question whether some Lewy bodies seen in ET are simply related to aging [24]. At this stage, there are insufficient data to confirm the presence of two pathological subtypes of ET.

In terms of pathophysiology, ET is considered a cerebellar disorder. Pathological changes in ET are seen in the cerebellum itself or in neurons that synapse with Purkinje cells. Functional imaging studies corroborate cerebellar dysfunction in ET [25, 26]. The location of the central oscillator in ET is a matter of debate. The cerebellum and the olivopontocerebellar pathways are favored. However, the ventral intermediate nucleus (VIM) of the thalamus may be an alternative location. Of note the VIM thalamus is the preferred surgical target for deep brain stimulation (DBS) in ET [27]. Noninvasive diffusion tractography from tremor-suppressive VIM DBS electrode contacts demonstrated a highly reproducible network that included motor cortical, subcortical, and cerebellar sites and the brain stem and was felt to be the anatomic basis for the effects of VIM stimulation [28].

29.5 Parkinson's Disease

A "pill-rolling" rest tremor is the typical tremor of PD. In practice, various combinations of rest and postural tremors are seen [5, 29]. Reemergent tremor occasionally seen in PD can resemble the postural tremor of ET. In most cases, the rest tremor of PD subsides when the hands are held outstretched, but in some cases a postural tremor may reemerge after a short duration. The latency from the time the hands are held outstretched to onset of tremor is longer in PD compared to ET [30]. Video 29.3 demonstrates the typical rest tremor seen in PD. PD tremor is usually unilateral in onset and may remain so for several years in contrast to ET. Further clues to a diagnosis of PD tremor include the presence of bradykinesia and rigidity. Often "cogwheel rigidity" is described in PD patients, which refers to the combination of a palpable tremor superimposed on underlying lead pipe rigidity [6]. Tremor is the presenting complaint in 60–70 % of cases of PD and may remain the main manifestation of the condition for several years without development of significant bradykinesia or gait disorder, a condition referred to as benign tremulous PD [31]. Of note, in approximately 10–30 % of PD cases, tremor may be completely absent [32]. The diagnosis of PD is based on clinical symptoms, and the use of formal criteria such as the United Kingdom Parkinson's Disease Society Brain Bank criteria can increase the probability of an accurate diagnosis [33].

The location of the tremor generator in PD is poorly understood, and tremor severity correlates poorly with the nigrostriatal dopaminergic deficit [34]. The loss of particular subgroups of mesencephalic neurons may determine severity of PD tremor [35]. The neurodegeneration of the retrorubral area (A8) is more prominent in tremor-predominant PD, while the lateral substantia nigra (A9) shows more significant degeneration in the akinetic-rigid form. Serotonin systems may also play a role in tremor generation. Reduced 5HT1-A binding has been correlated with tremor but not rigidity or bradykinesia [36]. Possible locations of the central oscillator responsible for PD tremor include the cerebellum, the thalamus, the globus pallidus, and the subthalamic nucleus [37, 38]. During microelectrode recording for DBS, "tremor cells" can be demonstrated in the VIM nucleus of the thalamus, the globus pallidus, and the subthalamic nucleus [39]. It is postulated that these cells form an unstable oscillating network responsible for the tremor. Lesioning in these nuclei or DBS may disrupt this network, resuming normal unsynchronized activity, leading to improved tremor control [37].

29.6 Cerebellar Tremor

Cerebellar tremor is a proximal action tremor of large amplitude with low frequency (3–5 Hz). Lesions of the deep cerebellar nuclei or outflow pathways in the superior cerebellar peduncle cause this tremor [40]. The intention component of kinetic tremor is characteristic of cerebellar tremor. The tremor tends to increase as the target is approached, which is referred to as a terminal tremor [4]. However, various types of postural tremor are also seen. Titubation is a postural tremor of the head and trunk, most pronounced when the patient is standing. It is uncommon for cerebellar tremor to occur in isolation. Associated findings including ataxia and gait disorder are common [5].

