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Essential pitfalls in "essential" tremor

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Abstract

While essential tremor has been considered the most common movement disorder, it has largely remained a diagnosis of exclusion: many tremor and non-tremor features must be absent for the clinical diagnosis to stand. The clinical features of "essential tremor" overlap with or may be part of other tremor disorders and, not surprisingly, this prevalent familial disorder has remained without a gene identified, without a consistent natural history, and without an acceptable pathology or pathophysiologic underpinning. The collective evidence suggests that under the rubric of essential tremor there exists multiple unique diseases, some of which represent cerebellar dysfunction, but for which there is no intrinsic "essence" other than a common oscillatory behavior on posture and action. One approach may be to use the term "essential tremor" only as a transitional node in the deep phenotyping of tremor disorders based on historical, phenomenological, and neurophysiological features, to facilitate its etiologic diagnosis or serve for future gene- and biomarker-discovery efforts. This approach deemphasizes essential tremor as a

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diagnostic entity and facilitates the understanding of the underlying disorders in order to develop biologically tailored diagnostic and therapeutic strategies.

Keywords

Essential tremor; tremor; biomarkers; nomenclature

Essential tremor (ET) has been defined clinically as a disorder manifested by bilateral, largely symmetric, postural or kinetic tremor involving the hands, with with variable combination of midline tremors (head, vocal cords and face), in the absence of abnormal posturing, task specificity, or position dependence.[1] In the seminal description by Critchley, ET variations involve the legs, in which there may be “dyskinetic movements”, ataxia, “foot clubbing” or “evidence of peroneal atrophy”.[2] ET has remained conceptualized as a single disorder rather than a syndrome comprised of several distinct disorders in part because we, as clinicians, have accepted its unclear boundaries: it affects both hands, but can be asymmetric or even (if rarely) unilateral;[3] it can occur over a wide, non-specific frequency range (4–12 Hz);[4] it may exceed its postural amplitude at rest (as in parkinsonian tremor) or on action (as in cerebellar outflow tremor);[5] and it may affect handwriting but not exclusively at onset (as in primary writing tremor).[6] The diagnosis of ET is, thus, based on excluding distinctive tremor types rather than asserting what the tremor of ET is. It is now clear that no existing definition of ET converges into a single disease. As a result, ET has not been associated with a key neurophysiologic marker or a defined genetic etiology despite its apparent autosomal dominant pattern of inheritability. The diagnosis of ET has been largely one of exclusion.

High rate of misdiagnosis

The misdiagnosis rate of ET in two studies has been reported to range from 37%[7] to 50%.[8] While Parkinson’s disease (PD) and dystonia may be under-recognized when tremor is prominent, neuropathic tremor, unilateral leg tremor, drug-induced tremor, and functional tremor may also be misreported as ET.[7, 8] In patients with orthostatic tremor (OT), “postural upper extremity tremor while seated”, documented in 22.8% of 184 patients with OT, has been suggested to represent coexistent ET rather than a harmonic of the original high frequency tremor characteristic of OT.[9]

Other important entities that may be commonly misattributed to ET include enhanced physiological tremor,[10] spinocerebellar ataxia type 12,[11] Fragile X tremor-ataxia syndrome,[12] dystonic tremor,[13] cortical tremor (truly a form of rhythmic cortical myoclonus), and benign tremulous parkinsonism (most of which represent PD).[14] The latter may actually represent either dystonic tremor or mono- or oligo-symptomatic PD, poorly responsive to levodopa but with very slow progression and restricted pathology.[15]

The pitfalls in the diagnosis of ET

Lack of consensus on clinical boundaries

The clinical separation is initially impeded by the problem with the very nomenclature of *essential,* which is shrouded in as much obscurity as the terms *primary*, *idiopathic*, and *senile* (Table 1). The adjective *essential* does not truly appear to uncover the diagnostic *essence* of any disorder and may instead provide a false sense of security that obscures critical knowledge gaps. More detailed clinical characterization of patients and large families, has served to replace such reductive terminology with more appropriate syndromic or etiologically appropriate labels, in some cases with genetic and molecular ascertainment, amenable to inclusionary rather than exclusionary diagnosis.

