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It is Time to Remove the 'Benign' from the Essential Tremor Label

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Abstract

In recent years, studies of essential tremor (ET) have demonstrated that the disease is associated with functionally-relevant cognitive abnormalities, a mood disturbance and other psychiatric co-morbidities, a functionally significant gait disorder, hearing deficits, and a variety of types of tremor. The tremor has been shown to be progressive in nature and quite disabling for a large number of sufferers. Also, recent clinical-epidemiological studies have linked prevalent ET to other neurodegenerative diseases and at least one study has demonstrated an increased risk of mortality in an ET cohort. While many of these studies are derived from clinic-based samples, population-based studies have also substantiated these findings, suggesting that even in the general population, the disease is associated with disability and with co-morbidity. Based on these available studies, it would seem inaccurate to append the word "benign" to ET. Not unlike the word "essential" itself, the word "benign" is an antiquated and outdated term that reflects an era where little was understood about ET. Historically, the general doctors who frequently encountered the disorder would educate patients that it was a benign, non-progressive condition not associated with any co-morbidity or risk of long term worry. This notion, conceived by prior generations of physicians, is now known to be inaccurate. It is therefore our recommendation that the medical community open the dialogue to consider formally discontinuing this nosology ("benign essential tremor") and to adopt the use of the term "essential tremor." Use of the word "benign" is a mischaracterization of the disease course, and could be prove misleading especially

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in the evolving doctor-patient relationship. In those cases with currently-mild tremor, the nosology "mild essential tremor" would be a more accurate reflection of disease.

Keywords

Essential tremor; benign; clinical; cognition; gait

Introduction to "Benign Essential Tremor"

The term "essential tremor" was initially coined and then first used by European physicians in the later decades of the nineteenth century to describe an inherited, constitutional malady that was characterized by kinetic tremor in the absence of other neurological signs [1]. Historically, the disease entity was commonly referred to as "benign essential tremor", a term which reflected a view of this entity as mild, non-progressive and self-contained [2]. The nosology of medicine is cluttered by a variety of left-over-terms (e.g., "idiopathic", "essential") that no longer appropriately label or describe the conditions to which they are appended. Aside from the use of the term "essential tremor" in medical textbooks, the term is used in peer-reviewed manuscripts, albeit with less frequency over time. Thus, a PubMed search from 1966 until January 2011 yielded 34 journal articles in which the term "benign essential tremor" was used in the abstract (10 in the 1970s, 16 in the 1980s, 4 in the 1990s, and 4 in the year 2000 or after) [3, 4]. The use of the term is ever present in numerous medical websites as well (for example, to list only a few: www.essentialinfo.com; www.webmd.com; www.essentialtremor.org; www.drugs.com; rarediseases.info.nih.gov), indicating that the term is still very much in common use by those who disperse medical information to the public.

In a medical context, "benign" is a word used to indicate an illness that is either of a mild type or character, which does not threaten health or life, has no significant effect, is harmless, is of no danger to health, or is not recurrent or progressive.

Over recent years, the older view of ET as a simple, monosymptomatic condition has been challenged, as new data have emerged painting a picture of a progressive disorder associated with several co-morbidities, and possibly even an increased risk of mortality [5]. We now raise the question, is it time that the medical community formally drop the word "benign"? In this paper, we review the published data that support the position that the term should be dropped.

Search Strategy and Selection Criteria

References for this review were identified by searches of PubMed from 1966 until January 2011. The terms "essential tremor", "clinical", "benign", "morbidity", "mortality", and "cognition" were crossed together in the search engine. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed.

Increased Co-morbidity in ET

In the literature of the past decade, there has been a growing awareness of the presence of additional co-morbidities associated with ET [5] including cognitive, psychiatric, motor and perhaps even sensory phenomenon. ET patients do not necessarily have to have all co-morbidities, but rather, having ET increases the probability of possessing one or more of these co-morbidities. The underlying pathophysiology of several of these co-morbidities has not been worked out.

