



Published in final edited form as:

Curr Neurol Neurosci Rep. 2013 June ; 13(6): 353. doi:10.1007/s11910-013-0353-4.

What is essential tremor?

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Abstract

Classic essential tremor is a clinical syndrome of action tremor in the upper limbs (at least 95% of patients) and less commonly the head, face/jaw, voice, tongue, trunk, and lower limbs, in the absence of other neurologic signs. However, the longstanding notion of that essential tremor is a monosymptomatic tremor disorder is being challenged by a growing literature describing associated disturbances of tandem walking, personality, mood, hearing and cognition. There is also epidemiologic, pathologic and genetic evidence that essential tremor is pathophysiologically heterogeneous. Misdiagnosis of essential tremor is common because clinicians frequently overlook other neurologic signs and because action tremor in the hands is caused by many conditions, including dystonia, Parkinson disease and drug-induced tremor. Thus, essential tremor is nothing more than a syndrome of idiopathic tremulousness, and the challenge for researchers and clinicians is to find specific etiologies of this syndrome.

Keywords

essential tremor; physiologic tremor; dystonia; Parkinson disease

Introduction

Essential tremor (ET) is widely recognized as a common condition that is frequently associated with significant physical and psychosocial disability. The literature is now full of seemingly conflicting opinions and experimental observations pertaining to ET. I believe this confusion stems largely from the fact we are still in the process of defining it, and we frequently lose sight of the fact that ET is a clinical syndrome, not a specific disease. Consequently, discussions regarding etiology, pathogenesis and clinical phenomenology of ET are often unnecessarily contentious and confusing. These issues and possible remedies are discussed in this review.

Historical review of essential tremor

The term “essential tremor” was first used by Buresi in 1874 to describe patients with action tremor and no other neurologic signs, and early writers noted that this condition was often hereditary [1, 2•]. While ET was usually described as a monosymptomatic disorder, patients with dystonia of the neck or face and myoclonus were often included in discussions, and congenital and senile varieties were also described [2•]. Most early writers emphasized that idiopathic tremulousness was common and different from Parkinson disease.

Conflict of Interest

Rodger J. Elble has received honoraria from Kinetics Foundation and Movement Disorder Society.

Critchley [2•] noted that patients with longstanding mild ET often exhibit accelerated progression late in life, suggesting a role for “normal aging” or age-associated disease in the clinical expression of the disorder. Supporting the role of age-associated co-morbidities was the observation that “Additional neurological features may at this stage now make their appearance for the first time” [2•]. Late-onset ET is associated with increased risk of dementia [3], Parkinson disease [4], death [5], and more rapid progression [6], supporting the notion of senile tremor as a subtype [7•].

Marsden and coworkers [8] defined four types of ET and emphasized that ET is not a single entity. Type 1 ET is a mild hand tremulousness that is produced by enhanced mechanical-reflex oscillation [9•]. This so-called enhanced physiologic tremor is produced by hyperadrenergic states (e.g., anxiety, drug withdrawal), thyrotoxicosis and tremorogenic drugs such as lithium and valproic acid. The tremor frequency decreases with inertial loading of the hand [9•]. Type 2 ET is more severe than type 1 and often involves the lips, chin, tongue, voice, head, and sometimes even the legs. This tremor is produced by a central neurogenic oscillation at a frequency that is not a function of limb inertia or reflex arc length [9•, 10]. It is often hereditary, and it is often disabling, even though most patients with this tremor have not been diagnosed by a physician [11–13]. Type 3 ET is severe, disabling tremor of the magnitude that often leads to stereotactic surgery. Type 3 tremor is a natural progression of type 2 ET in some patients, but there are reasons to believe that this is not always the case. Many type 3 patients do not have a family history, and other subtle neurologic signs (e.g., mild dystonia and parkinsonism) are often overlooked by clinicians [14••]. Marsden’s type 4 ET is nonspecific action tremor of the upper limbs that is believed to be secondary to a specific disease, such as hereditary demyelinating neuropathy, dystonia and Parkinson disease. The clinical characteristics of ET in the upper limbs are nonspecific, and identical action tremor can be the sole presenting symptom in patients with Parkinson disease [15, 16] and dystonia [17–20].

