

Tics and Tremors

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Glossary

Deep brain stimulation (DBS) Neurosurgical procedure involving the implantation of a medical device that sends electrical impulses, through implanted electrodes, to specific parts of the brain.

Electroencephalogram (EEG) Measuring and recording of the electrical activity of the brain, involved with epilepsy research since its invention and development 80 years ago.

Electromyography (EMG) Electrical recording of muscle activity used in the diagnosis of neuromuscular disease.

Positron-emission tomography (PET) A functional imaging technique that produces a virtual image of functional processes in the body detecting pairs of gamma-rays emitted indirectly by a positron-emitting radionuclide (tracer) introduced into the body.

Introduction

Movement disorders can be classified into two broad categories of akinetic/rigid and hyperkinetic disorders. Hyperkinetic movement disorders (hyperkinesias) are manifested by abnormal, uncontrollable, and unwanted movements. Hyperkinesias include six main phenotypic categories, which can appear in isolation or in variable combinations: tremor, chorea, tics, myoclonus, dystonia, and stereotypies (Albanese & Jankovic, 2012b).

Tics

Tics are sudden rapid, recurrent, nonrhythmic twitches or vocalizations that interfere with ongoing behavior. Tics are frequently preceded by premonitory sensations or urges and range from 'simple,' involving one muscle group or simple noises or sounds, to 'complex,' involving groups of muscles or the production of complete words or phrases. Tics are often present between the ages of four and six years, with a male-female ratio of approximately 4:1 (Robertson & Cavanna, 2008). Attributes have been added to emphasize the variable phenomenology of tics: 'Clonic' tics are usually abrupt in onset, fast and brief; 'dystonic' tics are slow and sustained; 'tonic' tics are manifested by sudden cessation of movement because of isometric muscle contractions; and 'blocking' tics are manifested by inhibition of voluntary movement. The duration of each tic movement is characteristic of that tic, and the duration does not generally vary between different repetitions (Jankovic, 1997).

Characteristics of tics include predictability, suggestibility, and exacerbation during excitement or stress and also after stress (rebound), and brief voluntary suppressibility. The tic movements may appear purposeful (touching, throwing, hitting, jumping, and kicking) or nonpurposeful (head shaking and trunk bending). Complex motor tics may resemble normal motor acts or gestures but are generally inappropriate in intensity and in time (Jankovic, 1997). Complex motor tics also include copropraxia (grabbing or exposing one's genitals) or echopraxia (imitating gestures).

Rarely, the tic movements can be so severe as to cause neurological sequels, with reports of compressive cervical

myelopathy resulting from recurrent head thrusting and violent neck hyperextension (Krauss & Jankovic, 1996). Motor tics are almost invariably accompanied by vocal or phonic tics. Simple phonic tics involve brief occurrences of sniffing, throat clearing, grunting, screaming, coughing, blowing, sucking sounds, or pathological laughter (Cavanna et al., 2010). Complex phonic tics are semantically meaningful utterances and include coprolalia, or shouting of obscenities, profanities, or other insults. Complex phonic tics also include repetition of someone else's words or phrases (echolalia) and repetition of one's own utterances, particularly the last syllable, word, or phrase in a sentence (palilalia). The differential diagnosis of tics is summarized in Table 1.

Tics may occasionally be continuous and disabling, resulting in a 'tic status' (Collicott et al., 2013) or in severe, self-injurious, even life-threatening behaviors, also named 'malignant Tourette syndrome' (Cheung et al., 2007).

Tics are currently viewed as a disorder of synaptic transmission involving disinhibition of the cortico-striatal-thalamic-cortical circuitry (Bronfeld & Bar-Gad, 2013). Animal models directly linking basal ganglia dysfunction and motor tics indicated that local disinhibition within the basal ganglia input structure, the striatum, induces the appearance of motor tics in rats and monkeys (McCairn et al., 2009). That tics are generated by the basal ganglia is also supported by studies based on deep brain stimulation of the internal globus pallidus or the thalamus (Hariz & Robertson, 2010).

