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Essential Tremor as a Neuropsychiatric Disorder

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Abstract

The traditional view of essential (ET) tremor is as a mono-symptomatic condition characterized by action tremor. Over the past decade, researchers have learned that this picture is an over-simplification. First, it is clear that many patients also have other motor manifestations (e.g., ataxic gait). Second, the presence of a variety of non-motor features, both cognitive and psychiatric, is now appreciated. Mild cognitive changes (esp. executive dysfunction) have been documented in several studies. More recently, two population-based studies have demonstrated an association between ET and dementia. Clinically, while most of these cases developed Alzheimer's disease, the neuropathological underpinnings of this dementia have not been fully explored. Psychiatric manifestations include specific personality traits, anxiety, social phobia, and depressive symptoms. Depression may be a primary manifestation of the illness rather than a secondary response to disability. The emerging view of ET is that it is a disease whose central feature is action tremor but in which both motor and non-motor features occur. As in other neurodegenerative conditions, ET appears to be more than a disease of the motor system. Further study of these non-motor phenomena will advance our understanding of disease mechanisms and enhance the quality of clinical interactions with patients.

Keywords

essential tremor; cognition; dementia; neuropsychiatric; depression; epidemiology; clinical

Introduction

Essential tremor (ET) is the most common pathological tremor in humans; in some studies it is twenty times more prevalent than Parkinson's disease [1]. The most recognizable and

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defining feature in patients with ET is an 8 – 12 Hz kinetic tremor (i.e., tremor that occurs during voluntary movement) of the arms and sometimes tremor of the head and voice. ET is among the most common and widespread of the neurological diseases. In the United States alone, thirteen million people are estimated to be affected [2], and the condition is clearly global, affecting human beings in a variety of settings, ranging from the remote Okapa sub-district of Papua New Guinea to the urban Washington Heights-Inwood community in northern Manhattan, New York [3–10]. Human beings have left a written commentary about tremor for several thousand years, indicating that this is a condition that has accompanied humans for some time [11]. The prevalence of ET has been estimated to be 4.0% – 5.6% among individuals age ≥ 40 years [1,6] and 9.0% or higher among individuals ≥ 60 years of age. The etiologies of this widespread disease are likely to be diverse and many. Indeed, both genetic [12–15] and environmental [16–20] factors are implicated.

Pathophysiology

Despite being such a common disease, little progress was made during the nineteenth and most of the twentieth century in terms of understanding the underlying mechanisms of ET [21]. Review articles and textbook chapters on this disease very often did not include sections devoted to its pathophysiology. The existence of a central tremor pacemaker was posited, based on physiological considerations, although the anatomical correlate was not clearly established. In the 100 year period between 1903 (the first reported postmortem on ET) and 2003, there had only been 15 postmortem examinations [21]. Most did not use rigorous methodologies, and none used age-matched control brains for comparison. Hence, the search for a structural brain correlate had not begun with any rigor and the traditional view that there was “no pathology” in ET was based on absence of proof rather than proof of absence.

During the past decade, an ever expanding clinical literature has implicated that the cerebellum might be centrally involved in ET. First, cerebellar-like problems, with abnormalities in tandem gait and balance, have been repeatedly described in ET patients [22–26]. Intention tremor of the hands occurs in 58% of ET patients [27,28], and, in 10% of ET patients, intention tremor spreads to the head [29]. Second, unilateral cerebellar stroke has been reported to abruptly terminate ipsilateral arm tremor in ET [30] and cerebellar outflow pathways are the target of deep brain stimulation, which is an effective treatment for ET [31,32]. In addition, numerous neuro-imaging studies have provided evidence of cerebellar hemispheric dysfunction in ET, including functional magnetic resonance imaging (fMRI) [33], positron emission tomography [34–41], and [^{1}H] magnetic resonance spectroscopic imaging (MRSI) studies [42,43].