Cognitive Disturbance

Beginning with studies published a decade ago [6, 7], investigators first began to demonstrate mild cognitive and neuropsychological differences between ET patients and controls. Problems with verbal fluency, recent memory, working memory, and mental set-shifting have been described in these studies. The number of these studies has multiplied with time [3, 6–12], indicating the likely presence of a mild non-motor component to ET. That these cognitive features are disease-linked, rather than mere signs of aging, is evidenced by the fact that many of these studies also enrolled age-matched normal comparison groups [6, 8, 9, 11]. Moreover, in a recent population-based study in Spain, 135 ET cases and 2,184 controls were followed for three years and, within that time interval, the mini-mental status test scores declined at a rate in ET that was seven-times faster than in controls. These data provided some reasonable evidence that the cognitive deficits in ET were not static and that they may be progressing at a faster rate than in elders without the disease [13]. These data are not without implications and, later in this paper, we will discuss the epidemiological studies that have demonstrated links between prevalent ET and incident dementia [14, 15].

Although these cognitive deficits in ET are notable, they can be clinically subtle [10] and their clinical-functional relevance has only recently been investigated. A growing number of studies have suggested that the cognitive deficits of ET are associated with clinical correlates. In a population-based study conducted in Spain, ET cases with lower cognitive test scores also had more difficulty with a variety of functional activities requiring cognitive processing (e.g., remembering appointments) [16]. Further, in a clinic-based study conducted in New York, mini mental status test scores in ET correlated with several functional measures, and worse cognitive performance was associated with greater dysfunction [17]. Another group of investigators in New York reported on ET patients residing in a long-term care facility, and the data revealed that mini mental status test scores were associated with activity of daily living scores (i.e., worse cognitive test performance was associated with greater difficulty with activities of daily living) [12]. These studies, conducted in three different settings, provide evidence that the cognitive decline of ET, though in many cases *clinically subtle*, is not necessarily *subclinical*. Additionally, the cognitive decline has been associated reproducibly with functional difficulties.

Psychiatric Co-morbidities

In addition to the cognitive manifestations of ET, a number of psychiatric co-morbidities have come under increased scrutiny in recent years. Thus, anxiety [18, 19], depressive symptoms [19–22], and social phobia [23] have also been shown to occur to a greater extent in ET cases than controls. The traditional view is that these represent a psychiatric response to disabling tremor [24]. However, the data from a study in Spain [20] would challenge this long held belief. In that study [20], prospective analyses indicated that depressive symptoms preceded the onset of the tremor, suggesting that the mood disorder could be a primary manifestation of the underlying disease process (as occurs in Parkinson's disease (PD) [25] and Huntington's disease). This primary manifestation would be distinct from but would not preclude the occurrence of a secondary psychiatric response to the disabling motor symptoms [24].

Impaired Gait and Balance

In a growing number of studies, changes in gait and balance have been identified in patients with ET [26–29], and the constellation of impairments has been similar to that seen in patients with cerebellar ataxic gait. The gait abnormality in ET seems to be most evident in patients with cranial (i.e., midline) tremors (e.g., head, voice, jaw) [29, 30], and does not correlate with the severity of limb tremor, suggesting that this difficulty is symptomatic of a

disturbance of cerebellar regulation of the midline, which is distinct from its regulation of the limbs [29]. Although the gait abnormality in ET has been documented as milder than that seen in patients with cerebellar ataxias, it does seem to have clinical/functional consequences, with at least one study now indicating that ET patients (and especially those with head tremor) have reduced functional mobility both in terms of self-reported measures of gait confidence and in performance-based measures of gait and balance [30]. More specifically, ET patients, and particularly those with head tremor, felt less confident in their balance and more likely that they would lose their balance or become unsteady in a variety of daily situations, and they performed more poorly during a broad range of common activities (rising from sitting, walking and turning, ascent of stairs, descent of stairs) [30].

Hearing Impairment

Hearing issues have long been suspected to be associated with ET. In a population-based study, self-reported hearing impairment was more prevalent in ET cases than controls [31]. Additionally, in a clinic-based study [32], ET patients had significantly more self-reported hearing difficulty (i.e., they had scores on a hearing handicap scale that were nearly twice as high as controls). Of further interest is that this hearing impairment was functionally relevant in many cases; while only 0.8% of controls wore hearing aids, 16.8% of cases did [32].