Three tic disorders are included in the DSM-5: Tourette's disorder (also called Tourette syndrome (TS)), persistent (also called chronic) motor or vocal tic disorder, and provisional tic disorder (American Psychiatric Association, 2013). A provisional tic disorder is defined by single or multiple motor and/or vocal tics, present for less than 1 year since first tic onset; a persistent (chronic) motor or vocal tic disorder is defined by single or multiple motor or vocal tics that may wax and wane in frequency but have persisted for more than 1 year since first tic onset. Both provisional and persistent tic disorders must have onset before age 18 and should not be attributable to the physiological effects of a substance or another medical condition. The term 'stereotyped' has been removed from the definition of tics to avoid confusions with stereotypic movements.

Table 1 Differential diagnosis of tics

<i>Characteristic of tic</i>	<i>Differential diagnosis</i>
Abrupt	Chorea Myoclonus Paroxysmal dyskinesia Seizure
Improves with concentration	Akathisia Psychogenic
Increases with stress	Most hyperkinesias
Multifocal/migratory	Chorea Myoclonus Paroxysmal dyskinesia
Patient unaware	Chorea Seizure
Premonitory sensation/urge	Akathisia Dystonia
Present during sleep	Myoclonus (segmental) Painful legs/moving toes Periodic limb movements of sleep Seizure
Suppressible	Chorea Restless legs syndrome Stereotypy

Tourette Syndrome

In 1885, Georges Gilles de la Tourette, a Charcot's student, described a disorder with symptoms consisting of sudden movements and shouting out of obscene language, which was afterwards named 'la maladie des tics de Gilles de la Tourette' (Gilson, 2012). At the beginning of 1900, the disease was considered as a purely psychiatric disorder. The perception of TS changed in the 1960s with the beneficial effects of neuroleptic drugs on the symptoms. This observation shifted focus from psychogenic to organic etiology (Jankovic & Kurlan, 2011).

The first consensus criteria for 'definite Tourette syndrome' were assembled in 1993 (The Tourette Syndrome Classification Study Group, 1993). The American Psychiatric Association has repeatedly classified tic disorders providing criteria for the diagnosis of TS. In the latest version of the Diagnostic and Statistical Manual (American Psychiatric Association, 2013), tics are classified under anxiety and obsessive-compulsive disorders (OCD), and TS is diagnosed when there is childhood onset of motor and phonic (vocal) tics, lasting a cumulative total of at least 1 year, in the absence of a known medical cause. In the older DSM versions, TS would not be diagnosed if there were a tic-free period of greater than 3 months during the first year: this criterion has been removed from the DSM-5, because prolonged remission, followed by recrudescence of symptoms, can occur in TS patients.

TS has a broader phenomenology encompassing also relevant nonmotor features, such as OCD, attention-deficit/hyperactivity disorder (ADHD), and other comorbid behavioral problems, particularly impulse control disorder, oppositional defiant disorder, anxiety, depression, conduct disorder, severe temper outbursts, rage attacks, and inappropriate sexual behavior (Albanese & Jankovic, 2012b). So, TS holds a unique status as quintessentially neuropsychiatric condition at the interface between neurology (movement disorder) and psychiatry

(behavioral dysfunction) (Cavanna & Rickards, 2013). Sensory symptoms are also increasingly recognized in TS. Although children are less likely to refer them, most adults with TS experience uncomfortable internal sensations (sensory phenomena) or premonitory urge (unease or anxiety relieved by performing the movement) just prior to their tics (Shprecher et al., 2014).

OCD comorbidity rates range from 11% to 80%, ADHD comorbidity rates range from 60% to 80%, and OCD is more common in family members of TS patients (Jankovic & Kurlan, 2011). The current view is that TS and OCD can share some neurobiological underpinnings and that specific obsessive-compulsive symptoms are likely to be intrinsic to TS (Cavanna & Rickards, 2013), whereas the precise nature of the relationship between TS and ADHD is complex and still debated. Depression comorbidity varies from 13% to 76% of cases, and it has been associated with tic severity and duration, complex tics, premonitory sensations, sleep disturbances, OCD, aggression, childhood conduct disorder, and ADHD (Cavanna & Rickards, 2013), but the etiology of depression in TS remains unclear.