There also remains an undefined boundary between *senile tremor* (ranging from Critchley's "senile variety of essential tremor"[16] to Deuschl's "age-related tremor" [17]) and the reported distinct second epidemiological age peak of ET. Tremor onset after the age of 65 years is associated with an increased risk of dementia, a different natural history than those with tremor onset earlier in life.[18] On the other hand, family history and alcohol responsiveness may be more common in early-onset "ET",[19] and may be associated with other tremor syndromes to a similar or greater extent. Yet they continue to be used as supportive of the diagnosis of ET.[20, 21] Another controversial entity is *isolated head tremor*, which represents in most instances tremulous cervical dystonia. In fact, of 50 patients diagnosed as "essential tremor" randomly reviewed at the National Hospital for Neurology and Neurosurgery in London, only 25 (50%) were confirmed to have ET on subsequent analysis.[8] Patients received alternative diagnoses (dystonia in 4, neuropathic tremor in 2, drug-induced tremor, functional tremor and myoclonus in 3 other cases) or atypical features suggested an alternative diagnosis of dystonic or parkinsonian tremor (7 cases with rest tremor, 2 with reduced arm swing), functional tremor (2 with sudden onset), and tremor associated with dystonia (1 case with a family member with an 'isolated head tremor'); others had tremor in other body sides, including unilateral leg tremor in 2 cases.[8] The authors concluded that the diagnosis of ET was overused and other types of tremor were overlooked when making this diagnosis.

Although the current diagnostic criteria of ET imply the lack of other overt neurological signs, many publications have assumed that ET and dystonia or PD may actually co-exist instead of representing ET mimics such as 'tremor associated with dystonia' and 'Type II PD tremor', respectively.[1] For instance, in a large study on 463 patients from 97 kindreds with autosomal dominant mode of inheritance, "pure" ET was present in 365 individuals whereas remaining cases were felt to have a distinct ET subtype, "ET associated with dystonia" .[22] Similar nosological confusion has affected PD research, resulting in the pursuit of a common genetic underpinning with ET.[23, 24]

A retrospective review of 350 patients with a diagnosis of ET found that 47% of patients had associated dystonia (spasmodic torticollis in 27%, writer's cramp in 14%, blepharospasm in 7%, and spasmodic dysphonia in 4%) and 20% had parkinsonism.[25] Nevertheless, the authors concluded that there was "no support for differentiation of ET subtypes" and that "although heterogeneous in its clinical presentation, [ET] is a single disease entity."[25]

However, head or hand tremor can be the sole initial manifestation in patients with mutations in the anoctamin 3 (*ANO3*) gene, which results in autosomal dominant craniocervical dystonia (DYT24), often misdiagnosed as ET.[26] Indeed, epidemiologic, clinical, and neurophysiologic data support non-task-specific dystonia as the appropriate nomenclature for a large proportion of patients currently classified as ET.[27]

Because postural and action tremor is a nonspecific feature of many diseases, there has been a large diversity of manifestations reported to be associated with ET (including the increased risk of PD, see also *Long-term prognosis* section below) based on the assumption of shared common biological mechanisms. For instance, some non-motor features have been recently suggested to represent "core non-motor symptoms" of ET: hyposmia,[28] hearing impairment,[29] cognitive impairment,[30] and depression.[31] Impairments in verbal fluency, naming, mental set-shifting, verbal memory, and working memory compared to a normative sample were reported in 18 ET surgical candidates, in a pattern similar to PD (not adjusting for depression, other comorbidities, or medication exposure).[32] In a population based study, after adjusting for age, stroke, and educational level, patients with tremor onset after the age 65 were 70% more likely to be demented than controls.[18] Hearing, olfactory, and cognitive impairments in each case appeared to be non-specific for a single entity, such as ET. In fact, the reported hyposmia of ET becomes indistinguishable from that of controls when the effects of age, age of onset, gender, and smoking are taken into account.[33]

Lack of consensus on prevalence

Because age-dependent tremors continue to be classified as ET there is wide variability in the reporting ET prevalence. Indeed, prevalence estimates vary 2,750 fold (8 to 22,000 cases per 100,000 population) among 20 studies.[34] Similarly, "mildly abnormal tremor resembling mild ET"[35] or any "signs of tremor"[36] are documented in unselected ostensibly normal individuals with a mean of 74[36] to 76 years.[35] Thus, the cutoff between "senile" and ET tremor is poorly defined, suggesting either a substantial phenotypic heterogeneity in ET or a variety of disorders that exhibit tremor as one of their features.