ET as an Entrée to Other Neurodegenerative Conditions

There is accumulating evidence that ET is a risk factor for other neurodegenerative conditions. It is well-known clinically that patients with many years of ET can later develop PD (i.e., ET-PD) [33–36]. Case-control studies have shown a five-fold increased co-occurrence of the two disorders in the same individuals above that expected by chance alone [37]. A recent prospective analysis has similarly demonstrated that patients with prevalent ET have a 4 – 5-fold increased risk of developing full-blown incident PD during follow-up [38]. Of course, one must be careful in the interpretation of these studies to distinguish mild action tremor, a common and early feature of PD, from prevalent ET. The presence in many cases of classical, medication-responsive ET for decades prior to the co-development of PD, suggests that the prevalent “ET” cases actually had ET.

Epidemiological studies in both Spain and New York have recently demonstrated that prevalent ET is associated with both a 1.5 – 2-fold increased odds of having prevalent dementia [14, 39] and a 1.5 – 2-fold increased risk of developing incident dementia during follow-up [14, 15]. In the prevalence studies, 11.4% of ET cases vs. 6.0% of controls (combined mean age = 75.8 years)[39], and 25.0% of ET cases vs. 9.2% of controls (combined mean age = 77.6 years)[14] had prevalent dementia. The pathological basis of this dementia has not been clearly delineated. In epidemiological studies, the clinical diagnosis was Alzheimer’s disease (AD) [14, 39] in the bulk of the cases. The studies do not imply that all ET patients will develop dementia but merely that their risk of dementia seems to be elevated.

Progressive Nature of ET

Despite the high prevalence of the disorder, there are very few longitudinal data on the rate at which the action tremor of ET increases in severity over time, and there are no such data from community-based settings. One study demonstrated an approximate 12% yearly increase in tremor amplitude [40], although the study was clinic-based. Patients who elect to return for follow-up clinical visits are, in general, a self-selected group who often have tremor that is progressively worsening; patients with stable tremor are generally less inclined to return. Hence, the study was likely to have over-estimated the rate of decline in

tremor over time. In a more recent study [41], cases were seen longitudinally in a research setting and they were not self-selected for follow-up based on a need for clinical care. In that study, the majority of ET cases exhibited a modest yet progressive worsening in action tremor scores with time, with the average annual increase in tremor severity from baseline estimated to be between 3.1% and 5.3%.

It is important to keep in mind that action tremor is not the only type of tremor seen in patients with ET. Both rest tremor [42] and intention tremor [43] in ET have been associated with illness of longer duration, indicating that not only the severity of action tremor, but the complexity of tremor phenomenology seems to progressively increase with longstanding disease.

Functional Disability in ET

More than 90% of ET patients who seek medical attention report disability [22] and severely-affected patients are frequently unable to feed or dress themselves [44]. Between 15% and 25% of patients are forced to retire prematurely, and 60% choose not to apply for a job or promotion because of uncontrollable shaking [45]. That is the view of ET frequently observed by clinical neurologists. Yet population-based studies indicate that the bulk (90 – 99%) of ET cases do not seek medical attention [19, 46]. To some measure, this may be a feature of the limited access to care or due to the low level of educational attainment that characterizes many of the populations sampled rather than the result of the mildness of tremor in these population-dwelling ET cases. Also, one must be cautious in interpreting these statistics, as ET cases might mention the tremor to their primary care doctor during the course of a more general and comprehensive medical discussion, even if they did not seek treatment specifically and exclusively for that tremor. Interestingly, when researchers examined the issue of disability in population settings, the majority (73%) of these cases reported some disability, with most experiencing difficulty in multiple functional domains [22] and the majority demonstrated moderate or greater difficulty on multiple tasks during a performance-based test of function that included a variety of common, daily activities. This suggested that even the milder form of ET that exists in the community is associated with functional disability. Moreover, a recent study in Spain demonstrated that morale was lower in these community-dwelling ET cases when they were compared to similarly-aged controls, further underscoring the effect of their tremor on quality on life [47]. Nonetheless, there is a need for longitudinal studies, examining clinical progression and accrual of disability over time in population-based settings, as to extent to which there are subgroups of community-dwelling ET cases with a relatively mild disorder is not known.

