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Tremor and Other Hyperkinetic Movements

Reviews

Dystonia and Tremor: The Clinical Syndromes with Isolated Tremor

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Abstract

Background: Dystonia and tremor share many commonalities. Isolated tremor is part of the phenomenological spectrum of isolated dystonia and of essential tremor. The occurrence of subtle features of dystonia may allow one to differentiate dystonic tremor from essential tremor. Diagnostic uncertainty is enhanced when no features of dystonia are found in patients with a tremor syndrome, raising the question whether the observed phenomenology is an incomplete form of dystonia.

Methods: Known forms of syndromes with isolated tremor are reviewed. Diagnostic uncertainties between tremor and dystonia are put into perspective.

Results: The following isolated tremor syndromes are reviewed: essential tremor, head tremor, voice tremor, jaw tremor, and upper-limb tremor. Their varied phenomenology is analyzed and appraised in the light of a possible relationship with dystonia.

Discussion: Clinicians making a diagnosis of isolated tremor should remain vigilant for the detection of features of dystonia. This is in keeping with the recent view that isolated tremor may be an incomplete phenomenology of dystonia.

Keywords: Dystonia, essential tremor, tremor, dystonic disorders, movement disorders

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Introduction

Dystonia and tremor are two movement disorders that are not rare and may occur independently or coexist. Dystonic tremor is part of the clinical spectrum of dystonia.[1,2] Dystonic tremor is usually associated with other features of dystonia, but may also occur in isolation.[3] Different dystonia syndromes can present with or without tremor and there is no unequivocal phenomenology for the distinction of dystonic tremor from non-dystonic.[2] Patients with isolated tremor and no features of dystonia pose a diagnostic challenge of whether the tremor is part of an incomplete phenomenology of dystonia (so-called "formes frustes"[4]), making the differential diagnosis of isolated tremor particularly difficult.[5]

Essential tremor (ET) is considered a prototypic syndrome of isolated action tremor.[6] Diagnostic uncertainty on the definition and diagnosis of ET has delayed the finding of genes for this entity: reliable biomarkers or imaging markers for ET do not exist, and pathologic investigations do not play a role in establishing or confirming the diagnosis. Clinical expertise still provides the mainstay for the diagnosis of isolated tremor syndromes.[6]

Here, we review the phenomenology of tremor and dystonia; we highlight similarities and differences, diagnostic uncertainties, and review in detail the clinical syndromes with isolated tremor.

Phenomenology

Tremor

Tremor is a rhythmic oscillation of a body part that occurs physiologically in some specific conditions (e.g., fear, cold) or as a movement disorder. The involuntary, rhythmic, oscillatory movement may affect one or several regions of the body about a joint axis.[5] Tremor is usually produced by alternating and synchronous contractions of reciprocally innervated agonistic and antagonistic muscles that generate a relatively symmetric displacement in both directions about the midpoint of the movement.[7] Tremor syndromes are the most common movement disorders encountered in clinical practice,

although only a fraction of patients who have tremor seek medical attention. In one epidemiological study it was found that 96% of normal people have a clinically detectable tremor.[8]

The anatomical origin and pathophysiologic mechanism of tremor are not fully understood and may vary depending on the type of tremor disorder. The oscillation is generated by rhythmical discharges in a neuronal network that are maintained by feedback and feed-forward loops.[9] Typically, a negative feedback loop may oscillate under specific circumstances (Figure 1). The cerebello-thalamo-cortical pathway is involved in virtually all pathologic tremors; its oscillation is likely to be impeded when stereotactic ablations or high-frequency stimulations are applied to the ventrolateral thalamus, a treatment that is efficacious in various tremor disorders.[10]

Tremor phenomenology can be described according to several criteria, such as distribution, frequency, etiology, and inheritance pattern. These are useful to convey information about the tremor type and to provide signposts toward differential diagnosis. Tremors are usually described by the context in which they appear: rest or action. A resting tremor occurs in a body part that is relaxed and completely supported against gravity (e.g., resting an arm on a chair).[11] Most tremor types, however, are action tremors that occur during voluntary contraction of a muscle. Action tremors can be further subdivided into postural, kinetic, task-specific, and isometric tremors. Further descriptors of tremor include age at onset, anatomic distribution (e.g., head, tongue, voice, limb, trunk), frequency, amplitude and regularity, and combination with other movement disorders or with other neurological signs. In isolated tremors, the only clinical sign is tremor; combined tremors, instead, may be associated with another movement disorder or other neurological or systemic manifestations.[6]