The most common causes of cerebellar tremor include MS, mass lesions, and vascular and degenerative diseases. Cerebellar degeneration may result from alcohol abuse or toxicity from drugs such as anticonvulsants, neuroleptics, or lithium. The tremor in these cases tends to be bilateral. In contrast, tremor from a structural lesion such as a mass, infarct, or plaque tends to be unilateral [5]. Cerebellar tremor may occasionally be a delayed sequela to a head injury, either as a result of direct injury to the dentate nucleus or due to shear injury to cerebellar axons in the outflow pathways [41]. Inherited spinocerebellar ataxias [42] and paraneoplastic syndromes [43] are other important causes. Lesions in the deep lateral cerebellar nuclei and their outflow pathways up to the red nucleus can cause cerebellar tremor. Lesions of

the red nucleus and beyond cause Holmes tremor. Lesions proximal to the decussation of the outflow pathways result in ipsilateral tremor, and distal lesions result in contralateral tremor. Injury to the cerebellar cortex itself does not cause tremor [44].

29.7 Holmes Tremor

Holmes tremor (rubral tremor or midbrain tremor) refers to a combination of rest, postural, and action tremors due to midbrain lesions. Common causes include strokes, tumors, MS, or vascular malformations. As the lesion is typically in the vicinity of the red nucleus (which is part of the cerebellar outflow tract), the tremor phenotype is similar to that of a cerebellar tremor in that the tremor is irregular with a low frequency [45].

The tremor has a static and dynamic component. The former consists of a coarse tremor with a frequency of 3–5 Hz that increases with attempts at inhibition. The dynamic component consists of an irregular intention tremor similar to that seen in MS. Associated findings may include diplopia, ptosis, oculomotor palsies, hemiparesis, hemianopia, and parkinsonian features [45]. Holmes in 1904 suggested that involvement of the red nucleus was a key anatomic component, leading to the term "rubral tremor" [45]. However, the advent of improved imaging techniques demonstrated that lesions in other midbrain structures as well as the thalamus could also cause this tremor. Hence, the term "rubral tremor" has been abandoned in favor of the term Holmes tremor [4].

29.8 Dystonic Tremor

A dystonic tremor occurs in a body part that is simultaneously affected by dystonia. The tremor is irregular and jerky in nature and interrupted with sustained dystonic spasms. Dystonic tremor is typically position sensitive. For example, when the patient is allowed to move the affected body part to the position of maximal pull, a null point is reached and tremor often ceases [46]. The tremor may be relieved with complete rest or touching the affected body part (*geste antagoniste*) [47].

The pathophysiology of dystonic tremor is poorly understood [48]. Two types of tremor may occur separately or together, an ET-like tremor and a dystonic tremor. The ET-like tremor has a higher frequency with a peak at 9–11 Hz, whereas the dystonic tremor has a peak at about 5 Hz [47].

29.9 Task-Specific Tremor

Task-specific tremor (occupational tremor) is a kinetic tremor that appears during the performance of highly skilled, learned motor tasks such as writing or playing a musical instrument. The most frequent task-specific tremor is primary writing tremor. This tremor often has a dystonic component and may also be classified as a focal dystonia [6, 49]. The tremor may resemble an essential tremor or a dystonic tremor or have features common to both on clinical examination as well as on EMG analysis [47, 50].

29.10 Orthostatic Tremor

Orthostatic tremor (OT) typically involves the legs and trunk and is present when standing still. It generally improves with walking [51]. A latency period of 3–5 min may be present before the tremor is seen. OT is more common in women and usually presents in the sixth or seventh decade. OT has a more rapid frequency than other tremors, in the 13–18 Hz range [52, 53]. While present primarily during standing, OT may also be precipitated by isometric contraction of the upper limbs. Thus, it is more likely related to isometric force control rather than regulation of stance [54]. Orthostatic myoclonus is similar but appears to be a distinct disorder. Patients complain of leg jerking during upright posture. There is a gradual decline of gait, often described as "apraxia" or "gait initiation difficulty" in these patients [55].