Lack of consensus on electrophysiology

The diagnosis of ET cannot be confirmed with electrophysiology given the wide range of allowable frequency, 4 to 12 Hz,[1] and the many allowable clinical variations, including the presence of both synchronous and alternating contraction of agonist and antagonist muscles.[37] Surface electromyography and accelerometry can be used to support the presence of other tremor disorders rather than to confirm ET. In a population study from South Tyrol, tremor analyses of clinically suspected ET patients forced a substantial number to be reclassified as enhanced physiological tremor (because of reduction of the tremor frequency with weight loading in the latter), restricting the diagnosis of ET to the identification of a central tremor component on accelerometry.[38] Electrophysiology has been used to separate ET from dystonic (evidence of overflow, effect of sensory tricks) and functional tremor (variability in frequency, entraintment),[39, 40] but not from some forms of cerebellar tremor (the tremor generator likely differs in cerebellar neurodegenerative disorders compared to cerebellar lesions, such as in multiple sclerosis).[5] In fact, there is no neurophysiological marker or single brain tremor-generating region common to what has been believed to

represent ET.[41] A synchronous rather than an alternating EMG burst pattern has been considered a hallmark of dystonia (assumed to represent co-contraction) but its diagnostic accuracy is debatable. More recently, temporal discrimination has been found to distinguish "tremor associated with dystonia" from ET[42] and, interestingly, the same technique served to place isolated head and voice tremors fall into the category of dystonic tremors.[43]

Lack of consensus on pathology

Pathology studies have not yielded consistent findings, which may be due to the brain banking of heterogeneous "ET" populations. On one end of the spectrum, Lewy bodies in the locus ceruleus and torpedos in Purkinje cells have been reported by one group in a study of 33 ET brains.[44, 45] A separate postmortem study of 24 brains of patients diagnosed with ET, however, found cerebellar gliosis and locus coeruleus depletion but no torpedos or Lewy bodies.[46] The loss of Purkinje cells remains also confounded by the unclear long-term effect of medications and alcohol used to abate tremor and the extent to which it may be associated with disease duration. Nevertheless, a study comparing Purkinje cells in 7 ET and 6 PD brains found no difference across them, or with age-matched healthy controls.[47]

Lack of consensus on long-term prognosis (and the ET-PD conundrum)

While some epidemiologic studies have suggested that ET increases the risk of PD four- to five-fold,[48] possibly reflecting the "Lewy body variant of ET",[44] other studies have suggested no such shared risk or pathology.[46, 49] Nevertheless, this potential association raises the possibility that in some patients diagnosed with ET, this tremor represents a 'transitional' manifestation of a disorder yet to be characterized. This is supported by the fact that fewer than 10% of community dwellers with a diagnosis of ET had been diagnosed by their primary physician as having ET and only 5% were taking an anti-tremor medication,[50] which suggests that those who come to medical attention have an unusually severe form of the disorder, a different disorder altogether, or a separate neurological abnormality beyond tremor. Further compounding the assessment of long-term outlook is the reported bimodal distribution of the age at onset of ET, a first peak in late teens and a second in late adulthood, which suggests the existence of at least two different pathophysiologic entities –and therefore two different courses. In particular, the late-onset ET group may be associated with dystonic features on exam (e.g., isolated rest tremor or the jaw and/or head and spasmodic dysphonia, which have a gender predilection for women) [34] or with non-motor symptoms possibly representing the aforementioned 'transitional' manifestations to developing PD, dementia[51] and postural impairment.[52]

In sum, as a syndrome whose only "essence" is the abnormal oscillation in motor pathways resulting in rhythmic modulation of motor unit activity, ET lacks an electrophysiologic signature to distinguish it from most other tremor disorders, an identified gene or genes despite its prevalence, a consistent natural history, and an acceptable underlying pathological substrate.