Tremor covers a wide syndromic spectrum. There is no diagnostic standard to distinguish among different tremor syndromes, making clinical assessment a challenging exercise. The different types of tremors are best divided into those occurring mainly at rest, mainly on posture, and mainly during movement (Table 1). This phenomenological approach is of great help for orientating the diagnosis.

Dystonia

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions that cause abnormal, often repetitive, movements and postures, or both. Dystonic movements are typically patterned and twisting, and dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.[12] This recent definition of dystonia recognizes that tremor falls within the phenomenological spectrum of isolated dystonia and that dystonic tremor may be difficult to distinguish from other tremor types. Currently, there is no consensus on diagnostic criteria for dystonia and the diagnosis is based on the recognition of its typical phenomenology, consisting of specific physical signs[13] (Table 2).

Body regions involved in dystonia are the upper or lower cranial region, the cervical region, the larynx, the trunk, the upper limbs, or the lower limbs. These different territories may be involved individually (focal dystonias) or in different combinations (segmental, multifocal, or generalized dystonias). Body distribution may change over time, typically with progression to previously uninvolved sites. Some dystonias occur only during particular activities or tasks, known as action- or task-specific dystonias (e.g., writer's cramp, musician's cramp). As for tremor, the clinical manifestations of dystonia vary widely: dystonia may be the only clinical sign (isolated dystonia), or it may be associated with another movement disorder or other neurological or systemic manifestations (combined dystonia).[12]

In isolated forms, dystonia is the only clinical sign: usually no secondary causes can be identified and there is no consistently associated brain pathology, a combination traditionally described as "primary dystonia."[14] Dystonia may emerge at any age, and age at onset is a relevant variable for the clinical presentation and the prognosis.[15] Some isolated dystonias can be attributed to a genetic cause. Currently, three genes are known to cause isolated dystonia, *TOR1A*, *THAP1*, and *GNAL*. In addition, three other genes have recently been implicated (*CIZ1*, *ANO3*, and *TUBB4*), which still await independent confirmation.[16]

At the anatomic level, several brain regions have been implicated in the pathophysiology of dystonia, leading to the concept that dystonia is not necessarily caused by the dysfunction of a specific brain region but rather may arise from dysfunction of a motor network.[17] In particular, there is increasing evidence that regions other than the basal ganglia are involved in dystonia. Isolated dystonia is presently regarded as a circuit disorder, involving the basal ganglia-thalamo-cortical and cerebello-thalamo-cortical pathways.

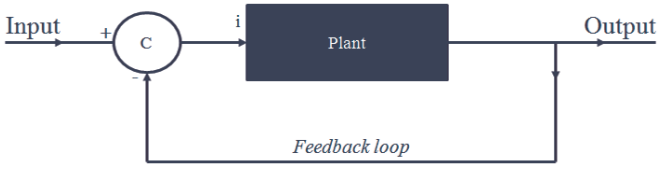

Figure 1. **Tremor generation by an oscillating circuit.** An oscillation may arise whenever there is a delay in a negative feedback loop or an increase in gain in the control signal. A reference signal provides input about the target or goal state; a comparator compares the sensed information and the reference signal; gain transforms comparison into a control signal (i) that brings the sensed position closer to the reference signal, thus negating the error; the plant converts control signals into real output.

