Published in final edited form as:

Parkinsonism Relat Disord. 2018 January ; 46(Suppl 1): S70–S74. doi:10.1016/j.parkreldis.2017.07.010.

Essential Tremor Then and Now: How Views of the Most Common Tremor Diathesis Have Changed Over Time

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Abstract

Background—Essential tremor (ET) is the most prevalent tremor diathesis. In this “then” and “now” piece, I detail how views of this disorder have changed over time.

Methods—A PubMed search was conducted on June 15, 2017. The term “essential tremor” was crossed in sequential order with 14 second search terms (e.g., genetics, clinical).

Results—The traditional view of ET was that it was monosymptomatic. An emerging view of ET is as a more clinically-complex entity with a range of possible motor and non-motor features. Traditionally, ET was viewed as autosomal dominant with complete penetrance by age 65. Current thinking is that, in addition to monogenic forms of ET, the disease is likely to be complex, with incomplete penetrance into advanced age. While non-genetic factors were traditionally presumed to exist, epidemiological studies have explored several potential environmental toxicants. The traditional olivary model of ET posited the existence of a central oscillator; an alternative is the cerebellar degenerative model, which is now under consideration.

Conclusions—For ET, there is clearly a “then” and “now” when one assesses changes in our understanding of the disease with time. Indeed, concepts relating to the clinical features, disease etiology and pathogenesis have all changed substantially.

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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; genetics; epidemiology; harmaline; clinical; pathophysiology; cerebellum; neurodegenerative; Purkinje cell

Introduction

Essential tremor (ET) is one of the most common movement disorders and the most prevalent tremor diathesis among humans [1]. With more than 30 population-based prevalence studies spanning five continents and patients cared for by a wide variety of practitioners ranging from general practitioners to movement disorder neurologists, the disease has a global presence [1].

In this “then” and “now” piece, I detail how views of this disorder have changed over time. I discuss disease etiology (i.e., the prime causes of the disease [factors that precede the onset of the disease], including both genetic and environmental factors), disease pathogenesis and pathophysiology (i.e., the constellation of tissue-based changes and altered physiological processes that arise after onset of the disease), and clinical features. After a brief history, I begin with clinical features, as these are most familiar to practitioners.

Methods

A PubMed search was conducted on June 15, 2017. The term “essential tremor” was crossed in sequential order with 14 second search terms, restricting the searches to English language human subject studies and those which contained the two terms in the title or abstract (Table 1).

History

Human beings have been writing about their tremors for millennia; however, historically, the term *tremore semplice essenziale* (i.e., simple essential tremor) was not used until 1874, when Buresi described an 18-year-old patient with severe and isolated action tremor [2]. Early in the 20th century, the term “essential tremor” began to appear with greater frequency in medical literature and by mid-twentieth century, both the familial distribution and core motor feature of ET had been well-documented by clinicians [2].

Clinical Features

Then

The traditional view of ET was that it was monosymptomatic, with no neurological signs or symptoms other than action tremor [3]. Indeed, the Consensus Statement on Tremor of the Movement Disorder Society required that, other than action tremor and Froment’s sign, patients with definite ET have no abnormal neurological signs [4]. However, even proponents of the monosymptomatic view of ET raised several caveats, which included the presence of intention tremor, mild gait ataxia, and mild cognitive problems in some patients [3].

Now

Emerging over the past five to ten years is a view of ET as a more clinically complex entity [5]. This complexity incorporates the presence in some patients of a range of both motor and non-motor features.

Motor Features—A discussion of the motor features of ET should begin with tremor. Although kinetic tremor is the hallmark feature of ET [6], tremor phenomenology in ET can be quite nuanced and complex [7]. Indeed, authors have pointed out that the tendency to overlook such nuances results in the over-diagnosis of ET in as many as 30–50% of patients [8]. Patients with ET may manifest with a variety of tremors that (1) may appear under different activation conditions, including kinetic, postural, intentional, and rest, (2) may affect a number of different bodily locations (e.g., neck, jaw, voice, limbs) to differing degrees and in specific manners, and (3) often follow specific and defined patterns of onset and progression over time. These issues are treated elsewhere in greater detail [6,7], however, I provide here several examples to provide the reader with a few introductory insights. Thus, in ET, the amplitude of the kinetic tremor is generally greater than that of the postural tremor; the opposite, with postural tremor of greater amplitude than kinetic tremor, may be a clue that the diagnosis is not ET [6]. As an additional example, the neck tremor of ET is a postural tremor, observed while the patient is seated or standing; it generally resolves when the patient's neck is at rest (i.e., while the patient lies down).