In 1994, Bain and coworkers noted that “The assumption that hereditary essential tremor and the sporadic essential tremors are the same entity has arisen insidiously within the literature but may not be true” [21•]. They examined the characteristics of people from 20 families with an autosomal dominant pattern of inheritance. Tremor invariably started in the upper limbs and was symmetrical in about 80%. There were no instances of isolated tremor in the head, tongue, voice, jaw, trunk or lower limbs. The upper limbs were the only affected body parts in 66% of affected relatives of 20 probands. The other relatives exhibited abnormal action tremor in the legs (~30%), the head (~17%), jaw (5.7%), tongue (3.8%), facial muscles (3.8%) and voice (5.7%). Tremor severity correlated with patient age and duration of tremor. Age of onset was before age 65 in all cases. No family member exhibited dystonia or Parkinson disease. More than 85% of affected people exhibited Marsden’s type 2 ET and the remainder type 3. However, other investigators have found that many families with reportedly “pure ET” include patients with focal (mainly cervical) and segmental dystonia [22], and some experts routinely include patients with dystonia in their working definition of ET [23].

A *circa* 1995 survey of members of the Movement Disorder Society by Chouinard and coworkers [24] revealed widely varying inclusion and exclusion criteria for the diagnosis of ET. Isolated tremor of the head or voice was viewed by 81% and 70% of specialists as being compatible with the diagnosis of ET. Fifty-nine percent thought that a specific duration of tremor was not necessary in making the diagnosis, and only 10% required a history of tremor for at least 5 years. Only 40% required bilateral upper extremity tremor. Twenty-nine percent thought that tremor in a dystonic limb was compatible with the diagnosis, and 52% thought that dystonia elsewhere was compatible. Only 46% thought that the presence of

neurological signs excluded the diagnosis of definite ET, and 42% thought that the presence of Parkinson disease was compatible!

Recent attempts to define essential tremor

In the past 20 years, investigators have sought a more stringent definition of ET that would increase the chances of capturing a single entity. In particular, they have excluded Marsden's types 1 and 4, and when this is done, ET becomes a clinical syndrome of action tremor in the upper limbs (at least 95% of patients) and less commonly the head (at least 34%), face/jaw (approximately 7%), voice (at least 12%), tongue (approximately 30%), trunk (approximately 5%), and lower limbs (approximately 30%) [25], in the absence of other neurologic signs. Approximately 70–80% of people with this syndrome have mild tremor and have not seen a physician for this condition [12, 21, 26–28]. Lower extremity tremor is usually mild or asymptomatic [21, 25].

Excluding Marsden's type 1 is not easy. Enhanced physiologic tremor has a frequency that is a function of the mechanical stiffness and inertia of the joint (e.g., the wrist) and also the stretch reflex loop time (mechanical-reflex tremor). Therefore, adding mass to the hand, reduces the tremor frequency [9•]. ET has a frequency that is independent of these mechanical and reflex properties (central neurogenic tremor). However, these neurophysiologic properties have limitations. Very mild ET is often so intermittent that the bursts of motor unit activity perturb the limb intermittently, instead of driving it rhythmically. Therefore, very mild type 2 ET may exhibit the neurophysiologic characteristics of mechanical-reflex (type 1) tremor [9•]. Another limitation is that nearly 10% of clinically normal people exhibit a central neurogenic 8–12 Hz tremor, in addition to a normal mechanical-reflex oscillation [29]. The 8–12 Hz central neurogenic component of physiologic tremor was once hypothesized to be a *forme fruste* of ET [10], but the frequency of motor unit entrainment is 8 Hz or less in most patients with definite ET, and the neurophysiologic transition from normal to abnormal in two people with hereditary ET did not include the manifestation of an 8–12 Hz central neurogenic tremor [30]. Therefore, this neurophysiologic test for essential hand (wrist) tremor is unequivocally abnormal only when there is a central neurogenic tremor at 4–8 Hz, and central neurogenic tremors in the same frequency range can be seen in Parkinson disease and dystonia [9•].

Other investigators have used stringent amplitude criteria, assessed with clinical rating scales, to exclude enhanced physiologic tremor [31, 32]. By setting the amplitude requirement high enough, patients with physiologic and enhanced physiologic tremor will be excluded with a very high degree of certainty, but some patients with mild ET will also be excluded [31, 32]. Consequently, some investigators combine the neurophysiologic characterization of tremor with clinical ratings to diagnose mild ET [33]. Motion transducers can be used to quantify tremor amplitude precisely, but variability in tremor amplitude is so high that there is significant moment-to-moment overlap in values of patients and controls [10].

