Published in final edited form as:

Parkinsonism Relat Disord. 2018 January ; 46(Suppl 1): S87–S91. doi:10.1016/j.parkreldis.2017.07.004.

The Evolving Definition of Essential Tremor: What are We Dealing With?

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Abstract

Background—Although essential tremor (ET) is commonly encountered in clinical practice, historically, there has been considerable disagreement as how to best define it, and now with a growing sense of its clinical complexity, how to best encapsulate it. Here, I draw attention to five issues of current uncertainty.

Methods—A PubMed search conducted on June 19, 2017 crossed “essential tremor” with 9 second search terms (e.g., definition, diagnosis).

Results—There are several major issues of clinical and diagnostic uncertainty. Underlying each issue is a larger question about the nature of the underlying pathophysiology of ET. Does age of onset of ET matter? How much dystonia is acceptable in ET? How much in the way of “cerebellar signs” are acceptable? Are non-motor features due to the underlying disease or merely secondary to the clinical features? Is ET a single disease entity or something else?

Conclusions—We are learning more about ET and, as a by-product of these efforts, are struggling with its definition. Further understanding the nature of the underlying disease pathogenesis as well as the role the cerebellum and cerebellar relays play in this process will likely provide important clues to enable us to bring order to areas of uncertainty.

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Conflicts of Interest

The author has no conflicts of interests.

Authors' Contributions

Conception and design of study/paper; acquisition, analysis and interpretation of data from the literature review; drafting/editing manuscript; final approval of work (E.D.L.).

Keywords

essential tremor; definition; diagnosis; clinical; dystonia; ataxia; cognition; premotor; pathophysiology; cerebellum

Introduction

Essential tremor (ET) is among the most prevalent neurological disorders and is a clinical malady of interest to a broad array of treating physicians, from general practitioners to neurologists. Given its very high prevalence, ET is commonly encountered in clinical practice. Historically, ET has been a disorder with a relatively simple and straightforward clinical picture [1]. Given this situation, it is curious that there has been considerable disagreement as how to best define ET, and now with a growing sense of its clinical complexity, how to best encapsulate this somewhat enigmatic clinical entity [2–4]. In this paper, I draw attention to five issues of current clinical and diagnostic uncertainty (Table 1). Underlying each is a larger issue that underscores our uncertainty about the underlying pathophysiology of ET.

Methods

A PubMed search was conducted on June 19, 2017. The term “essential tremor” was crossed in sequential order with 9 second search terms, restricting the searches to human subject studies in English and those which contained the two terms in the title or abstract (Table 2).

Historical Definition and Evolving Mélange of Definitions

Before discussing the five issues of current clinical and diagnostic uncertainty, it is important to briefly review historical and evolving definitions of ET. In one of the earliest and most thorough treatises on ET, Critchley documented the primary feature of ET, writing that in “the majority of cases, essential tremor appears as a monosymptomatic peculiarity” [5], and then added: “The tremor generally appears first in a hand or forearm” [5].

Half a century later, in 1998, the first consensus statement of the movement disorders society similarly defined ET as a bilateral, largely symmetric postural or kinetic tremor involving hands and forearms that is visible and persistent. It was noted that additional or isolated tremor of the head may occur but in the absence of abnormal posturing. Among the nine exclusionary criteria was other neurological signs, especially dystonia [6]. This point is important to our discussions below.

Shortly after the consensus criteria were released, members of the Tremor Research Group, including several authors of the consensus criteria, put forward another set of criteria [7], which elaborated on several of the points made in the Consensus statement [6]. The core criteria for ET were bilateral action tremor of the hands and forearms (but no rest tremor), absence of other neurological signs (with the exception of cogwheel phenomenon), possible presence of isolated head tremor with no signs of dystonia [7]. Secondary criteria were long duration (> 3 years), positive family history, and beneficial response to alcohol. It is noteworthy that among the diagnostic red flags indicating tremor disorders other than ET

was gait disturbance, which was considered most likely to be a marker for Parkinson's disease or "cerebellar tremor" [7]. This point is also pertinent to our discussions below.

Recently, in 2017, the consensus statement has been revised, and the revised statement recognizes the presence in some patients of a more complex phenotype [4]. In terms of nomenclature, the terms "simple ET" and "complex ET" (or "ET plus") have been proposed to deal with the presence of these two types of patients [4]. While this nomenclature has some benefits, a problem is that it does not recognize that there may be a continuum rather than two clearly separable categories. Furthermore, patients may at different points in their disease have one of the other, i.e., evolving from simple ET into complex ET.