Dystonic tremor

Tremor has been recognized as a clinical feature of dystonia and patients with dystonia commonly present with tremor.[12] Prevalence rates for tremor in dystonia vary from 11% to 87% across studies.[18] Tremor in dystonia manifests during posture or voluntary movements (action tremor), even though some dystonic patients may have tremor at rest, and is frequently unilateral; in patients with bilateral tremor it is often asymmetric.[19] Clinical studies of adult-onset isolated dystonia suggest that tremor usually starts at or after dystonia onset in body parts affected or unaffected by dystonia.[20] Some patients display focal tremor in the absence of any signs of dystonia, which may not become apparent until many years later.[3] Tremor in dystonia may affect the

Table 1. Common Tremor Disorders Classified According to Two Main Criteria

Relation to Voluntary Movement	Relation to Body Part
Rest tremor	Head tremor
Parkinson disease	Cerebellar disease
Other parkinsonian syndromes	Dystonia
Tardive (drug-induced) parkinsonism	Essential tremor (rarely when isolated)
Vascular parkinsonism	Chin tremor
Hydrocephalus	Parkinson disease
Psychogenic (functional) tremor	Hereditary geniospasm
Action tremor	Jaw tremor
Postural tremor	Parkinson disease
Physiologic tremor and enhanced physiologic tremor	Dystonia
Essential tremor	Palatal tremor
Dystonic tremor	Idiopathic (essential)
Parkinsonism	Owing to brainstem lesions (secondary)
Fragile X premutation (fragile X tremor–ataxia syndrome)	Owing to degenerative disease (adult-onset Alexander disease)
Neuropathies	Arm tremor
Tardive tremor	Cerebellar disease
Toxins (e.g., mercury)	Distonia
Metabolic disorder (e.g., hyperthyroidism, hypoglycemia)	Essential tremor
Psychogenic (functional) tremor	Parkinson disease
Kinetic tremor	Leg tremor
Cerebellar disease	Parkinson disease
Holmes tremor	Orthostatic tremor
Wilson disease	
Psychogenic (functional) tremor	

head, upper limbs, and voice; most studies report a higher incidence of head tremor than upper-limb tremor, and there is an even lower incidence of voice and leg tremor.[18] It has been suggested that dystonia has a higher tendency to spread in patients with associated tremor.[19,20] Dystonic tremor can be reduced by a geste movement or when the affected body part is positioned where dystonia tends to place it. Conversely, dystonic tremor is characteristically aggravated when a patient voluntarily orientates the affected body part against the main direction of dystonia pull (e.g., a patient with right torticollis may have an increase in dystonic tremor when attempting to turn the head to the left).

Syndromes with isolated tremor

Tremor with or without dystonia occurs in some typical syndromic aggregations that are repeatedly observed in the clinic. Some of these presentations are described in detail here.

Essential tremor

The term "essential tremor" refers to a syndrome where a 4–12 Hz action tremor (postural or kinetic) occurs in insolation in the absence of other neurologic signs.[21] No other movement disorders are present except for action tremor mostly involving the upper limbs (95% of cases), the

Table 2. Clinical Criteria for the Physical Signs Observed in Patients with Dystonia

Physical Sign	Description
Dystonic postures	Muscle contractions may be continuous, forcing limbs and trunk into sustained postures (not available for blepharospasm or laryngeal dystonia) A body part is flexed or twisted along its longitudinal axis Slowness and clumsiness for skilled movements are associated with sensation of rigidity and traction in the affected part
Dystonic movements	These features have to be looked for in all movement disorders, either fast or slow, also when the immediate impression is that of a tremor, tic, chorea, or myoclonus Tremor is a feature of dystonic movements and may appear as isolated tremor Movements are repetitive and patterned (i.e., consistent and predictable) or twisting Movements are often sustained at their peak to lessen gradually in a preferred posture (usually opposite to the direction of movement)
Gestes antagonistes (“sensory tricks”)	Are voluntary actions performed by patients that reduce or abolish the abnormal posture or the dystonic movements? They are usually simple movements involving, or directed to, the body region affected by dystonia These movements are natural and graceful, not consisting in forceful opposition to the phenomenology of dystonia The movement does not push or pull the affected body part, but simply touches it (“sensory trick”) or accompanies it during alleviation of dystonia Alleviation of dystonia occurs during the geste movement, usually soon after its start Alleviation may last for as long as the geste or slowly reverses spontaneously before its end
Mirror dystonia	It is evaluated in the upper or lower limbs. At least three different types of repetitive tasks (e.g., finger sequence, normal writing, or piano-like movements) are performed at low and fast speed in the non-affected limb It is a unilateral posture or movement with same or similar characteristics to the patient’s dystonia (usually postures and some movements) that can be elicited, usually in the more severely affected side, when contralateral movements or actions are performed
Overflow dystonia	It is observed at least once, usually ipsilaterally, in coincidence with the peak of dystonic movements It is an unintentional muscle contraction accompanying the most prominent dystonic movement, but in an anatomically distinct neighboring body region