Postmortem anatomical studies in TS patients found a reduction in the number of two types of striatal interneurons in the brains: the GABAergic fast-spiking interneurons and the cholinergic tonically active interneurons in the brain (Kalanithi et al., 2005). Another study of three TS brains found consistent increases in DAT and D2 receptor and D1 and α -2A density (Yoon et al., 2007). Neuroimaging studies using volumetric, metabolic, blood flow, ligand, and functional imaging techniques in TS showed that in both children and adults, microstructural changes can be detected in the corpus callosum, different parts of the basal ganglia, thalamus, frontal regions, and the connectivity in frontostriatal pathways. Moreover, alterations in the limbic system, somatosensory pathways, and the corticospinal tract have been detected in adults (Peterson, 2001). The results of a recent study in a large group of unmedicated adult TS patients (Muller-Vahl et al., 2014) are in line with these findings suggesting that tics are caused by alterations in the prefrontal areas, thalamus, and putamen and the additional changes in the cingulate gyrus are related to secondary compensatory mechanisms. Findings from these models suggest that disruption of the inhibitory circuits in the basal ganglia is a key element in the pathophysiology of motor tics in TS; a similar disinhibition in the associative and limbic circuits leads to behavioral abnormalities in TS (Bronfeld & Bar-Gad, 2013).

Family and twin studies have shown that genetic risk factors are important in the development of TS (Castellan et al., 2014). There is also a current debate on the role of immunologic mechanism in the pathophysiology of TS, as suggested by the exacerbation of tics after infection with beta-hemolytic streptococcus. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) stand as one of the most controversial topics in pediatric neurology (Macerollo & Martino, 2013).

Secondary Tic Syndromes

Secondary tics can be observed in association with different acquired and congenital neurological and neuropsychiatric diseases or on exposure to drugs (Kumar & Lang, 1997). The

term 'tourettism' has been used for secondary tics (Cardoso, 2012), which occur in a minority of patients with tics. Secondary causes of tics should be considered if other movement disorders or other neurological symptoms are also present.

Tics could be associated with brain developmental disorders such as mental retardation and autism. Particularly, some patients with autism described in literature meet criteria for TS (Jankovic & Mejia, 2006), up to 6% in American children with a diagnosis of autism (Cardoso, 2012). The coexistence of tics with chromosomal diseases such as Down syndrome, Klinefelter syndrome, fragile X syndrome, and mosaicisms was described (Kumar & Lang, 1997). Neurodegenerative diseases that can cause tics include Huntington disease, Wilson disease, neuroacanthocytosis, and neurodegeneration with brain iron accumulation type 1 (NBIA-1), and the coexistence of tics and dystonia was reported (Kumar & Lang, 1997). Other causes of new onset tics include vascular lesions of the brain (Kwak & Jankovic, 2002) and trauma (Krauss & Jankovic, 1997).

There are numerous reports of tics associated with central nervous system infections. Following the historic encephalitis lethargica pandemic, also known as von Economo disease, that occurred in central Europe around 1916, a group of subjects with motor and vocal or phonic tics was described (Kumar & Lang, 1997). Moreover, there are reports of tics associated with herpes simplex encephalitis and HIV encephalopathy and the previously reported association with beta-hemolytic streptococcus infection (Kumar & Lang, 1997).

Some drugs are involved in the development or worsening of tics. There are reports describing the onset of tics in patients treated with antiepileptic drugs carbamazepine, phenytoin, and phenobarbital. The association of tics and antidepressants such as imipramine, clomipramine, desipramine, fluoxetine, sertraline, and fluvoxamine was reported. There is interest in the relationship between induction or worsening of tics and use of stimulant agents such as cocaine, caffeine, and other agents (Shprecher & Kurlan, 2009).

predominantly postural high-frequency tremor occurring with central stimulant drugs, caffeine, and nicotine or with sleep deprivation, stress, ethanol withdrawal, fatigue, exercise, hypoglycemia, thyrotoxicosis, alcohol, pheochromocytoma, and hypothermia and typically reversing with their suspension (Elias & Shah, 2014).

Nonphysiological tremor is considered to be the most common movement disorder, known since the time of Galen, and defined as a rhythmic involuntary movement of one or several regions of the body (Albanese & Jankovic, 2012a). Many attempts have been made in the last century to define and classify normal and pathological tremors, but a comprehensive summary did not exist until the first Movement Disorder Society consensus review (Deuschl et al., 1998a).

The different types of tremor are summarized in Table 2. Tremor is part of the phenomenological spectrum of dystonia (Albanese et al., 2013), and isolated tremor may be difficult to distinguish from tremor occurring in dystonia syndromes (Lalli & Albanese, 2010a). Features of dystonia should be looked for in all cases of tremor (Albanese & Lalli, 2009).