29.11 Posttraumatic Tremor

Posttraumatic tremor is a challenging diagnosis with poorly defined criteria. The concept of tremor following a central injury is more accepted than a peripherally induced tremor [56, 57]. Retrospective studies suggest that following closed head injury posttraumatic tremor is the second most common movement disorder after dystonia. Posttraumatic tremor most often follows as a delayed sequela to severe head trauma, and there may be a significant delay between the injury and development of symptoms. In a survey of 289 children with severe head injury, tremor prevalence was about 45 %. The tremor occurred within the first 18 months after injury and subsided spontaneously in over half the cases [58].

29.12 Other Etiologies of Tremor

Expansions of the CGG repeats in the fragile X mental retardation 1 gene (FMR1) lead to clinical manifestations based on the number of repeats. Greater than 200 repeats are associated with developmental delay and autism. However, repeats in the premutation range (55–200) are associated with a tremor resembling ET. Additional symptoms include cerebellar gait ataxia, frontal executive dysfunction, and global brain atrophy and are grouped together as the fragile X-associated tremor/ataxia syndrome (FXTAS). Other associated findings may include mild parkinsonism, peripheral neuropathy, depression, and autonomic dysfunction [59].

Peripheral nerve disorders such as Charcot-Marie-Tooth disease (CMTD) may be associated with tremor. Associated findings include foot deformities, weakness, and atrophy affecting the anterior compartment muscles in the lower leg leading to the "inverted Coke bottle" appearance of the legs. A postural tremor resembling ET is present in about a third of patients with CMTD and can occur in both the demyelinating and axonal forms [60].

Wilson's disease (WD) is an important diagnostic consideration, especially in an adolescent or young adult [6]. Tremor is common in WD and can present as a rest tremor and/or postural tremor. A "wing beating" tremor may be seen when the arms are held in front of the body and flexed at the elbows [61]. Kayser-Fleischer rings may be seen in the cornea on direct exam or by slit-lamp examination and are present in most patients with this neurological disease [62]. Other etiologies of tremor include infectious diseases, trauma, and drugs. These and other rare etiologies of tremor have been reviewed elsewhere by Dalvi and Premkumar [6].

29.13 Psychogenic Tremor

Psychogenic tremor is the most common psychogenic movement disorder. Differentiating between psychogenic tremor and organic tremors can be challenging. The diagnosis is made based on the history as well as careful observation of the tremor [4]. Psychogenic tremors usually have an abrupt onset with maximal disability also often seen at the onset. The clinical course is variable and may include spontaneous remissions and recurrences. Tremors may affect the wrists, elbows, and shoulders but rarely the fingers [63]. The amplitude and frequency of psychogenic tremor is variable in response to attention or distraction. By contrast, with organic tremor although the amplitude may change with stress or emotions, the frequency tends to stay constant. Psychogenic tremor also commonly exhibits an entrainment phenomenon [64]. The frequency of the tremor in a limb may change to match the frequency of voluntary tapping in another limb. Psychiatric evaluation may not always be contributory, but depression and other psychosomatic conditions are common. Psychogenic tremors typically do not respond to conventional anti-tremor medications but may respond to antidepressants or psychotherapy [65].

29.14 Diagnostic Workup

The extent of laboratory investigations depends on the diagnostic certainty after clinical evaluation. Thyroid function tests and routine metabolic

tests are usually ordered as screening tests. Screening tests for WD include serum ceruloplasmin, which is usually low, and measurement of 24-h urine copper, which is increased. Further workup for WD includes a slit-lamp examination to look for Kayser-Fleischer rings. Genetic testing/liver biopsy for WD may also be warranted [62]. Electromyography (EMG) and nerve conduction tests are helpful in tremor associated with peripheral neuropathy such as CMTD. Supplementary investigations to consider when tremor and neuropathy coexist include serum protein electrophoresis, urinary Bence-Jones protein, and porphyrin screen. Tremor analysis with accelerometers and surface EMG can help characterize a tremor but has a limited practical role in diagnosis [6].