head (34%), the voice (12%), the face (5%), the trunk (5%), or the legs (20%).[22] Tremor mainly involves the upper limbs bilaterally and symmetrically. Although head tremor in the absence of hand tremor is not uncommon, it usually develops after hand tremor.[23] Involvement of other body parts such as the legs, chin, trunk, tongue, soft palate, and, in rare cases, the lips has been reported. Head tremor typically develops several years after the onset of arm tremor, and the converse (tremor spreading from the head to the arms) is distinctly unusual.[24]

Table 3 summarizes the clinical features considered typical of ET. ET is traditionally considered one of the most common neurologic movement disorders,[25] with a prevalence 20 times higher than Parkinson disease (PD).[26]

The definition of ET points to a relatively straightforward phenomenology of isolated action tremor, but this has not been considered to be a lifelong characteristic. ET has gradually come to be considered a syndrome combining tremor and other neurological features, as described below. More recently, it has become evident that differential diagnosis between dystonia and ET is a challenging exercise even for neurologists expert in movement disorders.[1] Generally, if head tremor is isolated, a diagnosis of cervical dystonia rather than ET is likely.[27]

The longstanding notion that ET is a monosymptomatic tremor disorder has been challenged by a growing literature describing cerebellar signs,[28,29] cognitive impairment,[30] psychiatric disturbances (e.g., anxiety, depression, and social phobia),[31] and sensory abnormalities (olfactory deficits and hearing loss),[32] as well as poor nocturnal sleep quality.[33] These disturbances are mild in many cases and may be secondary, supporting the practical notion that “classic” ET is still monosymptomatic. Nevertheless, these observations underscore the heterogeneity of ET and cast doubt on the validity of defining ET as a disorder with isolated tremor.

The prevalence of ET increases with age. Data have suggested a bimodal peak in age of onset, one in adolescence (15–20 years) and

Table 3. Features Considered Typical of the Essential Tremor Syndrome

Feature	Description
Tremor	4–12 Hz action tremor that occurs when patients voluntarily attempt to maintain a steady posture against gravity (postural tremor) or move (kinetic tremor) Tremor may be suppressed by performing skilled manual tasks Tremor resolves when the body part relaxes as well as during sleep Tremor at rest is not uncommon and observed in approximately 20% of patients
Age at onset	Adolescence (15–20 years) or late adulthood (50–70 years)
Distribution	Bilateral with minimal asymmetry
Affected body sites[1]	Upper limbs >> head >> voice >> face/jaw >> tongue >> trunk >> lower limbs
Progression	Tremor may initially be intermittent, occurring during periods of emotional activation, and then becomes persistent over time
Response to alcohol	Beneficial alcohol response present in 50–75% of patients
Family history	Positive family history present in 30–60% of patients

[1]Listed from most to least prevalent site affected.

a second in late adulthood (50–70 years), with a mean age at presentation of 35–45 years.[34] A strong correlation between age of onset before 20 years and positive family history has also been reported in ET.[34] Data on the progression of this condition have shown a decrease in tremor frequency over time with a linear relationship between age and tremor frequency decrement and a tendency to develop larger amplitudes.[35] The frequency of tremor is inversely related to age, with older patients generally exhibiting tremor frequencies that are at the lower end of this range.[35] Although tremor is progressive, no association has been found between age of onset and severity or disability. Life expectancy in ET is supposedly not different from that expected in normal controls.[36]

Whether ET is a disease or a syndrome is currently a matter of dispute. It has also been proposed that ET may be an anatomo-clinical entity with a specific cerebellar pathology consisting of gliosis, Purkinje cell loss, and increased Purkinje axonal swellings (torpedoes).[37] Whether the proposed anatomo-clinical correlates are specific (or even pathognomonic) for ET, similarly to Lewy body pathology in the nigra for PD, has been challenged.[38]