Notwithstanding, simple ET was defined as an (1) isolated tremor syndrome of bilateral upper limb action tremor, (2) of at least three years duration, (3) with or without tremor in other locations (e.g., head, voice, lower limbs), and an absence of other neurological signs such as dystonia, ataxia or parkinsonism. ET plus was defined as tremor with the characteristics of ET and additional neurological signs such as impaired tandem gait, questionable dystonic posturing, rest tremor, memory impairment or other mild neurologic signs of unknown significance that do not suffice to make an additional syndrome classification or diagnosis. These mild signs are "accepted as ET as long as the clinician deems these additional signs as related to ET" [4].

What can be seen from this evolution in definitions and terms is a recognition of the heterogeneity of ET and uncertainty as how to best incorporate this into a diagnostic, nomenclatural and underlying biological scheme. The remainder of the paper will focus on areas of current diagnostic uncertainty. The five I have chosen are particularly problematic, although there are others.

Current Areas of Uncertainty

Below I delve into a number of the current issues of uncertainty with respect to the diagnosis of ET.

Does age of onset of ET matter?—Recently, the term "aging-related tremor" has been introduced to deal with some variability in clinical features of cases with different ages of onset [3]. The authors of the report proposed labeling individuals whose tremor began after age 70 as "aging-related tremor" rather than ET because these individuals show worse aging parameters and mortality than controls and ET cases whose tremor began prior to that age cut-off [3]. Similarly, in an earlier report, ET cases with older age of onset (defined in that report as age 60 years) had a more rapid clinical progression than did those with younger age of onset [8]. Although interesting, these data are very preliminary. Moreover, the notion of age-related tremor is problematic for several reasons. First, as noted above, the evidence in favor of it is rather marginal at present. Second, when Parkinson's disease begins after age 70 years, we do not refer to it as "age-related tremor, bradykinesia, and rigidity" and when Alzheimer's disease begins after age 70 years, we do not refer to it as "age-related cognitive dysfunction". Indeed, I can think of no other example in which age of onset alone dictated that a disease designation could not be applied. In a related point, in Parkinson's disease, older age of onset is associated with poor survival, akin to what is seen

with ET, yet we do not remove the label “Parkinson’s disease” from cases whose onset is older. Third, normal and enhanced physiological tremor both worsen with age; however, these normal states should not be confused with a disease state; the converse is also true. Fourth, even if it were conceptually of merit, the cut-off point for such an age-related tremor is somewhat arbitrary. Even the authors who suggested this term, have defined “late-onset” differently in various papers (e.g., defining it as 46 years in another paper) [9]. In sum, while age of onset may be one of several determinants of clinical expression in ET (along with family history and gender), there is little current evidence to support the notion that age of onset is a nomenclatural gate keeper.

How much dystonia is acceptable in ET?—The presence of dystonia in some ET patients is an area of uncertainty, as can be seen in the evolution of the consensus statement and the choice of the term “questionable dystonic posturing” in the most recent version of the consensus statement [4]. The word “questionable” is somewhat ambiguous, indicating some degree of uncertainty as how to interpret the presence of this sign in a patient with ET.

The diagnostic interpretation of dystonic movements or postures in a patient with ET is an area of uncertainty and will be discussed below. As a brief aside, the converse, that is, the presence of tremor in a patient with dystonia, has been clarified to a slightly greater extent. Thus, in the prior consensus statement on tremor [6], tremor in a body part affected by dystonic postures/movements was labeled “dystonic tremor” whereas tremor in a body part not affected by dystonia, but in a patient with dystonia elsewhere, was labeled “tremor associated with dystonia”. Both tremors were linked in some way with dystonia. However, when to assign the more specific diagnostic label “ET”, in contrast to “tremor”, in a patient with a diagnosis of dystonia is less clear and is currently an area of uncertainty.