Brain MRI helps rule out structural etiologies of tremor such as MS or focal midbrain lesions that can lead to Holmes tremor [66]. The role of brain MRI in the diagnosis of parkinsonism is also mainly exclusionary. If present, characteristic radiological abnormalities can assist in the differential diagnosis of parkinsonism [67]. These may include midbrain atrophy in progressive supranuclear palsy, atrophy of the pons and cerebellum as well as the middle cerebellar peduncles (MCPs) in olivopontocerebellar atrophy, and focal cortical atrophy in corticobasal degeneration [68]. Signal hyperintensities within the pons and MCPs in multiple system atrophy (MSA) may occasionally result in the "hot-cross bun" sign [69]. Brain MRI changes in FXTAS include atrophy of the cerebrum, cerebellar cortex, corpus callosum, and pons. A distinctive abnormality of the middle cerebellar peduncles with increased T2 signal is a hallmark of FXTAS [70].

Single-photon computerized emission tomography (SPECT) techniques represent an advance in the ability to distinguish ET from parkinsonism. In cases of diagnostic uncertainty between degenerative parkinsonism and non-degenerative tremor disorders, baseline SPECT imaging with the dopamine transporter ligand (123)I ioflupane (DaTscan™) has shown 78 % sensitivity and 97 % specificity with reference to clinical diagnosis at 3 years, versus 93 % and 46 %, respectively, for baseline clinical diagnosis [71]. However, DaTscan imaging cannot readily differentiate between PD and atypical parkinsonism. Figure 29.1 compares the typical comma-shaped appearance of the DaTscan in ET (1a) with the period-shaped appearance in PD (1b) due to reduced dopamine transporter levels in PD.

29.15 Pharmacological Treatment of Essential Tremor

While no curative treatment for ET is available, medications may improve quality of life. Pharmacological treatment is based on reducing the sympathetic drive that exacerbates tremor, increasing GABAergic inhibition of the central oscillators that drive the tremor, and membrane stabilizing effects. Propranolol, primidone, and alcohol are the prototypical drugs that respectively represent these three mechanisms. Other comorbidities such as diabetes, cardiac failure, glaucoma, and renal failure should be kept in mind when tailoring the choice of drug to a particular patient. The American Academy of Neurology (AAN) has published a practice parameter for the therapy of ET as a guide to treatment [72]. Key pharmacotherapeutic agents are reviewed below.

29.16 Beta-Adrenergic Blockers

Propranolol was one of the earliest agents shown to be effective in ET [73]. It is still a mainstay of treatment and the only medication approved by the FDA for ET. About 50–70 % of patients had substantial relief in randomized controlled trials (RCTs) [73, 74]. The long-acting form of propranolol (propranolol-LA) may help with compliance when high doses are required [75]. Other beta-blockers used include atenolol, metoprolol, nadolol, sotalol, timolol, and arotinol. However, strong clinical evidence for their use is lacking [76]. Contraindications to beta-blockers include asthma, heart blocks, and concurrent calcium-channel blockers. They should be used with caution in diabetics as they can mask the sympathetic response to hypoglycemia [76].