The precise way that tremors emerge is not well known, but there are some hypotheses from new methodological approaches with animal models, positron-emission tomography (PET), and mathematical analysis of electromyography (EMG) and electroencephalogram signals (Hallett, 2014). Tremor is defined as rhythmic oscillatory activity of body parts. Four physiological mechanisms for this activity have been described: The first involves the mechanical oscillations of the extremity; the second is mediated through the central nervous system reflexes; the third refers to oscillations generated by central neuronal pacemakers (mediated by the rhythmic activity of a group of neurons within a nucleus or generated within loops consisting of neuronal populations or different nuclei and their axonal connections); and the fourth considers a malfunction of feedforward loops within the central nervous system, especially the cerebellum (Deuschl et al., 2001).

Tremor

The word 'tremor' derives from Greek, meaning 'to shake' and also 'to have fear,' as it was well known that anybody may tremble with fear. All humans have physiological tremor, an invisible mechanical vibration of a body parts. The existence of a physiological tremor at a peak frequency of 8–12 Hz during action and while maintaining a posture is established (Mehta et al., 2014). Enhanced physiological tremor is a visible,

Essential Tremor

The term 'tremore semplice essenziale' was first used in 1874 by Pietro Burresi, an Italian doctor at the University of Siena (Burresi, 1874). By the end of the nineteenth century, several authors had described similar cases and proposed the term 'essential tremor' to define what they considered a unique disorder (Louis et al., 2008). By the early twentieth century, the term ET began to appear with some consistency in medical

Table 2 Different types of tremor

Rest tremor	Produced when the affected part is at rest, without voluntary muscle activation and fully supported against gravity. Rest tremor is the main feature of Parkinson disease
Action tremor	Appears with voluntary muscle contraction and can be postural (appears when maintaining a posture against gravity), isometric (appears with sustained muscle contraction against a rigid object), and kinetic (appears along any voluntary movement)
Simple kinetic tremor	Appears during voluntary movements not target-directed
Intention tremor	A tremor that appears when the limb is reaching a target
Task-specific kinetic tremor	A kinetic tremor that appears during specific tasks
Position-specific tremor	A tremor that appears only in certain postures

publications to denote a form of kinetic tremor, which is commonly familial, for which no cause is known.

The predominant clinical finding in ET is a kinetic tremor of the arms, with a frequency between 4 Hz and 12 Hz. Yet, a recent cross-sectional study of more than 350 ET cases provided evidence that tremor in ET is kinetic (i.e., arm tremor during voluntary movements) rather than postural (Louis, 2013), and this is sharpened by the fact that over the past several years, consensus criteria have moved toward the requirement of kinetic tremor for the diagnosis of ET (Bain et al., 2000). ET affects the hands in 94% of cases, the head in 33%, the voice in 16%, the legs in 12%, the jaw in 8%, the face in 3%, and the trunk in 3% (Elble, 2006). Head tremor typically develops several years after the onset of arm tremor, and the converse (spread of tremor from the head to the arms) is distinctly unusual (Rajput et al., 2004).

The traditional view of ET as a monosymptomatic disorder has been challenged by hypothesizing that a number of additional features are part of the clinical phenomenology of ET and that a specific pathological marker may exist (Louis, 2009). However, this broad definition of ET has not been fully accepted by the scientific community.

ET still remains an overdiagnosed condition (Schrage et al., 1999) particularly at disfavor of dystonia (Lalli & Albanese, 2010a). A review of 350 patients diagnosed with ET has disclosed associated dystonia, including cervical dystonia, writer's cramp, spasmodic dysphonia, and cranial dystonia, in half of them (Lou & Jankovic, 1991).

ET has been considered the most common adult movement disorder, although its epidemiology is still uncertain as a result of application of imprecise and variable diagnostic criteria without a disease-specific marker to validate a clinical diagnosis. Prevalence estimated in community-based studies that provide diagnostic criteria for ET ranges from 0.4% to 3.9% in the total population (a 9.6-fold difference), with an increase with age being higher among persons over 60 years of age (Louis et al., 1998). The absence of a universally accepted set of diagnostic criteria thus influences the results of epidemiological studies.

More than half of patients with ET have affected family members. No genes have yet been identified in ET patients even if kindred with autosomal dominant inheritance of ET have been described (Deng et al., 2007) and genetic studies have showed that the LINGO1 gene is associated with an increased risk for ET (Stefansson et al., 2009; Tan et al., 2009). Therefore, factors other than genetics are likely involved. Current data indicate that environmental factors, like high levels of chronic ethanol consumption or cigarette smoking, may also play an important role in disease etiology (Elias & Shah, 2014) and might trigger the expression of underlying susceptibility genotypes.