Let us consider the possible interpretations of dystonic movements or postures in a patient with ET. The first issue is whether the initial ET diagnosis is correct. No one would debate that is not uncommon for patients with dystonic tremor to be mis-diagnosed as ET, particularly when dystonic postures or movements are subtle. That is, the initial ET diagnosis in these cases is incorrect. The contested issue is whether patients with *bone fide* ET, and especially long-standing and severe ET, may develop subtle dystonic posturing or movements. It is debated whether the dystonic postures or movements are simply a manifestation of their advanced ET or whether their presence predicates a second diagnosis or a retraction of the longstanding ET diagnosis. There is evidence that the former explanation is possible. Biologically, it would not be surprising for ET patients to develop some dystonia, as ET is a disorder of cerebellar dysfunction and possible degeneration [10,11] and there is increasing recognition of the fact that alterations in activity, connectivity, and structure of the cerebellum are associated with dystonia [12]. Indeed, neuronal dysfunction originating in the cerebellum can drive dystonic movements in rodent model systems. Imaging and neurophysiological studies in humans also suggest that the cerebellum plays a role in the pathophysiology of dystonia [12]. Hence, ET and dystonia may be different manifestations of abnormal cerebellar function.

As a corollary, one may ask whether patients with other cerebellar-linked diseases, aside from ET, may develop ET and, more specifically, whether those with spinocerebellar ataxia

(SCA) manifest with dystonia. Indeed, dystonia is quite common in the most prevalent forms of SCA (e.g., 29.4 – 33.3% of patients with SCA1, SCA2 and SCA3)[13] and it may even be the presenting symptom/sign in those diseases. Dystonia is also seen and has been well described in numerous other forms of SCA (e.g., SCA 7, SCA8, SCA16, SCA17, SCA36).

We know that as ET advances, patients accumulate a range of symptoms and signs in addition to kinetic tremor, each of which is associated with longer disease duration. These signs include intention tremor [14], rest tremor [15], head tremor [16] as well as gait ataxia [17]. Given the links between dystonia and the cerebellum and the links between ET and the cerebellum [11,12], it is entirely conceivable that dystonia could develop in patients with ET. Therefore, rather than conceptualizing the development of dystonia in ET as either (1) a second diagnosis or (2) a rationale to retract the initial ET diagnosis, it may represent a spread of the ET-related pathology in the cerebellum to involve whichever system in the cerebellum produces dystonic postures/movements.

Once one accepts the possibility of the presence of some dystonia in patients with ET, as is current consensus criteria begin to do, then how much is acceptable? How much in terms of (1) the absolute severity of dystonia, (2) the severity of dystonia relative to the severity of tremor, (3) the geographic extent of the dystonia (e.g., focal, segmental), (4) the specific bodily locations that may have dystonia (e.g., arm vs. neck), and (5) the time-course for developing dystonia (e.g., an early disease feature vs. a later disease feature)? These issues are presently unresolved and in part are likely linked with our incomplete understanding of cerebellar pathophysiology.

How much in the way of “cerebellar signs” are acceptable in ET?—Cerebellar signs may occur in patients with ET. Yet, how much ataxia and, as a corollary, which cerebellar signs are acceptable clinical examination findings in ET is unresolved?

We know that nearly one-half of ET patients may manifest intention tremor in the arms on finger-nose-finger maneuver [14]; such tremor becomes more prevalent with more longstanding disease. Such intention tremor may also occur in the head and legs. Also, some degree of gait ataxia is not considered to be inconsistent with the ET diagnosis (i.e., it is an accepted disease-linked clinical feature) [17]. It is generally stated that this ataxia is mild, although conceptually it is not clear why it couldn't be of somewhat greater severity, especially if one considers the cerebellum to be a focal point of disease-linked pathology in ET. Indeed, in several documented cases, the ataxia reached more moderate severity in ET [18]. This is an area for further investigation.

Subtle (i.e., subclinical) eye movement abnormalities, including reflexive saccadic dysmetria and slowing of smooth pursuit, have now been well-described in several reports [19,20]. One study reported that these abnormalities seem to be a late disease feature [20].

Furthermore, it has been reported that cerebellar timing function is altered in ET. Patients show an increased variability of rhythmic hand movements as well as diminished performance during predictive motor timing tasks [21].

On the therapeutic front, it has been observed that after deep brain stimulation (DBS) surgery, cerebellar signs (e.g., dysmetria, ataxia) may begin to emerge [22,23]. There is ongoing debate as to whether these signs reflect (1) an adverse effect related to the surgery, (2) an adverse effect related to repeated increases of stimulation intensity, (3) an unmasking of more subtle cerebellar signs that become apparent after therapeutic suppression of severe tremor, or (4) disease progression in ET.