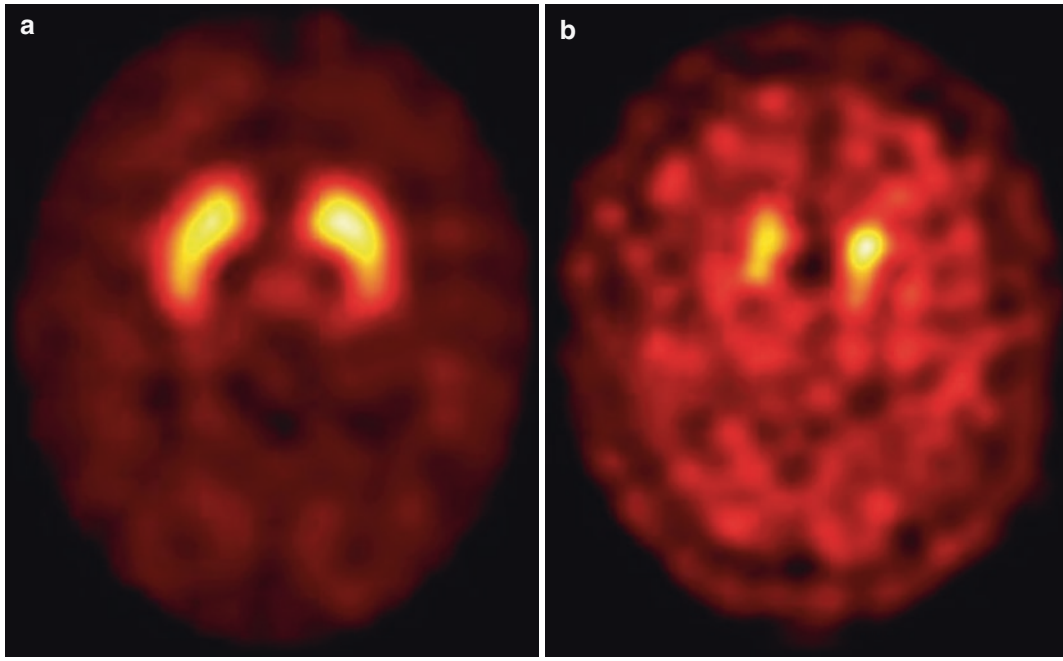

Fig. 29.1 (**a**) DaTscan of an ET patient showing comma-shaped appearance, indicating normal uptake of dopamine. (**b**) DaTscan of a PD patient showing period-shaped appearance, indicating reduced uptake of dopamine

29.17 Primidone

Primidone is as efficacious in ET as propranolol [77]. Doses for ET are lower than typical antiepileptic doses. Primidone is metabolized to phenobarbital and phenylethylmalonamide (PEMA). Primidone was found to be superior to phenobarbital suggesting that it has a direct effect rather than an effect through its metabolites [78]. Combination therapy with propranolol and primidone is useful in refractory tremor [79]. Daytime somnolence can limit the use of primidone, especially in the elderly.

29.18 Gabapentin

Though gabapentin is a structural analog of GABA, it has no affinity for the GABA receptor, and the mechanism of action in ET is unclear. Results from RCTs are mixed with gabapentin shown as equivalent to propranolol [80] or ineffective [81].

29.19 Topiramate

Topiramate has multiple mechanisms of action including glutamate antagonist and GABA-agonist activities. In a RCT, topiramate was found to be superior to placebo for ET [82]. A multicenter study confirmed this finding, when topiramate was used as monotherapy and as an adjunct to one other anti-tremor medication [83]. Topiramate should be avoided in patients with glaucoma or those at risk for nephrolithiasis and should be used with caution in the elderly as it carries a risk of cognitive side effects.

29.20 Benzodiazepines

Alprazolam, clonazepam, and lorazepam may suppress tremor through their GABA-agonist activity. They are especially useful in anxious patients. Alprazolam was shown to be effective in ET in a RCT [84], but clonazepam and lorazepam have not been tested in RCTs. Benzodiazepines are best used

as second-line agents due to the potential for tolerance and addiction. Rapid withdrawal should be avoided when these drugs need to be discontinued.

29.21 Botulinum Toxin

A number of patients with head tremor may have CD. The efficacy of botulinum toxins has been unequivocal in this condition. In patients with head tremor without CD, there is limited information from small trials [85]. The use of botulinum toxin in hand tremor is limited by lack of efficacy as demonstrated by functional rating scales, as well as a tendency to affect motor dexterity [86].