An intensive effort was launched in 2003 to collect, bank, and rigorously study ET brains [44]. Among other things, these brains were systematically examined to quantify cerebellar and other brain pathologies and they were compared to control brains for the first time. These studies, based on 33 ET brains, determined that there are identifiable structural pathological changes in all studied ET brains and the changes appeared to be of two types [21,45–48]. The most common type of ET (more than 75% of brains) was characterized by clear cerebellar degenerative changes, including a six-fold increase numbers of torpedoes (i.e., proximal swellings of the Purkinje cell axon that likely represent a cellular response to injury), a 40% reduction in number of Purkinje cells, and Purkinje cell heterotopia and dendrite swellings. These brains did not have Lewy bodies. A second type of ET was characterized by Lewy bodies confined mainly to the locus ceruleus; these brains did not have excessive torpedoes or Purkinje cell loss. These two pathological subtypes of ET were been labeled “cerebellar ET” and “Lewy body variant of ET” [LBVET]) [45–50].

These more recent postmortem studies have helped localize the possible source of the ET to degenerative structural alterations in the cerebellum and its connecting pathways. The primary

cerebellar pathology is most direct, but the LBVET is also a logical pathological pattern to produce ET, given the connections involved. The neurons of the locus ceruleus synapse with cerebellar Purkinje cell dendrites [51–53]. These projections are important for the normal development and maintenance of Purkinje cells, and locus ceruleus lesions may be associated with regressive Purkinje cell dendritic changes [54–58]. Furthermore, on a functional level, impaired activity in the locus ceruleus could result in a diminution of stimulatory output from that locus to the Purkinje cells. Whether through primary cerebellar degeneration or secondary effects on cerebellar outflow as a result of degenerative changes in the locus ceruleus, the consequence is de-regulation (through decreased cerebellar inhibitory output) of the neuronal pathway that involves the cerebellum, thalamus, and motor cortex (i.e., the cerebellar-thalamic-cortical pathway).

The Expanding Clinical Spectrum. Motor Features

Although the most recognizable and defining feature in patients with ET is a kinetic tremor of the arms, the older view that this is a monosymptomatic disease is no longer tenable. First, the tremor phenomenology itself is diverse and multifaceted. In addition to kinetic and postural tremor, intention tremor [27], and tremor at rest [59–61] may occur. Furthermore, the relative severity of different tremor types (kinetic > postural rather than the converse [62]), the favored sites of anatomical involvement (arm > head > jaw [63,64]), and the typical direction of somatotopic spread (from arms to head rather than the converse) [65] are distinctive, adding a level of clinical subtlety and complexity to a disorder that is often viewed as relatively non-descript and bland. Due in large measure to a widespread lack of familiarity with these issues, ET is misdiagnosed in 30 – 50% of patients [66–68], which may make this the most commonly misdiagnosed neurological disorder. Second, aside from the tremor phenomenology, other motor features have been described in ET. Perhaps most important of these are the complaints of gait difficulty, which are not uncommon in patients with ET. In several studies [22,23,27], postural instability and mild to moderate ataxic gait, beyond that seen in normal aging, have been demonstrated in patients with ET, and especially those patients with other cerebellar signs (e.g., intention tremor). This ataxic gait may actually improve with the administration of low doses of ethanol [26]. The functional implications of this gait disorder are not entirely clear and additional studies are needed. In addition to these gait problems, subtle eye movement abnormalities have also been observed in patients with ET [69], again implicating involvement of the cerebellum on a clinical as well as physiological level.

The Expanding Clinical Spectrum: Non-motor Features

While the motor features of ET have been the defining element of the disorder, there is emerging now over the past five to ten years a growing appreciation of the existence of a variety of non-motor features as well. A parallel may be drawn with a related tremor disorder, Parkinson's disease. While traditionally defined as a motor disorder without cognitive features, work over the past 20 – 30 years has shown that non-motor features, both psychiatric and cognitive, are a feature of that disorder as well [70–73].