Despite the demonstrated presence of such cerebellar signs in ET patients compared to their counterparts without the disease, “everything cerebellar” is not a feature of ET. For instance, it is generally accepted that ataxia is not an early disease manifestation in ET nor is marked ataxia a feature at any point. While some forms of nystagmus have been described in ET (e.g., positional downbeat nystagmus induced by the DixHallpike and straight head-hanging maneuvers) [24], marked nystagmus is not a disease-linked feature of ET. Similarly, scanning or cerebellar dysarthric speech are not features. Nor are dysmetria and dysdiadochokinesis features of ET. Why some cerebellar signs make it to the list of “yes’s” while others do not is not entirely clear. At the root of this issue, additional understanding of cerebellar pathophysiology in general and as it related to ET is needed.

Are non-motor features primary and due to the underlying disease-related pathology or merely secondary to living with the clinical features?—There is a growing appreciation of a wide range of non-motor features in ET. These comprise cognitive features (including a full spectrum from mild cognitive difficulty through to frank dementia), psychiatric features (including apathy, depression, anxiety, and personality characteristics), sensory features (hearing and possibly olfactory abnormalities), and other non-motor features (e.g., sleep dysregulation in some studies), and their presence in ET is disease-linked independent of their age-link (i.e., they are more prevalent in ET patients than in age-matched controls) [25]. While some of these features could very well be secondary (e.g., reactive depression or social phobia in the setting of disabling or embarrassing tremor), one question is whether one or more of these features could be primary. For example, there are data showing that depressive symptoms [26], cognitive changes [27], and changes in sleep [28] pre-date the motor features of ET. These limited data suggest that there may be a “pre-motor phase” in ET, just as there is in Parkinson’s disease and Huntington’s disease. Similarly, it is not clear whether the personality features that have been described in ET [25] are (1) a pre-morbid feature, (2) a direct expression of the underlying disease-related pathology, or (3) a secondary manifestation of living with the clinical features of the disease. We should be open to the notion that each of these is a possibility.

Is ET a single disease entity or something else?—A range of both genetic and environmental factors likely contribute to the etiology of ET; in other words, there are likely to be multiple causes of ET (i.e., etiological heterogeneity). Clinically, ET patients often differ with respect to the presence, evolution, and severity of neurological signs, indicating that there is clinical heterogeneity beyond what can be explained by disease duration and stage alone. In addition, patients differ with respect to response to pharmacological agents (i.e., heterogeneity in therapeutic response phenotype). Furthermore, some postmortem studies indicate the likely presence of pathological heterogeneity [10]. These parallel

observations, of etiological, clinical, therapeutic response, and pathological heterogeneity, have given rise to the question as to whether ET is a single disease entity or rather a family of diseases. In all likelihood, we are dealing with a family of disease, which differ with respect to etiology, pathogenesis and clinical features [2,29]. The nomenclatural issue that naturally follows this conclusion is whether the more appropriate term to use is the “essential tremors”. While some have questioned whether ET is merely a syndrome (i.e., a collection of symptoms and signs that run together)[30], ET is not merely a collection of clinical signs, but is rooted to underlying etiologies (causes, whether genetic or non-genetic) and tissue-based changes (pathogeneses). Indeed, it is likely that variation in the clinical picture will align with particular etiologies and also particular pathologies. Hence, just as the parkinsonisms are a family of diseases or the motor neurons diseases are a family of diseases united by common clinical features yet distinguished by etiological, pathological and clinical differences, the same may very well be the case with the essential tremors.

Summary/Conclusions

We are learning more about ET and, as a by-product of those efforts, are in the process of re-defining ET. In this paper, I have highlighted a handful of perplexing issues that are the subject of debate. Indeed, no one knows the correct answers to these clinical quandaries and flexibility of thought rather than a dogmatic approach is likely to be more fruitful. Further understanding the nature of the underlying disease pathogenesis as well as the role the cerebellum plays in this disease will likely provide important clues to allow us to bring order to the issues of current uncertainty.

Acknowledgments

Funding Acknowledgement

Dr. Louis has received research support from the National Institutes of Health: NINDS #R01 NS094607 (principal investigator), NINDS #R01 NS085136 (principal investigator), NINDS #R01 NS073872 (principal investigator), NINDS #R01 NS085136 (principal investigator) and NINDS #R01 NS088257 (principal investigator). He has also received support from the Claire O'Neil Essential Tremor Research Fund (Yale University).