Approach to postural and action tremor

Postural and action tremor can be seen in enhanced physiologic tremor due to many drugs or metabolic changes (mechanical-reflex oscillations), PD and other degenerative parkinsonisms, dopa-responsive dystonia, Wilson's disease, cerebellar diseases, and many other (central neurogenic oscillations) disorders. When a diagnostic work up fails to uncover an etiology, the term “ET” is generally applied and has become further enriched with a variety of features (Figure 1A) and associated movement disorders (Figure 1B). The reduction of postural and action tremor into the single *essential* construct of ET (exclusionary diagnosis if the features and any associated movements are “soft” or “non specific”) deserves reappraisal to facilitate its decomposition into what is most likely a number of distinct diagnostic etiologies (inclusionary diagnosis) and to assist future genomic and biomarker research.

An approach to tremor, as recently applied to a reclassification effort for dystonia (Figure 1C),[53] avoids accepting “associated signs” as permissible for “ET” and relies instead on a two-step approach to postural and action tremor as presenting in isolation or in combination with other movement disorders, permitting their separation into “isolated” and “combined” tremor (Figure 2). In addition to the determination of age of onset (childhood, adolescence to early adulthood, and older than 45 years)[19] and family history (of tremor, dystonia, parkinsonism, ataxia, and/or dementia), the following clinical characteristics of the tremor can facilitate the search for an underlying etiology: distribution (arms, legs, head, vocal cords, or a combination thereof), activating condition (rest, postural, action, intention, position/task specificity), and frequency (low [2–3], moderate [4–7], high [8 and above]). In the case of tremor presenting in combination with other features, key abnormalities to identify are dystonia (in the affected limb or distant body part), bradykinesia, and cerebellar features, with or without cognitive and/or gait impairment (Figure 2).

Subdividing cases in this fashion does not preclude combining categories when there is a clear justification for this. For example, the separation may permit the recognition of a genetic cause, which in turn may segregate with a broader clinical spectrum suggesting phenotypic heterogeneity with a single genetic cause. However, splitting into descriptive forms of isolated or isolated-plus tremors will reduce the “noise” that may prevent us from finding specific underlying causes.

Conclusions and future steps

Holding ET hostage to a single heteregenous construct may continue to prevent the identification of the constituent disorders that have been subsumed under this umbrella. While a change in nomenclature from ET to any other designation may not be critical in and of itself, the understanding that it represents a *starting point* rather than the end itself is important to facilitate etiologic diagnoses and a molecular approach to future therapeutic endeavors. To facilitate further studies, a better characterization of the historic and semiologic features of tremor are to represent the foundation for the ascertainment of unique etiologies. As a consequence of this approach, the waste basket of “ET” will continue to shrink from the absence of *essential* elements in its natural history, electrophysiology,

genetic underpinnings, and pathology. Assisted by efforts in genomics and biomarker development applied to large tremor populations, the field should evolve into an era of etiologically-defined tremor disorders. Only then will biologically tailored interventions be selectively developed for specific tremor disorders.