The non-motor features of ET may be divided into cognitive and psychiatric. Cognitive features, especially problems with executive function, were first appreciated in a 2001 study of Gasparini et al. [74] and then by other investigators in that same year [75] and soon after [76–80]. Importantly, several of these studies were case-control studies, in which ET cases were directly compared to age-matched controls [74,79,80], thereby demonstrating that the cognitive changes were above and beyond that expected with typical aging. Furthermore, one of the studies was population-based [79], sampling a largely untreated, mild group of cases. This suggests that the cognitive abnormalities are not merely a feature of a small, self-selected group of severe ET cases attending a specialty clinic or a surgical center, but rather, a broader

and more elemental disease-associated phenomenon. As summarized by Tröster et al. [78], in these various studies, ET patients have demonstrated significantly lower than expected scores on measures of complex auditory and visual attention, verbal fluency, and immediate recall. These types of deficits could reflect difficulty with initiation and maintenance of information processing strategies; such a mechanism is similarly thought to underlie cognitive changes in patients with Parkinson's disease. The observed deficits seem similar to those reported after cerebellar lesions and dysfunction, and thus, are consistent with cerebellar-thalamic-cortical pathway dysfunction. As noted by Tröster et al. [78], the deficits have generally been of a magnitude of approximately 1 – 1.5 standard deviations below normal, suggesting that the cognitive changes of ET reflect only mild clinical impairment. In the population-based study of Benito-Leon et al. [79], forgetfulness was reported in 50.4% of ET patients and 43.1% of controls, a difference that was marginally significant ($p = 0.05$), and which raised the possibility that the cognitive deficits in ET may not be entirely subclinical and may indeed be noticeable to patients. Cognitive complaints do occur in patients with ET in clinical settings; however, they are generally attributed to aging or medication effects. In all likelihood, some of these complaints are due to the underlying disease itself, and this is a feature of which treating physicians should perhaps be more cognizant. That cognitive deficits are a feature of ET furthermore raises the specter that, as in patients with Parkinson's disease, more profound problems with cognition and frank dementia may be associated with the disease.

A population-based study in 2006 in Madrid by Benito-Leon et al. [81] first demonstrated that the odds of dementia were nearly twice as high among older onset ET cases than age-matched controls without tremor. Similarly, in patients with Parkinson's disease, the association between older age at onset and dementia is well established (i.e., patients with older age at onset are more likely to be demented than are patients with younger age at onset, and older onset is a risk factor for incident dementia) [81]. More recently, in a second population-based study of the elderly in northern Manhattan, investigators found that ET was associated with a near-doubling of the odds of prevalent dementia [82], thereby confirming the results of the initial study in Madrid. In each study, the large majority of those with dementia had clinical diagnoses of Alzheimer's disease. Both studies were cross-sectional, so that it is possible that Alzheimer's disease led to ET rather than the other way round. However, the study in Spain reported that 83.9% of the demented ET cases reported that tremor preceded the onset of dementia rather than the converse [81], thereby suggesting that ET led to dementia.

The group in Spain performed a follow-up study in 2007, this time with a prospective design [83]. In that study [83], ET cases and matched controls, all of whom were non-demented at baseline, were followed for three years. The risk of developing incident dementia was nearly twice as high in the ET cases. This study indicated that ET increases the risk of incident dementia.

It is important to note that ET and Alzheimer's disease are common disorders. Although one would expect that the two would co-occur in some persons by chance alone, these epidemiological studies have demonstrated an association between the two that is above and beyond that expected due to such chance occurrence, a point that has been misconstrued by some investigators [84].