Excluding Marsden's type 4 ET is usually possible by clinical history (onset and duration of action tremor) and exam (identification of other signs). The clinical characteristics of ET in the upper limbs are nonspecific, and identical action tremor can be the sole presenting symptom in patients with Parkinson disease [15, 16] and dystonia [17–19]. Therefore, some patients with these diseases will be erroneously diagnosed as ET type 2 if they are examined before the manifestation of other diagnostic signs. Unfortunately, the duration of monosymptomatic tremor needed to safely exclude other disorders is unknown. According to the diagnostic criteria of the Tremor Investigation Group (TRIG), the diagnosis of definite ET is possible only when there is bilateral postural or kinetic tremor in the hands, without other neurologic signs, for at least five years [34••]. By contrast, the Consensus Statement of

the Movement Disorder Society (MDS) does not specify a required duration of tremor [34••]. Dopamine transporter imaging is helpful in identifying patients with Parkinson disease [35] but not in distinguishing type 2 or 3 ET from dystonia [36, 37].

Another problem in excluding type 4 patients is an uncertainty or bias in recognizing signs of mild dystonia and Parkinson disease. It is clear that movement disorder specialists have a different threshold for signs of these disorders, depending upon the clinical situation. For example, in studies of familial dystonia, a subtle head tilt or wrist extension is likely to be called dystonia (e.g., see video segment 1 in Schiebler et al. [18]), but in studies of ET, even greater head tilt is overlooked or dismissed as compensatory or insignificant (e.g., see video of case 2 in Deuschl et al. [34••]). Other examples of unrecognized dystonia are cited in the review by Quinn and coworkers (see also Louis et al. [22]) [14••]. A similar failure to recognize signs of parkinsonism is also common [38, 39]. Thus, patients with other neurologic conditions are often diagnosed as type 2 or 3 ET. The frequently dramatic suppression of ET by ethanol is not sufficiently sensitive or specific to be used diagnostically [21, 40, 41].

Yet another problem is disagreement regarding the inclusion of isolated head and voice tremors in the definition of classic ET. The Tremor Investigation Group (TRIG) required all patients to have bilateral postural or kinetic tremor in the hands, without other neurologic signs, and specifically excluded patients with isolated head or voice tremor [34••]. By contrast, the Consensus Statement of the MDS includes patients with isolated head tremor as definite or “classic” ET [34••]. Isolated head tremor is very rare in patients believed to have ET, and these head tremor patients are predominately women [42], whereas men and women are nearly equally represented in patients with hand tremor [43]. There is a growing belief that isolated head tremor and other focal or task-specific tremors are dystonia [14••]. Consequently, both the TRIG and the MDS Consensus criteria for classic ET exclude isolated position-specific or task-specific tremors (eg, occupational tremors, primary writing tremor) and isolated tremor in the voice [44], tongue, and chin [45] or legs [34••, 46].

While Marsden’s type 2 ET is regarded by all experts to be classic ET, the relationship of type 3 ET to type 2 is less clear. Type 3 patients have a slightly lower tremor frequency (4–6 Hz), and their tremor is much more severe than in type 2. Intention tremor in the upper limbs is disabling, and these patients often opt for surgery. Some type 3 patients simply progress from type 2 after many years of relatively mild tremor [21]. Other type 3 patients have tremor in association with unrecognized dystonia [14••].

To summarize, Marsden’s type 2 and 3 ET meet TRIG criteria and the MDS Consensus criteria for classic ET. TRIG and MDS criteria differ in the inclusion of isolated head tremor (MDS) and the required history of tremor for at least 5 years (TRIG). Additional amplitude criteria can be used in conjunction with the TRIG or MDS criteria to exclude people with enhanced physiologic tremor, and neurophysiologic testing can be used in conjunction with amplitude criteria to ensure the exclusion of enhanced physiologic tremor. Published difficulties in distinguishing type 4 patients from types 2 and 3 should serve as a warning to all clinicians attempting to diagnose classic ET. Furthermore, many patients with type 3 tremor have subtle dystonia, not classic ET.

Meanwhile, investigators are beginning to challenge the notion that classic ET is a monosymptomatic disorder. Disturbances of tandem walking, personality, mood, hearing and cognition are found in some patients [47–49]. The disturbance in tandem walking is consistent with the known cerebellar dysfunction in ET [48]. The nonmotor disturbances could be related to thalamic dysfunction [50], and some nonmotor disturbances could be secondary (e.g., depression and anxiety). These disturbances are subclinical in most patients,

so one could argue 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 pure tremor disorder, without other neurologic signs.

Etiology and Pathophysiology of classic essential tremor

The fundamental abnormality in ET is abnormal motor unit entrainment at frequencies of 4–12 Hz [7•]. Considerable clinical and neuroimaging data support the notion that this motor unit entrainment emerges from neuronal oscillation in the corticobulbocerebellothalamocortical loop [51•–56], but the cause of oscillation in ET is unknown. Furthermore, oscillation in the corticobulbocerebellothalamocortical loop is not specific for essential tremor and also occurs in Parkinson disease [57], Wilson disease [58], rhythmic cortical myoclonus [59] and even voluntary tremor [60, 61].