The available studies have generally focused on the effects of hand tremor on daily function and morale. Other studies have explored and demonstrated the functional consequences of cognitive difficulty in ET [12, 16, 17], hearing difficulty (i.e., increased need to use of hearing aids)[32], and gait difficulty and imbalance [30]. The disability associated with anxiety and depression remain largely unmeasured, although the increased prevalence of social phobia has been one indicator of the psychological toll of the tremor [23].

Risk of Mortality in ET

Although it is often written that there is no increased risk of mortality in ET cases compared to similarly-aged controls, few actual data support this notion. Early discussions in the literature promoted the view that ET cases seemed to live longer than controls because many ET cases were very old; however, this was a fallacy because older and older age is associated with an increasing likelihood of having ET (i.e., being in an older age category increases the likelihood of having ET rather than the converse)[48]. One retrospective, longitudinal, records-linkage-based investigation demonstrated no difference between ET

cases and a group of historical controls in their risk of mortality[49]. There are drawbacks and limitations of the retrospective design and also the use of historical control groups. A more recent prospective, population-based study showed a modest yet significant (45%) increased risk of mortality in ET, suggesting that ET could be a disease associated both with increased risk of morbidity and mortality [50]. There is a need for additional prospective, controlled studies to further examine the issue of mortality in ET.

ET as Seen in the Clinic vs. ET as Seen in the Community

It is clear from community-based studies [19, 46] that many ET cases have not been previously diagnosed with the disease, suggesting that the cases ascertained in clinics represent the tip of a larger iceberg. Additionally, it could be argued that for every ET case ascertained from a neurology clinic, there may be ten additional cases who did not self-select for attendance in that clinic. The cases seen in clinics clearly have the potential to be the ones of greater severity, with milder cases under-represented in this setting. These milder cases would be more likely to be present in community-based samples. This raises the question, what is the nature of ET in the community setting? As noted in previous sections of this manuscript, ET does not seem to be a completely benign entity in the community. When questioned, the majority of ET cases in the community report functional disability, with most reporting this difficulty in multiple functional domains [22], and a similar majority of cases demonstrated moderate or greater difficulty on multiple items on a performance-based test of function [22], suggesting that even the milder form of ET that exists in the community is generally associated with functional disability. Moreover, the cognitive deficits that have been observed in ET were not restricted to patients ascertained from clinic-based studies but also extended to those cases seen in population-based settings [8, 13]. Furthermore, it is in the setting of population-based studies that ET has been associated with more self-reported hearing impairment [31], more depressive symptoms [20], as well as increased risks of PD [38], AD [14, 15] and mortality [50].

Synthesis and Recommendation

The article serves as a review of studies that have accumulated over the past decade. In total, these studies characterize ET as a disease that is associated with functionally-relevant cognitive abnormalities, a mood disturbance and other psychiatric co-morbidities, a functionally significant gait disorder, hearing difficulty, and a variety of types of tremors, which are progressive in nature and can be quite disabling. Also, recent clinical-epidemiological studies have linked prevalent ET to incident AD as well as to incident PD, with at least one study demonstrating an increased risk of mortality. While a number of these studies are derived from clinic-based samples of cases, population-based studies have also given rise to a number of these findings, suggesting that even in the population, the disease is associated with disability and co-morbidity. Finally, with the advent of new therapies such as deep brain stimulation, there have been tens of thousands of patients presenting with disability significant enough to warrant a surgical therapy. This disability cannot be characterized as benign. Based on these studies and observations, it seems incongruent to use the term “benign essential tremor”. By analogy, one may examine the nosology of medical conditions more widely. Thus, when diabetes is mild (e.g., when it can be controlled by diet alone), it is not referred to as “benign diabetes”. Similarly, mild asthma that is brought on in the setting of activity is referred to as “exercise-induced asthma” rather than “benign exercise-induced asthma”. The word “benign” is an antiquated and outdated term that reflects an unsophisticated stage in the labeling and nosological classification of diseases. It is our recommendation that the medical community formally discontinues this nosology (“benign essential tremor”) and rather uses the term “essential tremor.” In those cases with currently-mild tremor, the nosology “mild essential tremor” is preferable.

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