ET can be familial in approximately 50% of cases, with an apparently autosomal dominant trait and high penetrance by age 65.[39] Studies of large families have identified candidate disease loci on chromosomes 3q13 (hereditary ET, type 1), 2p22–p25 (hereditary ET, type 2), and 6p23 (hereditary ET, type 3), and additional genetic loci are hypothesized.[40] The *ETM1* locus was mapped to chromosome 13q13 in 16 small Icelandic families,[41] the *ETM2* locus has been mapped to chromosome 2p24 in a very large Czech/American family,[42] and the *ETM3* locus has been mapped to chromosome 6p23 in one large American family, and in a second family co-segregation of markers in the *ETM3* region was shown.[43] The *ETM2* locus is based on a robust linkage result in one large family and could well harbor a gene for monogenic ET.[44] Genome-wide association studies have revealed that variant alleles of the *LINGO1* and *LINGO2* genes and of the glial glutamate transporter gene *SLC1A2* are associated with an increased risk of ET.[44] However, specific genes have not been identified, except for a possible rare mutation of the *FUS* (fused in sarcoma) gene that has been found in a large ET-affected family; moreover, a further screening of 270 ET cases identified two additional rare missense *FUS* variants.[45]

Head tremor

Tremor is a common feature in patients with cervical dystonia. Dystonic head tremor usually has a jerky attitude and a side prevalence, being more pronounced and forceful when the head is rotated on one side. Isolated head tremor is suggestive of concomitant dystonia. The phenotype of hereditary ET was studied in 20 index patients and their kindred: tremor of the head never occurred in isolation.[46] Moreover, it has been found that isolated head tremor without any arm tremor is rarely observed in young ET patients, as it is a late feature of the disease.[47] Therefore, it may be unwise to consider ET in subjects with isolated head tremor, which most likely may have an initial stage or a forme fruste of cervical dystonia.[48]

All forms of genetically determined dystonia may present with dystonic tremor of the head or hands.[1] Most dystonic movements are also accompanied by tremor. In some cases, tremor may occur in a limb that is not, or not yet, affected by dystonia. Furthermore, tremor may precede the onset of dystonic postural abnormalities. Cervical dystonia patients presenting with head tremor often also have hand tremor and a family history of tremor or other movement disorders.[49] Head tremor can be the presenting feature of cervical dystonia and

may remain isolated for long periods and even for the whole disease course. In such cases, the differential diagnosis with ET may be difficult. Head tremor in cervical dystonia more often persists when a patient lies down, whereas in ET head tremor may rather dissipate.[50]

Voice tremor

Voice tremor is a feature of a number of neurological conditions, including PD,[51] ET,[52] ataxic dysarthria,[53] and spasmodic dysphonia.[54] Spasmodic dysphonia affects the laryngeal muscles causing involuntary and sustained muscle contraction. Patients with isolated spasmodic dysphonia have an approximate 7% risk that dystonia may spread to another body part.[55]

Spasmodic dysphonia can encompass a variety of clinical manifestations, sometimes including a tremor component. The presentation may be that of an adductor-type or an abductor-type dystonia.[56] Adduction type dysphonia is a voice disorder characterized by a strained, strangled voice quality and intermittent voice stoppages, or breaks associated with over-adduction of the vocal folds, whereas abductor spasmodic dysphonia has intermittent breathy breaks associated with prolonged abduction of the vocal folds during voiceless consonants in speech. A recent study showed that patients with spasmodic dysphonia were 2.8 times more likely to have co-prevalent tremor than a control group with other voice disorders.[57]

The phonatory apparatus may be involved in 10–25% of cases in patients diagnosed with ET,[58] with some series reporting a prevalence as high as 62%,[28] a discrepancy highlighting inconsistency of sensitivity among examiners in recognizing the acoustic features of voice tremor. Although voice tremor is widely considered a typical manifestation of ET, typically occurring as a late feature in patients who already have upper-limb action tremor, some authoritative diagnostic schemes consider isolated voice tremor as incompatible with a diagnosis of ET.[22,59]