References

1. Elble RJ. Essential tremor is a monosymptomatic disorder. *Mov. Disord.* 2002; 17:633–637. [PubMed: 12210850]
2. Benito-Leon J. Essential tremor: from a monosymptomatic disorder to a more complex entity. *Neuroepidemiology.* 2008; 31:191–192. [PubMed: 18784419]
3. Deuschl G, Petersen I, Lorenz D, Christensen K. Tremor in the elderly: Essential and aging-related tremor. *Mov. Disord.* 2015; 30:1327–1334. [PubMed: 26095699]
4. Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, Raethjen J, Stamelou M, Testa CM, Deuschl G. the Tremor Task Force of the International Parkinson and Movement Disorder Society. Consensus statement on the classification of tremors, from the Task Force on Tremor of the International Parkinson and Movement Disorder Society. *Mov. Disord.* 2007 (In press).
5. Critchley M. Observations of essential (heredofamilial) tremor. *Brain.* 1949; 72:113–139. [PubMed: 18136705]
6. Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. *Mov. Disord.* 1998; 13(Suppl 3):2–23.
7. Bain P, Brin M, Deuschl G, Elble R, Jankovic J, Findley L, Koller WC, Pahwa R. Criteria for the diagnosis of essential tremor. *Neurology.* 2000; 54:S7. [PubMed: 10854345]

8. Louis ED, Faust PL, Vonsattel JP, Honig LS, Henschliffe C, Pahwa R, Lyons KE, Rios E, Erickson-Davis C, Moskowitz CB, Lawton A. Older onset essential tremor: More rapid progression and more degenerative pathology. *Mov. Disord.* 2009; 24:1606–1612. [PubMed: 19526587]
9. Hopfner F, Ahlf A, Lorenz D, Klebe S, Zeuner KE, Kühlenbaumer G, Deuschl G. Early- and late-onset essential tremor patients represent clinically distinct subgroups. *Mov. Disord.* 2016; 31:1560–1566. [PubMed: 27384030]
10. Louis ED. Re-thinking the biology of essential tremor: from models to morphology. *Parkinsonism. Relat. Disord.* 2014; 20(Suppl 1):S88–S93. [PubMed: 24262197]
11. Grimaldi G, Manto M. Is essential tremor a Purkinjopathy? The role of the cerebellar cortex in its pathogenesis. *Mov. Disord.* 2013; 28:1759–1761. [PubMed: 24114851]
12. Shakkottai VG, Batla A, Bhatia K, Dauer WT, Dresel C, Niethammer M, Eidelberg D, Raike RS, Smith Y, Jinnah HA, Hess EJ, Meunier S, Hallett M, Fremont R, Khodakhah K, LeDoux MS, Popa T, Gallea C, Lehericy S, Bostan AC, Strick PL. Current opinions and areas of consensus on the role of the cerebellum in dystonia. *Cerebellum.* 2017; 16:577–594. [PubMed: 27734238]
13. Jhunjhunwala K, Netravathi M, Purushottam M, Jain S, Pal PK. Profile of extrapyramidal manifestations in 85 patients with spinocerebellar ataxia type 1, 2 and 3. *J. Clin. Neurosci.* 2014; 21:1002–1006. [PubMed: 24602359]
14. Louis ED, Frucht SJ, Rios E. Intention tremor in essential tremor: Prevalence and association with disease duration. *Mov. Disord.* 2009; 24:626–627. [PubMed: 19185016]
15. Louis ED, Asabere N, Agnew A, Moskowitz CB, Lawton A, Cortes E, Faust PL, Vonsattel JP. Rest tremor in advanced essential tremor: a postmortem study of nine cases. *J. Neurol. Neurosurg. Psychiatry.* 2011; 82:261–265. [PubMed: 20802027]
16. Louis ED. When do essential tremor patients develop head tremor? Influences of age and duration and evidence of a biological clock. *Neuroepidemiology.* 2013; 41:110–115. [PubMed: 23860504]
17. Stolze H, Petersen G, Raethjen J, Wenzelburger R, Deuschl G. The gait disorder of advanced essential tremor. *Brain.* 2001; 124:2278–2286. [PubMed: 11673328]
18. Louis ED, Galecki M, Rao AK. Four essential tremor cases with moderately impaired gait: how impaired can gait be in this disease? *Tremor. Other. Hyperkinet. Mov. (N Y).* 2013; 3 eCollection 2013. doi: 10.7916/D8QV3K7G
19. Gitchee GT, Wetzel PA, Baron MS. Slowed saccades and increased square wave jerks in essential tremor. *Tremor. Other. Hyperkinet. Mov. (N Y).* 2013; 3 eCollection 2013. doi: 10.7916/D8251GXN
20. Wojcik-Pedziwiatr M, Plinta K, Krzak-Kubica A, Zajdel K, Falkiewicz M, Dylak J, Ober J, Szczudlik A, Rudzinska M M. Eye movement abnormalities in essential tremor. *J. Hum. Kinet.* 2016; 52:53–64. [PubMed: 28149393]
21. Bares M, Husarova I, Lungu OV. Essential tremor, the cerebellum, and motor timing: towards integrating them into one complex entity. *Tremor. Other. Hyperkinet. Mov. (N Y).* 2012; 2 http://pii: tre-02-93-653-1. Epub 2012 Sep 12.
22. Reich MM, Brumberg J, Pozzi NG, Marotta G, Roothans J, Astrom M, Musacchio T, Lopiano L, Lanotte M, Lehrke R, Buck AK, Volkmann J, Isaías IU. Progressive gait ataxia following deep brain stimulation for essential tremor: adverse effect or lack of efficacy? *Brain.* 2016 Sep 21. pii: aww223. [Epub ahead of print].
23. Shneyder N, Lyons MK, Driver-Dunckley E, Evidente VG. Cerebellar ataxia from multiple potential causes: hypothyroidism, hashimoto's thyroiditis, thalamic stimulation, and essential tremor. *Tremor. Other. Hyperkinet. Mov. (N Y).* 2012; 2 <http://10.7916/D8BP01H5>. Epub 2012 Mar 22.
24. Kim YE, Kim JS, Yang HJ, Yun JY, Kim HJ, Ehm G, Kim JM, Jeon BS. Perverted head-shaking and positional downbeat nystagmus in essential tremor. *Cerebellum.* 2016; 15:152–158. [PubMed: 26041074]
25. Louis ED. Non-motor symptoms in essential tremor: A review of the current data and state of the field. *Parkinsonism. Relat. Disord.* 2016; 22(Suppl 1):S115–S118. [PubMed: 26343494]
26. Louis ED, Benito-Leon J, Bermejo-Pareja F. Self-reported depression and anti-depressant medication use in essential tremor: cross-sectional and prospective analyses in a population-based study. *Eur. J. Neurol.* 2007; 14:1138–1146. [PubMed: 17708753]