Roughly 50% of patients have a family history of ET [27], and many cases appear to be inherited in a Mendelian autosomal dominant fashion with a high genetic penetrance by age 65 years [21, 62]. Studies of autosomal dominant pedigrees have identified candidate disease loci on chromosomes 3q13 (hereditary essential tremor, type 1) [63], 2p22-p25 [64], and 6p23 [23], and additional genetic loci are likely [65–68]. However, the specific genes have not been identified for these loci, so all should be regarded as unproven.

It is unclear why these genes have been so elusive. Large pedigrees with hereditary ET are common, and many pedigrees have been studied by competent teams of investigators around the world. The random intrusion of ET phenocopies into these families is one possible explanation. Sporadic cases of ET are common, so large families are likely to contain phenocopies. In addition, other modes of inheritance (autosomal recessive, mitochondrial, polygenic, epigenetic) have been hypothesized but have not been found [65, 69, 70].

Genome-wide association studies (GWAS) of large patient cohorts have been performed, looking for variant alleles that increase the risk of ET. Variant alleles of the LINGO1 and LINGO2 genes were found to be associated with increased risk (odds ratio of 1.6 or less), particularly in patients with a family history [71••–73]. The mechanism(s) by which these variant alleles confer risk is unknown [74, 75].

It is possible that alleles of many different genes are risk factors for ET as seen in other disorders such as Parkinson's disease. Thier and coworkers recently identified an intronic variant of the glial glutamate transporter gene SLC1A2 as a potential ET susceptibility gene [76]. No evidence of an association between GABA receptor or transporter genes has been found in patients with ET [77–79], even though the alcohol sensitivity of many patients has led investigators to hypothesize a disturbance of GABA inhibition in ET.

More than 50 autopsies have been performed using modern methods of postmortem investigation in ET patients. Louis and coworkers [80••, 81] found that ET patients tend to fall into one of two groups: patients with brainstem Lewy bodies (approximately 25%) and patients without Lewy bodies (approximately 75%). Those without Lewy bodies have reduced numbers of Purkinje cells and related pathology in the cerebellum [80••–84]. Other investigators have failed to corroborate these findings, and the significance of reported postmortem microscopic changes is hotly debated [81••, 85••, 86]. No patient studied died before age 70. Lewy bodies, torpedoes, and Purkinje cell loss are common in elderly controls, and even though these changes may be quantitatively greater in patients with ET, such pathology is not specific for ET [85, 87, 88]. Younger patients must be studied to exclude the possibility of spurious or coincidental age-associated pathology.

Epidemiologic studies

Several population-based epidemiologic studies of ET have been published, but all were derived from study populations of people age 65 and older [3, 4, 11, 89–91]. A particularly influential series of reports came from the Neurological Disorders in Central Spain (NEDICES) Study Project, which was a survey of major neurological disorders in people age 65 years living in three communities of central Spain [92]. Residents of these communities were first sent a screening questionnaire in which people were asked about head or limb tremor lasting longer than several days. People with affirmative answers were then examined by a neurologist, and if this neurologist identified ET, the patient was examined by two more neurologists to confirm the diagnosis. “Subjects were diagnosed as having ET if they had an action tremor of the head, limbs, or voice without any recognizable cause. The tremor had to be of gradual onset and either present for at least 1 year, or accompanied by a family history of the same disorder (at least one first-degree relative affected).” In the NEDICES project, 5,278 people were screened, 472 (8.9%) screened positively, but only 308 (65.2%) were evaluated by direct examination. One hundred and fifty four (32.6%) were diagnosed using medical records because they were inaccessible [92]. Of the 462 people with tremor, 269 (58.2%) were diagnosed with some other form of tremor, and 183 were diagnosed with ET. Seventy were excluded because of parkinsonism, and 16 were excluded for other causes of tremor. Interestingly, there was no mention of focal or segmental dystonia. An additional 73 people with ET were identified when this population was screened for other purposes (e.g., dementia, stroke or parkinsonism), even though these people screened negatively for tremor.