The term "essential voice tremor" has been introduced to indicate voice tremor occurring in isolation.[52] Isolated voice tremor has been described in patients diagnosed with either spasmodic dysphonia or ET. Whether isolated voice tremor can be considered part of the clinical spectrum of ET or is part of the clinical spectrum of dystonia is still debated. A recent study has found that somatosensory temporal discrimination processing is normal in patients with familial tremor and in patients with sporadic ET involving the upper limbs.[60] By contrast, somatosensory temporal discrimination is altered in patients with isolated head tremor and voice tremor, suggesting that isolated head and voice tremors might possibly be considered separate entities from ET.

Jaw tremor

Jaw tremor is a recognized feature of PD and related parkinsonian syndromes.[61] Jaw tremor has also been described in patients with ET,[46] usually in addition to arm tremor or as a component of other neurological disorders, such as hereditary geniospasm.[62] Jaw tremor can also be secondary to neuroleptic treatment[63] and is observed in normal situations, such as shivering.[64] In most of these conditions, jaw tremor is associated with tremor or other abnormal involuntary movements affecting additional body parts, and the tremor frequency usually does not exceed 12 Hz.

A high-frequency idiopathic isolated jaw tremor of 14–16 Hz has also been described. It has been speculated that it could be a focal variant of primary orthostatic tremor affecting the masseter muscles.[65] Both parkinsonian and high-frequency jaw tremor may benefit from botulinum toxin treatment.[66,67]

Jaw tremor is uncommon in patients with a diagnosis of ET, its prevalence ranging from 7.5% to 18%.[68] These patients usually have associated postural limb tremor. Suspicion of misdiagnosis should be raised for such cases, as patients referred for essential jaw tremor may have dystonia or PD, particularly the latter if rest tremor is also observed.[68] Patients with dystonic jaw tremor and jaw tremor associated with dystonia have been described.[69]

Upper-limb tremor

Writing tremor (previously also called primary writing tremor) is a condition in which tremor, usually characterized by prominent pronation/supination wrist movements, occurs predominantly or exclusively during writing.[70] No other neurological signs are evident except for slight postural and terminal kinetic tremor. Writing tremor can be task-induced or position-sensitive. The epidemiology and the natural course of writing tremor have not been fully elucidated. Age at onset varies, and cases manifesting during childhood have been reported. The disorder begins slowly, progresses for years, and becomes stabilized. Family history is generally unremarkable.[71]

Writing tremor has been variably classified as an independent entity, an ET variant, a focal dystonia, or a bridging entity.[72] In the first reported cases, the writing disorder and tremor were both temporarily abolished by a partial motor point anesthesia of the pronator teres, suggesting that tremor was caused by an abnormal central response to muscle spindle discharges originating in the pronator teres.[70] Although it resembles ET (because tremor is present on action and on maintenance of a posture, and may affect handwriting), the task-specific nature, lack of response to propranolol, and a documented effect of central cholinergic drugs[71] suggest that writing tremor is more closely related to dystonia than to ET. The observation of abnormal co-activation of antagonist muscles also supports this view.[73] However, writing tremor has been differentiated from focal task-specific dystonia (such as writer's cramp) by the lack of excessive overflow of electromyography activity into the proximal musculature, and the absence of reciprocal inhibition of the median nerve H-reflex upon radial nerve stimulation.[74]

Hand and arm tremors have been described in patients with primary cervical dystonia[75] and in patients diagnosed with ET[58] or PD.[76] Dystonic upper-limb tremor usually has the same frequency and recruitment characteristics as physiologic tremor and has been considered a variant of physiologic tremor.[77] Some of these patients have been considered to have ET in addition to dystonia.[22]