Motor features other than tremor increasingly have been described in ET. In numerous studies [9], postural instability and mild ataxic gait, beyond that seen in normal aging, have been demonstrated in ET. In addition, subtle saccadic eye movement abnormalities have been observed [10]. These, along with studies demonstrating abnormalities in motor timing, support the notion that there is cerebellar dysfunction in this disease.

The presence of dystonia in some ET patients is an area of uncertainty. While it is not uncommon for patients with dystonia to be mis-diagnosed as ET, particularly when dystonic postures or movements are subtle [3,8], patients with long-standing, severe ET may develop subtle dystonic posturing. It is debated whether this is simply a manifestation of their advanced ET or whether it predicates a second diagnosis or a retraction of the longstanding ET diagnosis.

Non-motor Features—The possible presence of non-motor features in ET was alluded to above, even among those who supported the notion of ET as a monosymptomatic illness [11,12]. Numerous studies now substantiate the presence of a range of these features occurring in excess in ET cases compared to age-matched counterparts without ET. These comprise cognitive features (including a full spectrum from mild cognitive difficulty through mild cognitive impairment to frank dementia in excess of that seen in controls), psychiatric features (including apathy, depression, anxiety, and personality characteristics), sensory features (hearing loss in several studies and mild olfactory abnormalities in some yet not other studies), and other non-motor features (e.g., sleep dysregulation) [11,12]. In one study, depressive symptoms preceded the onset of the motor manifestations, suggesting that they could be a primary manifestation of the disease [11]. These data suggest that, as in several

other progressive, late-life motor disorders such as Parkinson's disease and Huntington's disease, cognitive-neuropsychological features can be part of the clinical spectrum.

Etiology – Genetics Factors

Then

Traditionally, ET was viewed as highly genetic, autosomal dominant and possibly mono-genetic, with complete penetrance by age 65 [13]. Twin studies reported approximately 60% concordance for ET in monozygotic twins [14,15].

Now

Current thinking is that, in addition to monogenic forms of ET, the disease is likely to be a complex (i.e., multiple genes in combination with environmental factors likely co-contribute to disease etiology within a single individual). Alternative modes of inheritance aside from autosomal dominant are likely to be relevant. Furthermore, the penetrance of the disease is not complete, even into the 70s; in a study of more than 200 relatives of ET cases and a similar number of relatives of controls, among older case relatives (> 60 years of age), there was an increased prevalence of higher tremor scores than in such relatives of controls, suggesting that in that age group, subclinical ET may be present and penetrance still may not be complete [16]. Identifying underlying genes in both monogenic and complex forms of ET has been a challenging task. Recent discoveries linking Leucine Rich Repeat And Ig Domain Containing 1 (LINGO1), Fused in Sarcoma (FUS) and Teneurin transmembrane protein 4 (TENM4) to ET has been met with cautious optimism [17].

Etiology – Environmental Factors

Then

Traditionally, ET was viewed largely as a genetic disorder, although it was never seen as an exclusively genetic disorder. Even early classical discourses on the ET recognized the presence of both familial and non-familial forms of the disease [18]. While non-genetic factors were presumed to exist, little research was performed to identify potential environmental risk factors.

Now

Over the past decade, epidemiological studies have researched several potential environmental toxicants. These were implicated because they are toxic to the cerebellum (i.e., a brain region implicated in ET), they produce tremor in laboratory animals, and are widespread, as is ET [19]. Toxicants include β -carboline alkaloids (e.g., harmine and harmaline, a group of highly tremorogenic dietary chemicals) and lead [20,21], for which there is some published evidence of an association with ET. One study also demonstrated that higher levels of baseline ethanol consumption were associated with increased risk of developing ET, an observation that is interesting in light of the known cerebellar toxicity of ethanol [22]. Other studies have pointed to a possible protective role of cigarette smoking in ET [23], parallel with the situation observed in patients with Parkinson's disease.

Pathogenesis/Disease Mechanisms

Then

The traditional “olivary model” of ET posited the existence of a central oscillator, with the main support for this notion being the existence of an animal model of action tremor using the neurotoxin harmaline [24]. The idea arose that a physiological derangement in the inferior olivary nucleus, a structure with inherent oscillatory-pacemaking properties, was the prime mover in ET, although there was little empiric support for this physiological construct. Indeed, rhythm generating networks (i.e., pacemakers) are a non-specific finding in the central nervous system, and are located throughout the brainstem and cerebral cortex including the locus ceruleus, dorsal raphe nucleus, thalamus, and cerebellum (Purkinje cells) [24]. The role of such pacemakers, whether in the inferior olivary nucleus or elsewhere, in the generation of ET has never been empirically demonstrated. With regards to the inferior olivary nucleus, specifically, positron emission tomography studies, emerging in the 1990s, have not demonstrated abnormalities in the inferior olivary nucleus in ET, and postmortem studies have not revealed structural changes in that nucleus either, furthering casting doubt on any role this nucleus might play in generating ET [24].