The ultimate tally in the NEDICES project was 256 people with ET, as defined in this study, and 84.8% of these people had tremor only in the upper limbs. Furthermore, 80% were mild and had not been previously diagnosed (Marsden’s type 2). The overall prevalence was 4.8%, but the prevalence rose sharply from the 65–69 age group (~3.7%) to the 85+ age group (~7.5%) [92]. In a related study, the 3-year incidence increased with age, except in the oldest old (85+ years) [11]. The NEDICES investigators noted that ET is probably a heterogeneous disorder, and their data appear to support the role of age-associated factors in the pathogenesis of ET [92].

The NEDICES project also found that the absolute risk of dementia was increased by 4% in the people with late-onset (after age 65) ET but not in people with early-onset ET [3, 90]. Factor analyses revealed that age-associated diseases (e.g., Alzheimer disease) are probably responsible for the cognitive dysfunction in most cases [93]. The NEDICES project also revealed a greater incidence of Parkinson disease in people with ET (absolute risk 3%; 6 of 201 cases) compared with controls (absolute risk 0.7%; 24 of 3574 controls) observed for a median of 3.3 years [4]. It is doubtful that Alzheimer disease and Parkinson disease [94] are etiologically related to ET, but pathogenetic processes of one could affect the other [95]. For example, Louis and coworkers found that patients with Alzheimer disease and Parkinson disease also have increased Purkinje cell pathology of the type found in ET [87], and such pathology could compromise the nervous system’s ability to control ET, even if it is not the cause (etiology). Similarly, Lewy body degeneration of the locus ceruleus could promote deleterious oscillation in thalamic networks [50].

A relationship between age of onset and pathology may also be true for loss of GABAergic innervation of the locus ceruleus. Shill and coworkers found postmortem evidence of reduced parvalbumin, a marker of GABAergic neurons, in the region of the locus ceruleus of people with ET [96], but Deuschl discovered that this finding was attributable to those people with late-onset ET (after age 65), even though these people had a much shorter duration of tremor [97].

Conclusions

The notion that ET is a monosymptomatic disorder is being challenged by a growing literature [98], and Louis has made a strong case for considering ET to be a family of diseases [80••]. Action tremor in the hands is caused by many conditions, and patients presenting with hand tremor often develop other neurologic signs, such as dystonia and parkinsonism. Misdiagnosis of ET is common, and other diagnostic signs are commonly missed, even by experts. I believe that the emphasis on excluding other neurologic signs in ET studies has resulted in a biased underreporting of these signs and in premature closure on the clinical diagnosis of ET. Clinicians making the diagnosis of ET should remain vigilant for the development of signs, symptoms and historical clues to the diagnosis of specific conditions that may present as nonspecific action tremor in the hands, keeping in mind that ET is a clinical syndrome, not a specific disease.

The characteristics of ET in many large families support the present definition of classic ET as a monosymptomatic disorder, but there are other families that suggest that classic ET is too narrowly defined. An excessively narrow definition of the clinical manifestations of Parkinson disease led to the initial failure of investigators to find evidence of a genetic contribution in identical twins [99]. Has an overly narrow definition of classic ET been an impediment to finding ET genes? Instead of defining ET as a monosymptomatic action tremor with no other neurologic signs, perhaps ET should be defined as an action tremor of unknown etiology, occurring in the absence of other diagnostic signs [1, 2•], recognizing that many patients have mild or questionable signs and comorbidities of uncertain significance (e.g., depression, restless legs syndrome, migraine, subtle head tilt, rest tremor, questionable dystonic posturing of a hand, very asymmetric upper extremity tremor, hearing loss, and mild cognitive impairment). This broader definition of ET emphasizes the complete and unbiased characterization of tremor and all associated signs, symptoms and medical conditions in each patient, without concern for whether the patient fits some *ad hoc* definition of classic ET. This broader definition of ET would not preclude planned or *post hoc* analyses of those patients with classic ET by any definition (e.g., TRIG or MDS criteria), but casting a wider net for ET might enhance our ability to find causative genes and facilitate our understanding of epidemiologic associations.

In conclusion, ET is a deceptively simple clinical syndrome that is associated with a complex web of clinical, pathological and genetic phenomena. The heterogeneity of ET is probably a major reason for our poor success in finding effective drugs and disease-causing genes. However, the highly effective and nonspecific tremorolytic effect of stereotactic thalamic/subthalamic surgery should serve as a continuing reminder that a complete understanding of a heterogeneous disorder is not always necessary for finding an effective treatment. Thus, a risk-factor gene, discovered with GWAS, could conceivably reveal an “Achilles heel” for pharmacologic treatment of ET, even though the gene is not causative or predictive of ET [100].

Acknowledgments

Supported by the Spastic Paralysis Research Foundation of Kiwanis International Illinois-Eastern Iowa District.

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- Of major importance

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