Diagnostic uncertainties

Misdiagnosis of tremor syndromes is common, because clinicians frequently overlook additional neurologic signs. Action tremor in the hands is caused by many conditions, including dystonia and PD. Isolated tremor is likely over-diagnosed as ET, whereas dystonia syndromes are under-recognized.[78] A collection of physical signs of dystonia has been proposed recently (Table 2). By some estimates, as many as 30–50% of supposed ET cases have other diagnoses, especially dystonia and PD.[79,80] The clinical characteristics of ET in the upper limbs are difficult to systematize, and an identical action tremor can be the sole presenting symptom in patients with PD[81] or dystonia.[82] Highly asymmetric ET is possible but still debated. Notwithstanding, some patients can be erroneously diagnosed as having ET if they are examined before the onset of dystonia or parkinsonian features. Even resting arm tremor has been observed in ET, mainly in advanced cases,[83] and similar features have been described also in patients with isolated dystonia.[84,85]

A review of 350 patients diagnosed as ET disclosed dystonia in half of them, including cervical dystonia, writer's cramp, spasmodic dysphonia, and cranial dystonia.[27] The suggestion that dystonic patients are frequently misdiagnosed as ET has been recently confirmed.[86] ET and dystonia may have overlapping clinical features. For example, head tremor may occur with similar features in patients with either ET or cervical dystonia, and at times there can be considerable diagnostic uncertainty, for example when head tremor is mild or not associated with twisting movements or head deviation.[87] Misdiagnosis of dystonia in favor of ET may also depend on the observation of confounding clues in tremulous dystonic patients, such as autosomal dominant family history or alcohol responsiveness.[88] The recognition of specific features for tremor phenomenology has a potential diagnostic value for the practicing clinician: isolated focal, position-specific, and task-specific tremors are likely not to be ET and are often associated with subtle dystonia.

Dystonic tremor may be mistaken for parkinsonian tremor, particularly when a resting component is observed. In conditions of incomplete arm rest, the positional component of dystonia may lead to the diagnosis of a parkinsonian rest tremor instead of dystonic tremor. In addition, dystonic slowness can resemble bradykinesia observed in PD[89] and upper-limb dystonia causes reduced arm swing.[84] A full set of maneuvers is required to detect parkinsonian bradykinesia[90] and the features of dystonia;[13] therefore, incomplete examination may lead to a diagnostic mistake emphasizing the most visible physical sign: tremor.

Many patients with dystonic tremor can reduce tremor amplitude by using their own tricks, a feature that has not been described in ET, and is well documented in dystonic head and upper-limb tremor. Other important, albeit less specific, diagnostic clues of dystonia are the focal nature and low frequency of dystonic tremor. In addition, dystonic tremor may also be suspected by the observation of a "null point" (a specific position that, when held by the patient, alleviates the tremor), or of other features uncommon in ET, such as lack of tremor when the finger touches the nose, but severe tremor when attempting an arm movement toward an extended target such as an examiner's finger.[91]

Since its discovery, dopamine transporter imaging has been considered a tool for distinguishing ET from PD patients.[92,93] Recently, it has been reported that a significant proportion of patients without dopaminergic denervation (between 11% and 15%) received a diagnosis of PD at expert centers.[94,95] Interestingly, the main diagnosis (alternative to PD) in such patients was not ET, but dystonia.[96] Dystonic tremor, slowness, and reduced arm swing were the most likely confounding factors.[84] It has been suggested that clinical peculiarities suggesting dystonic, rather than parkinsonian, tremor are subtle dystonia, thumb extension tremor, "flurries" or task/position-specific tremor, head tremor, dystonic voice, no progression to develop features other than tremor and dystonia, no clear fatiguing, or decrement of repetitive movements.[96]

Mirror movements have been described in ET, PD, and dystonia syndromes, where they are characterized by a dystonic appearance, so-called mirror dystonia that is typically observed in the upper limbs.[97] The distinction between mirror dystonia and mirror movements without features of dystonia[98] allows dystonia to be distinguished from ET or PD in many instances.

In summary, clinical features that increase the odds of over-diagnosing ET have been identified. They include unilateral arm tremor, isolated head or leg tremor, re-emergent tremor, presence of a null point or sensory trick, tremor directionality, and reduced arm swing.[79] However, the diagnostic exercise remains challenging in patients with tremor syndromes, where clinical skills provide the most reliable tool for establishing the diagnosis.

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