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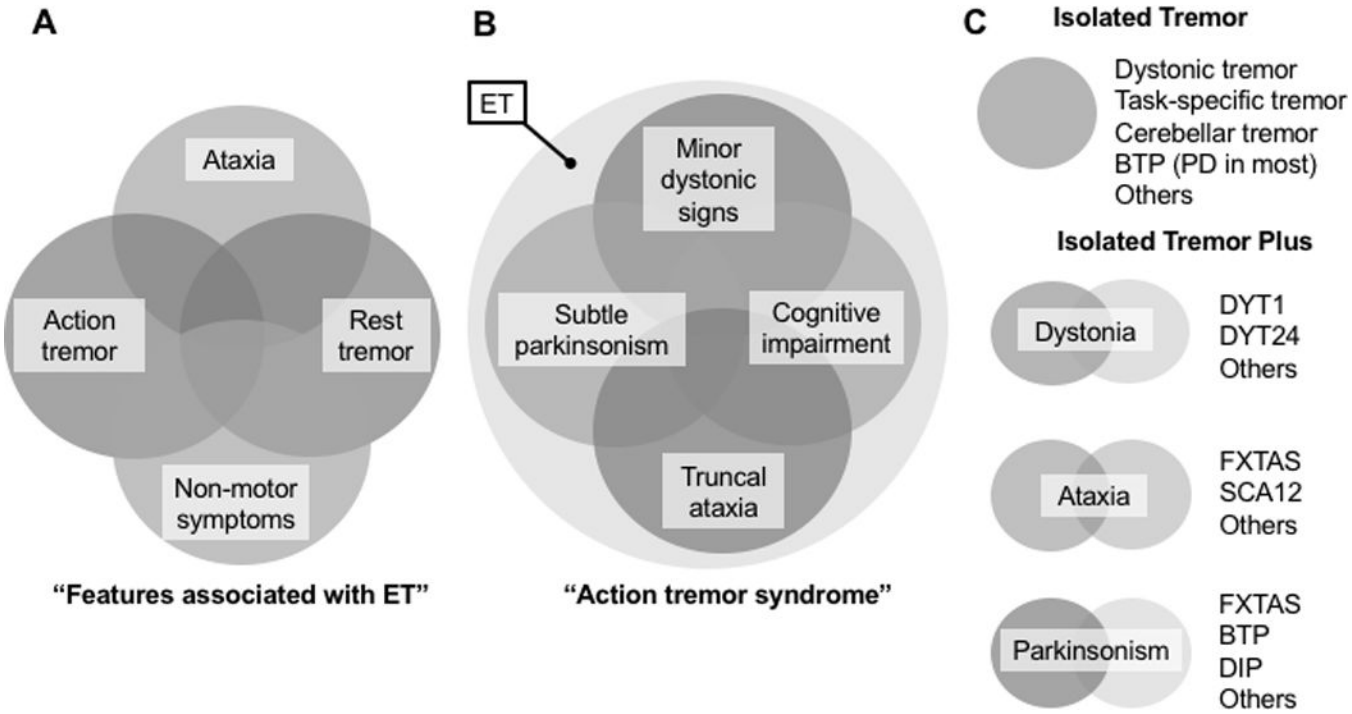

Figure 1. Models of tremor

ET has been viewed as a single but heterogeneous disorder (**A**, model adapted from Louis et al[60]) and as an "isolated action tremor syndrome" encompassing other movement disorders (**B**; accounting for cases where "classic ET is too narrowly defined"[61]). An alternative model (**C**, brought to the fore in the reclassification effort for dystonia[53]) relies on the phenomenological characterization of tremor as a movement presented in isolation or in combination with other movement disorders. ET: essential tremor, BTP: benign tremulous parkinsonism; DIP: drug-induced parkinsonism; DYT: designation for genes associated with dystonia; PD; Parkinson disease; FXTAS: Fragile X tremor ataxia syndrome; SCA: spinocerebellar ataxia