The observation that ET seems to be associated not only with mild cognitive changes, but also increased risk of dementia, raises several issues. First, why has it taken so long for this observation to emerge? Here, a parallel may be drawn with Parkinson's disease, where the latency from the initial disease description to an appreciation of the cognitive deficits was more than 150 years. Patients with Parkinson's disease and ET are often elderly and there has been a tendency to attribute their cognitive difficulties and dementia to advanced age. Second, the association between ET and dementia, while robust and significant, is not of the magnitude

seen in patients with Parkinson's disease, where the odds ratios are higher (e.g., 3.75) than those reported in ET [72]. Third, it is important to note that both studies, in Madrid [81] and New York [82], were population-based. Patients who are seen in clinical settings (esp., movement disorder practices) are probably self-selected to have a movement disorder rather than dementia as their primary issue, thereby minimizing any apparent association between ET and dementia in those samples. Demented cases are more likely to attend a memory clinic. Also, onset of dementia may make attendance at a clinic practically more difficult, especially if the motivation for attending that clinic is marginal to begin with (e.g., longstanding, slowly-worsening tremor that responds only marginally to medications).

A second issue is the mechanistic basis for the association between ET and prevalent dementia. There are several possible explanations. Recent post-mortem studies have demonstrated an increased prevalence of brainstem Lewy bodies in ET cases [45,47,49,85]. These post-mortem cases raise the question as to whether ET cases with prevalent dementia have cortical Lewy body pathology. Alternatively, other pathological mechanisms (e.g. cerebrovascular, Alzheimer's-type changes) may better explain this association. There are no imaging or postmortem studies comparing the prevalence of subcortical vascular pathology in ET cases compared with controls, and this is worthy of investigation. The studies in Madrid [81] and New York [82] both noted that the majority of their ET cases with dementia had clinical diagnoses of Alzheimer's disease. Of interest is that a recent postmortem study of ET [45] found slightly more Alzheimer's type plaque and tangle pathology in ET cases than age-matched controls. The mechanistic basis for the dementia in ET clearly merits additional study.

The final issue is that of treatment. The results of recent studies suggest that cognitive issues should enter the clinical dialogue with ET patients rather than being brushed aside as normal features of aging. Furthermore, possible treatment of dementia should be considered.

Aside from the cognitive features of ET, a number of psychiatric correlates have come under greater scrutiny in recent years. The presence of specific personality traits [86,87] has been demonstrated. In one of these studies [86], patients with ET were characterized as having higher harm-avoidance scores, meaning that they were more worrying and shy than controls. The scores did not correlate with the severity of tremor or with subjective and objective scales of disability, suggesting that the personality profile observed was not entirely related to functional disability caused by tremor; in other words, it may have been a primary disease feature [86].

Anxiety [88], depressive symptoms [89–92], and social phobia [93] have also been shown to occur in ET patients to a greater extent than in controls [94,95]. Traditionally, these have been viewed as a psychiatric response to disabling tremor. Yet in one recent study [90], depressive symptoms were more common in ET cases than controls, and these symptoms seemed to precede the onset of the motor manifestations in prospective analyses (i.e., the presence of baseline self-reported depression was associated with an increased risk of developing incident ET at follow-up). While depression may be a consequence of the tremor and disability, it is possible that a mood disorder is part of the underlying disease process rather than a response to the tremor. In this scenario, the mood disorder could further contribute to the functional disability. Depression has been shown to precede the motor manifestations of both Parkinson's disease and Huntington's disease, suggesting that a mood disorder may also be a primary feature of the underlying disease process and not merely a response to disease manifestations [96–99].

Synthesis. ET as a Neuropsychiatric Disorder

The traditional paradigm, held for many years, regarded ET as a benign, mono-symptomatic condition whose sole manifestation was a single affectation of the motor system. In recent years, this older view has been challenged with new knowledge [100]. The emerging view of

ET is that it is a neurological disease characterized by a number of motor and non-motor features that accompany the readily recognizable action tremor. Recent studies suggest that, as in several other progressive movement disorders (Parkinson's disease and Huntington's disease), cognitive-neuropsychological features are a part of this disease in addition to involuntary movements. While these cognitive issues may be less marked than those in Parkinson's disease and Huntington's disease, they do seem to be genuine. However, they have not entered the clinical dialogue in any meaningful way. Incorporating an assessment of these issues as well as considering their treatment would enhance the quality of care provided to patients with this common neurological disease.

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