The pathophysiology of ET remains unknown. Clinical and imaging data point to neuronal loop involving cerebello-thalamo-cortical pathways in ET (Louis, 2014). Imaging studies have also confirmed cerebellar dysfunction in ET patients including hypermetabolic activity identified by PET, activation of the ipsilateral cerebellum during a task identified by functional MRI, and altered cerebellar connections identified by spectroscopy (Louis et al., 2014). Some postmortem examinations have shown Purkinje cell loss in the cerebellum (Babji

et al., 2013). Moreover, improvement with ethanol and primidone implicates a possible role of GABAergic transmission (Elias & Shah, 2014). Electrophysiological recordings from stereotactic surgery identified 'tremor cells' that synchronously discharge with muscle activity, but the relation with ET appearance remains unknown (Molnar et al., 2005).

Other Tremors

Dystonic tremor

The term 'dystonic tremor' appeared in the 1980s in papers recognizing that dystonic patients sometime have rhythmic movements, particularly in the arms and neck, manifesting as tremor (Jankovic & Fahn, 1980). This concept was not easy to accommodate, and the current consensus statement from the International Parkinson and Movement Disorder Society defines dystonic tremors by three features: an associated dystonic posture, irregular amplitudes and frequency (usually 7 Hz), and postural/intentional tremor rather than resting tremor (Deuschl et al., 1998b). This consensus attempted to distinguish dystonic tremor from tremor associated with dystonia, a more generalized tremor type observed in limbs that are not affected by the dystonia. This is a relatively symmetrical type, often seen in the upper limbs in patients with spasmodic torticollis (Munchau et al., 2001). Isolated action tremor can be the initial symptom of dystonia, and dystonia may develop years after the onset of isolated tremor in the neck, trunk, or limbs (Deuschl, 2003). Consequently, isolated focal and task-specific tremors should raise the suspicion of dystonia, and long-term follow-up may be confirmatory.

Dystonic tremor is part of the phenomenological spectrum of isolated dystonia. The prevalence of dystonic tremor is not still well known as dystonic tremor is a relatively new and still a poorly defined and recognized clinical entity. A large prospective study showed that tremor was an even more common feature in adult-onset primary dystonia being present in 55.4% of patients with postural, kinetic, or rest tremor (Erro et al., 2013). The most frequent types of tremor were postural and kinetic tremors with 7 Hz frequency and featured essential tremor type (Rudzinska et al., 2013); however, dystonic tremor may also appear as rest tremor, in which case it may be associated with reduced arm swing resembling a Parkinsonian condition (Albanese & Lalli, 2010; Schwingenschuh et al., 2010). The diagnosis of dystonia can be missed or delayed in a number of patients with task- and position-specific tremors, particularly primary writing tremor, occupational tremors, or isolated voice tremor, as typical features of dystonia may not develop until after many years from onset (Rivest & Marsden, 1990). The differential diagnosis between ET and dystonia may be difficult, and their phenomenological overlap is well accounted (Lalli & Albanese, 2010b).

Primary writing tremor is a variant of dystonic tremor, usually characterized by prominent pronation/supination wrist movements that occur predominantly or exclusively during writing (Rothwell et al., 1979). No other neurological signs are evident except for slight postural and terminal kinetic tremor. The same as dystonia, primary writing tremor can be task-induced or position-sensitive. Age at onset varies and cases manifesting during childhood have been reported. The disorder begins slowly, progresses for years, and becomes stabilized.

Primary writing tremor can be differentiated from focal task-specific dystonia (such as writer's cramp) by the lack of excessive overflow of EMG activity into the proximal musculature and the absence of reciprocal inhibition of the median nerve H-reflex upon radial nerve stimulation (Bain et al., 1995; Modugno et al., 2002).

Parkinsonian tremor

The cardinal motor features in Parkinson disease (PD) are resting tremor, bradykinesia, and rigidity, which develop after significant dopaminergic cell loss in the substantia nigra. Tremor occurs in 75% of PD patients and may range from mild to severe. The typical Parkinsonian tremor is an asymmetrical, moderate-amplitude, resting tremor of 3–7 Hz, attenuated at movement onset, involving the thumb (the rhythmic movement of this finger against the index finger is called 'pill rolling'), and worsening with cognitive tasks or emotion (Pont-Sunyer et al., 2012b).