29.22 Pharmacological Treatment of Other Tremor Disorders

29.22.1 Parkinson's Disease

The treatment of tremor associated with PD involves addressing the underlying dopaminergic deficit. The mainstay of treatment is levodopa in one of its forms, with dopamine agonists, monoamine oxidase type B inhibitors, catechol-O-methyltransferase inhibitors, and amantadine as adjuncts or alternates in early disease [87]. Anticholinergic drugs can be used but cognitive side effects are a limitation.

29.23 Multiple Sclerosis and Cerebellar Tremor

About 25–60 % of patients with MS have tremor. In addition to the postural tremor, there is an ataxic component, which is harder to treat. Isoniazid in high doses, carbamazepine, propranolol, and glutethimide have been reported to provide some relief [88].

29.24 Dystonic Tremor

Distinguishing ET from dystonic tremor is important in choosing the appropriate therapy. Benzodiazepines including clonazepam, lorazepam, and diazepam are often used. However, the therapeutic dose is often also one at which significant drowsiness or fatigue is observed [47]. As a result, chemodenervation with botulinum toxin has become the first-line treatment for some forms of dystonic tremor such as CD [89]. The dystonic component of primary writing tremor may also respond to clonazepam and EMG-guided botulinum toxin injections [89].

29.25 Holmes Tremor

Holmes tremor has components of rest tremor and postural tremor. As secondary etiologies are frequent, the first step is to treat the underlying etiology if possible. The postural component may respond to ET medications such as propranolol and primidone. The rest tremor component is harder to treat but may respond to levodopa [45].

29.26 Orthostatic Tremor

OT was initially classified as an ET variant. However, first-line drugs for ET are rarely of benefit. Clonazepam may be effective in some cases [90]. The most practical treatment is the use of a walker with a seat that allows the patient to sit when the OT becomes severe.

29.27 Surgical Treatment of Tremor

Surgical treatment is an option for intractable tremor [27]. Video 29.4 demonstrates the impact of DBS on ET. Regardless of etiology, the motor thalamus is the preferred surgical target, which may be explained by its central position between subcortical and cortical tremor networks [91]. Surgical methods for tremor include thalamotomy and DBS. Due to the irreversible nature of thalamotomy and the high risk of hypophonia, dysarthria, and cognitive deficits following bilateral ablation, DBS has become the preferred surgical modality [92]. The surgical treatment of choice for ET is DBS of the VIM nucleus of the

thalamus. Lyons and Pahwa reviewed eight outcome studies of DBS for ET, covering 158 patients implanted unilaterally and 68 with bilateral DBS [93]. Across studies, over 33 months of mean follow-up, activities of daily living improved on average by 46 %. There was a reduction in overall tremor of 48 %, including 73 % for hand tremor. Head tremor improved only 35 % in unilaterally implanted patients but 81 % in bilateral patients, and the same was generally true for voice tremor. Complications were rare and generally led to no permanent deficits [93]. A meta-analysis of the complications of DBS for 1,154 patients showed the following common adverse events: mental status or behavioral changes (16.6 %), infection (2.2 %), speech disturbance (2.0 %), symptomatic intracerebral hemorrhage (2.0 %), seizures (1.0 %), misplaced electrodes (1.6 %), and asymptomatic intracerebral hemorrhage (1.2 %). Hardware-related adverse events occurred in 8.7 % of patients [94]. Other tremor etiologies have been shown to be responsive to DBS as well. The mixed rest and tremor components of Holmes tremor have been reported to be amenable to multitarget dual electrode DBS techniques [95, 96]. Dystonic tremor as well as other symptoms of CD were shown to be responsive to pallidal DBS in a sham-controlled trial [97]. Although tremor from PD can be well controlled by VIM DBS, the usual surgical targets in PD are the subthalamic nucleus or the globus pallidus as DBS as these sites can improve other PD symptoms in addition to tremor [98].

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