The olivary hypothesis regarded ET as a manifestation of an abnormality in a central electrophysiological circuit. This stands in contrast to the notion that ET, like Parkinson’s disease and other neurodegenerative disorders, could be grounded in a set of abnormal molecular changes, which give rise to a cascade of degenerative changes with resultant altered neuronal function. The olivary hypothesis arose in a scientific environment in which there had been no substantive attempt to search for such structural brain correlates in ET. In fact, during the 100 year period between 1903 (i.e., the first published postmortem on ET) and 2003, there had only been 15 postmortem examinations, many of which were published in the earlier part of that time period. Most did not use rigorous methodologies, and none used age-matched control brains for comparison.

Now

An alternative to the olivary model of ET is the cerebellar degenerative model [25–27], which is now under consideration. Evidence for this will be reviewed below. In recent controlled postmortem studies that have undertaken detailed studies of the cerebellum, the large majority of ET cases have demonstrated degenerative changes present in and restricted to the cerebellum [25,26]. These changes, described below, may be broadly classified as early, middle, and late changes, although this remains a theoretical construct only. The prime molecular event or events that sets these changes in motion is not currently known.

The early changes are signs of compromised Purkinje cells, and include both axonal and dendritic changes (Table 2). In the axonal compartment, studies demonstrate a 6 – 7-fold increase in the number of swellings of the proximal portion of the Purkinje cell axon (i.e. “torpedoes”). Torpedoes occur in injured Purkinje cells; however, whether they represent a pre-terminal cellular response or a regenerative response is not entirely clear. Ultra-structurally, torpedoes are comprised of massive accumulations of proteinaceous material (i.e., neurofilaments), which occur in disordered arrangements, and which are associated

with problems in axonal transport [25,26]. Similarly, in the dendritic compartment in ET, one sees an increase in the number of dendritic swellings [25,26]. The observation that there is a strong correlation between the number of Purkinje cell dendritic swellings and the number of torpedoes suggests that these postmortem structural changes may be connected, each reflecting a compromised population of Purkinje cells [25,26]. More subtle changes in the Purkinje cell dendritic compartment also raise the possibility of an underlying degenerative process in ET. Before degeneration, the metabolic economy of neurons is often severely challenged, and they are unable to maintain their extensive cytoskeleton. This manifests as regressive changes in dendritic morphology (e.g., a truncation of the dendritic arbor). In a study of cerebellar cortical tissue from ET cases and age-matched controls in which tissue was processed by the Golgi-Kopsch method and Purkinje cell dendritic anatomy was quantified, ET cases demonstrated significant reductions in dendritic complexity and spine density compared with controls [25]. Other changes are of similar interest. Climbing fibers provide one of the major excitatory inputs to Purkinje cells, and climbing fiber-Purkinje cell connections are essential for normal cerebellar-mediated motor control. The distribution of climbing fiber-Purkinje cell synapses on Purkinje cell dendrites is dynamically regulated and may be altered in disease states. Normally, climbing fibers form synapses mainly on the thick, proximal Purkinje cell dendrites in the inner portion of the molecular layer, whereas parallel fibers form synapses on the thin, distal Purkinje cell spiny branchlets. In a study of ET cases and matched controls, ET cases had decreased climbing fiber-Purkinje cell synaptic density, more climbing fibers extending to the outer portion of the molecular layer, and more climbing fiber- Purkinje cell synapses on the thin Purkinje cell spiny branchlets [28]. The interpretation of these abnormalities is not clear; however, they are not unexpected in the presence of Purkinje cell dendritic arbor regression [28].

After the early changes, described above, middle changes are indicative of continued Purkinje cell compromise, responsive Purkinje cell remodeling, and in some cases, eventual Purkinje cell death. As noted above, torpedoes are present in greater numbers in ET cases than controls. Yet there are also more subtle morphometric changes in the Purkinje cell axons in ET [25]. Calbindin D28k immunohistochemistry was used in a detailed morphological analysis of the Purkinje cell axonal compartment in ET and control brains, and changes in axonal shape (i.e., thickened axonal profiles) and axonal connectivity (i.e., axonal recurrent collaterals, axonal branching, terminal axonal sprouting, and other changes) were all present to an increased degree in ET cases versus controls (Table 2) [25]. On a mechanistic level, several of these changes are likely to be compensatory changes in response to Purkinje cell injury, thus illustrating an important feature of Purkinje cells, which is that they are relatively resistant to cell death and capable of mobilizing a broad range of axonal responses to injury. Physiologically, axonal remodeling (i.e., terminal axonal sprouting with the formation of large abnormal sprout plexus) in ET likely results in the formation of aberrant Purkinje cell-Purkinje cell synapses and the creation of new/abnormal cortical circuits in ET.