The exact origin of Parkinsonian tremor is still unknown. It is generally agreed that central rather than peripheral mechanisms underlie Parkinsonian tremor. Two overlapping central networks are considered candidate generators: the cerebello-thalamo-cortical circuit and the basal ganglia-cortical motor loop (McAuley & Marsden, 2000). Recently, a direct relationship between the synchronization of cerebral oscillations in a network, including the subthalamic nucleus, primary motor cortex, premotor cortex, and posterior parietal cortex, and Parkinsonian rest tremor was reported (Hirschmann et al., 2013).

Cerebellar tremor

Cerebellar tremor is diagnosed according to the following clinical criteria: pure or dominant intention tremor; mono-lateral or bilateral; tremor frequency below 5 Hz; and postural but no rest tremor may be present (Deuschl, Bain, & Brin, 1998b). Intention tremor is used synonymously with cerebellar tremor. The typical cerebellar tremor is intention, kinetic, goal-directed, action tremor. It is considered as symptomatic tremor, and other signs of cerebellar involvement (ataxia, nystagmus, and dysmetria) can be present. It has a frequency of 3–8 Hz in the upper limbs and 3 Hz in the lower limbs.

The pathophysiology of cerebellar tremor has been studied extensively in animals, and it may be closely related to the ET: the malfunction of the cerebellum causes a pathological feed-forward control. Additionally, an oscillator within the cerebellum or its input/output pathways may cause this tremor (Deuschl, Raethjen, Lindemann, & Krack, 2001). When affecting the cerebellorubral and cerebellothalamic pathways, lesions in multiple sclerosis cause cerebellar tremor. Other causes of cerebellar tremor include tumors, strokes, metabolic diseases, and neurodegenerative diseases.

Holmes tremor

Holmes tremor, also known as rubral tremor, midbrain tremor, or thalamic tremor, is a combination of rest, action, and postural tremors in the upper limbs with the frequency around 4.5 Hz. Stroke and trauma to the midbrain are the most common causes of Holmes tremor. Infectious brain diseases, midbrain neoplasms, and paraneoplastic syndrome also have been described

after radiation therapy in midbrain region had been described as cause of Holmes tremor (Kobayashi et al., 2014).

Postmortem and imaging studies have shown that concomitant damage to the cerebellothalamic and nigrostriatal pathways is necessary to cause Holmes tremor (Deuschl, Raethjen, Lindemann, & Krack, 2001). Movement disorders occur uncommonly after stroke and include both hyperkinetic and hypokinetic disorders. Strokes in the midbrain, superior cerebellar peduncle, and cerebellum could induce tremor, usually associated to other neurological signs. Hemorrhagic strokes appear to be more likely to lead to movement disorders than ischemic ones (Kim, 2001).

Holmes tremor and symptomatic palatal tremor are the two more frequently reported tremors after stroke, but irregular tremor associated to dystonia after thalamic lesion has been also described (Pont-Sunyer et al., 2012a). Immediate onset after stroke has been reported, but stroke-related tremor usually has a late onset after insult (Bansil et al., 2012).

Orthostatic tremor

Primary orthostatic tremor is a tremor of the legs and trunk that appears while standing and disappear when walking or sitting. The diagnosis is based on EMG findings as observation may not show a visible tremor. EMG shows coherent (phase-locked) 13–18 Hz rhythmic bursts of activity in all four limbs and in some cranial muscles within 30 s of standing. The prevalence is unknown, but it was thought to be rare.

Recently, the clinical findings have been reported in a population of orthostatic tremor patients (Yaltho & Ondo, 2014). A mild postural hand tremor was frequent, usually more prominent while standing. One-half of patients had a family history of tremor, and additional neurological features were seen in 11% of patients.

The anatomical and pathophysiological basis of orthostatic tremor is not known. There is evidence of a contribution from the brain stem, but recently, the focus has shifted to supratentorial areas for the efficacy of high-frequency stimulation treatment of the ventrolateral thalamus in five patients with orthostatic tremor (Muthuraman et al., 2013).

Drug-induced tremor

Iatrogenic tremor should be considered in tremor presenting after the initiation of a drug. Age and polypharmacy represent risk factors. The most common presentation is an enhanced physiological tremor-like and postural-intentional tremor similar to essential tremor.