27. Benito-Leon J, Louis ED, Sanchez-Ferro E, Bermejo-Pareja F. Rate of cognitive decline during the premotor phase of essential tremor: a prospective study. *Neurology*. 2013; 81:8160–66.
28. Benito-Leon J, Louis ED, Bermejo-Pareja F. Short sleep duration heralds essential tremor: a prospective, population-based study. *Mov. Disord*. 2013; 28:1700–1707. [PubMed: 23847150]
29. Louis ED. 'Essential tremor' or 'the essential tremors': is this one disease or a family of diseases? *Neuroepidemiology*. 2014; 42:81–89. [PubMed: 24335621]
30. Elble RJ. The essential tremor syndromes. *Curr. Opin. Neurol*. 2016; 29:507–512. [PubMed: 27257943]

Table 1

Five issues of current clinical and diagnostic uncertainty in ET

1	Does age of onset of ET matter?
2	How much dystonia is acceptable in ET?
3	How much in the way of “cerebellar signs” are acceptable in ET?
4	Are non-motor features primary and due to the underlying disease-related pathology or merely secondary to living with the clinical features?
5	Is ET a single disease entity or something else?

Table 2

Search strategy from PubMed using various keywords and their combinations

Key words and combinations	Number of publications
Essential tremor AND definition	19
Essential tremor AND diagnosis	309
Essential tremor AND clinical	795
Essential tremor AND dystonia	262
Essential tremor AND ataxia	58
Essential tremor AND cognition	32
Essential tremor AND premotor	22
Essential tremor AND pathophysiology	115
Essential tremor AND cerebellum	142