There is also evidence that the Purkinje cells become overwhelmed to some extent in ET and that there is limited Purkinje cell death, although studies have found differing results with respect to this one change (Table 2) [25,29].

The late changes comprised an increase in the number of heterotopic Purkinje cells (i.e., Purkinje cells whose cell body lies outside of the Purkinje cell layer), abnormal basket cell axons with a dense and tangled appearance (“hairiness”) surrounding the Purkinje cell soma and elongated LINGO1 pinceau processes surrounding the Purkinje cell axon. These changes might represent secondary architectural changes/remodeling in response to Purkinje cell dendritic arbor regression and Purkinje cell death [25].

In one postmortem series, Lewy bodies were observed in a portion of ET brains as well [25,26], indicating the possible presence of pathological heterogeneity in ET. In that series, Lewy bodies were abundant in the locus ceruleus and either absent or infrequent in other brainstem structures (dorsal vagal nucleus, substantia nigra pars compacta). The locus ceruleus is the principal source of norepinephrine in the central nervous system and among its main efferent connections are Purkinje cells. Each locus ceruleus neuron is thought to terminally project onto numerous Purkinje cells and these connections are important for the normal function of Purkinje cells and their inhibitory output. Hence, it is conceivable that lesions in the locus ceruleus in ET could plausibly result in subtle Purkinje cell changes and/or altered Purkinje cell output.

Nearly all changes described in the cerebellum in preceding paragraphs are centered on and around the Purkinje cell. Even in the brains with Lewy bodies, there is a potential connection with Purkinje cells. Purkinje cells are inhibitory neurons; their dysfunction and possible death likely result in decreased inhibitory modulation from the cerebellum, with possible resultant diminished motor control and, particularly, problems of dysrhythmia, including tremor. Further research is needed.

In summary, while the olivary model of ET was traditionally applied to ET, the model has a number of problems and may not be relevant to ET. With the passage of time, alternative models, which posit a more direct involvement of the cerebellum, are now currently also under consideration.

ET - One or More Entities?

Then

The traditional view of ET was that it was a single disease entity or, at most, two entities – familial vs. non-familial ET. This view is changing.

Now

As noted above, 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. 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., therapeutic response phenotype). Furthermore, postmortem studies indicate the likely presence of pathological heterogeneity [26]. These parallel observations, of etiological, clinical and pathological heterogeneity, have given rise to the question as to whether ET represents a single disease entity or rather a family of diseases

[30]. In all likelihood, we are dealing with a family of disease, which differ with respect to etiology, pathogenesis and clinical features. The nomenclatural issue that naturally follows is whether the more appropriate term is “essential tremors”. While some have questioned whether ET is merely a syndrome (i.e., a collection of symptoms and signs that run together), ET is not merely a collection of clinical signs, but is rooted to underlying etiologies and tissue-based changes. Indeed, it is likely that variation in the clinical picture will align with particular etiologies and also particular pathologies.

Conclusions

For ET, there is clearly a “then” and “now” when one assesses changes in our understanding of the disease with time. Indeed, concepts relating to disease etiology, pathogenesis and clinical features have changed substantially. Despite this, there is much to learn about this enigmatic and highly prevalent condition.

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).

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Table 1

Search strategy from PubMed using various keywords and their combinations

Key words and combinations	Number of publications
Essential tremor AND history	198
Essential tremor AND genetics	45
Essential tremor AND genes	74
Essential tremor AND epidemiology	41
Essential tremor AND risk factors	39
Essential tremor AND toxicants	7
Essential tremor AND clinical	795
Essential tremor AND non-motor	37
Essential tremor AND cognition	32
Essential tremor AND pathophysiology	115
Essential tremor AND cerebellum	114
Essential tremor AND neurodegenerative	98
Essential tremor AND Purkinje cell	44
Essential tremor AND inferior olive	18

Table 2

Degenerative Changes in the ET Cerebellum

Cerebellar compartment	Cerebellar Morphological Change
Purkinje cell dendrite	
	1. Increase in Purkinje cell dendritic swellings
	2. Dendritic pruning
	3. Loss of dendritic spines
Purkinje cell body	
	4. Reduction in Purkinje cell linear density
	5. Increase in Purkinje cell heterotopias
Purkinje cell axon	
	6. Increase in Purkinje cell torpedoes
	7. Increase in Purkinje cell axonal recurrent collaterals
	8. Increase in Purkinje cell axonal branching
	9. Increase in Purkinje cell terminal axonal sprouting
	10. Increase in Purkinje cell arciform axons
	11. Increase in Purkinje cell thickened axonal profiles
	12. Increase in Purkinje cell infraganglionic plexus
Basket cell axonal processes	
	13. Increase in hairy baskets
	14. Elongated LINGO1 pinceau processes