Common tremor-inducing drugs include β -receptor agonists, theophylline, antidepressants, lithium, sodium valproate, thyroxine, and amiodarone; substances like caffeine, alcohol, marijuana, cocaine, and amphetamines can also induce tremors.

Tardive tremor is a rare form observed after long-term intake of antidopaminergic drugs, including antipsychotics (haloperidol, quetiapine, risperidone, and olanzapine), antiemetics (metoclopramide and prochlorperazine), tetrabenazine, cinnarizine, and flunarizine (Alty & Kempster, 2011). Drug-induced tremor should reduce and disappear after withdrawal of the responsible medication.

Palatal tremor

Essential palatal tremor is an uncommon disorder, distinct from secondary palatal tremor, but characterized by superficially similar rhythmic movements of the soft palate, usually vertical oscillations at 1–3 Hz (Zadikoff et al., 2006).

Essential palatal tremor can be distinguished from the secondary forms by the lack of associated neurological deficits. Essential palatal tremor has been segregated into three overlapping clinical variants (Biller & Espay, 2013): psychogenic, where a variable and suppressible tremor occurs against the will ('antivoluntary'); secondary, partially volitional and temporarily suppressible ('unvoluntary'); and volitional, where there are complete control and no disability.

While the pathophysiology of the secondary form has been relatively well defined, this is not the case in essential palatal tremor (Deuschl et al., 1990).

Neuropathic tremor

Neuropathic tremor occurs in association with a peripheral neuropathy and no other neurological diseases associated with tremor. Immune-mediated demyelinating and hereditary peripheral neuropathies are frequent causes of such tremors. In inflammatory neuropathies, tremor is found in up to 80% of patients with IgM paraproteinemic neuropathy, in the recovery phase of Guillain-Barré syndrome and in patients with chronic inflammatory demyelinating polyradiculoneuropathy, and in inherited motor neuron disease such as X-linked bulbospinal atrophy (Kennedy disease), where up to 80% of patients may have postural tremor (Saifee et al., 2013).

The relationship between the occurrence of tremor and the severity of the neuropathy remains unclear. It is postulated that distorted peripheral inputs to a central processor produce tremor (Deuschl, Raethjen, Lindemann, & Krack, 2001). Recently, a central component in the pathophysiology was confirmed by an association between neuropathic tremor and synchronous oscillatory activity at 4 Hz in a network including ventral intermedial nucleus of the thalamus (Vim) and motor cortex contralateral to the trembling muscle (Weiss et al., 2011). This activity was suppressed by Vim-DBS in parallel with a marked tremor reduction.

Psychogenic (functional) tremor

The term psychogenic movement disorders has historically been used to disorders that manifest with abnormal movements but that cannot be attributed to any underlying structural deficit and that instead suggest a psychological causation (Ricciardi & Edwards, 2014). Usage of the term 'functional' has been recently proposed (Edwards & Bhatia, 2012).

Psychogenic tremor is the most common functional movement disorder, accounting for at least 50% of patients (Edwards & Bhatia, 2012). Clinical features suggesting functional tremor include sudden onset, variability in severity with remissions, and variability in the body part affected (hands and arms are most frequently involved), changing with the level of attention and worsening during examination. A combination of electrophysiological tests was able to distinguish functional and organic tremor with excellent sensitivity and specificity (Schwingschuh et al., 2011).

See also: INTRODUCTION TO ACQUISITION METHODS: MRI and fMRI Optimizations and Applications; Obtaining Quantitative Information from fMRI; INTRODUCTION TO ANATOMY AND PHYSIOLOGY: Basal Ganglia; Cerebellum: Anatomy and Physiology; Development of the Basal Ganglia and the Basal Forebrain; Motor Cortex; Thalamus: Anatomy; INTRODUCTION TO CLINICAL BRAIN MAPPING: Chorea and Other Hyperkinetic Disorders; Insights into Gilles de la Tourette Syndrome from the Neuroimaging Perspective; Mapping Neurobiological Alterations in Obsessive-Compulsive Disorder; The Anatomy of Parkinsonian Disorders; INTRODUCTION TO COGNITIVE NEUROSCIENCE: Impulsivity; Motor Decision-Making; INTRODUCTION TO SYSTEMS: Neural Correlates of Motor Deficits in Young Patients with Traumatic Brain Injury.

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