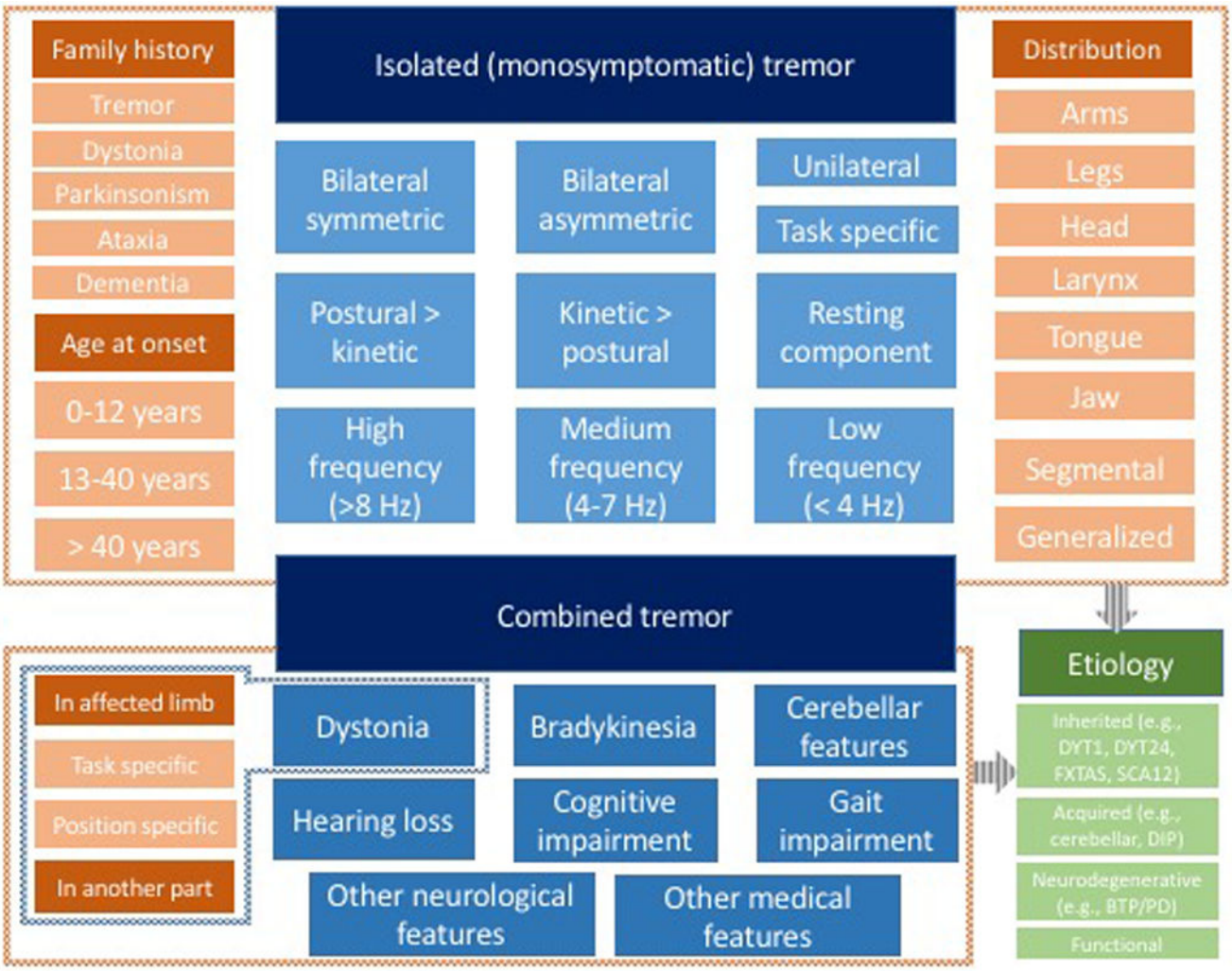

Figure 2. Approach to tremor

Historical (shades of red) and clinical features of isolated (upper box) or combined tremor (lower box) serve to provide the foundations on which the etiologic diagnosis (shades of green) can be formulated. The phenomenological clues and etiologic considerations stemming from them are similar to those used in the recent redefinition of dystonia.[53]

Table 1

Essential, *Primary*, *Senile*, and *Idiopathic*: Covering gaps in knowledge

Early nomenclature	Revised nomenclature	Implication
Primary dystonia	Isolated dystonia	"Primary": not reliable for etiology
Essential myoclonus	Myoclonus dystonia[54] Benign hereditary chorea[55]	"Essential myoclonus" encompassed a syndrome
Essential palatal tremor	Isolated palatal tremor including special skills, functional palatal tremor and tics[56], [57]	"Essential" included other recognizable palatal tremors
Senile gait	Highest-level gait disorder Parkinsonian gait	"Senile"[58] wrongly implied changes due to normal aging
Senile chorea	Most often late-onset Huntington disease, antiphospholipid antibody syndrome, hypocalcemia, or tardive dyskinesia[59]	"Senile" chorea wrongly suggests it may be due to normal aging
Idiopathic Parkinson's disease	PARK1, 2, 4, 7, 8… Ongoing genetic-molecular phenotyping	"Idiopathic" becomes an ever narrowing slice of PD, as genetic/molecular etiologies are unveiled