FIVE NEW THINGS

Essential Tremor

Five New Things

Abhishek Lenka, MBBS, PhD, and Sanjay Pandey, DM

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Correspondence
Dr. Pandey
sanjaysgpgi2002@yahoo.co.in

Abstract

Purpose of the Review

To highlight five new things in the research and clinical aspects of essential tremor (ET).

Recent Findings

The introduction of a new definition of ET and a new category "ET plus" were the major themes of the recent consensus statement. This new change demands a change in the approach to the clinical diagnosis of ET and related diseases. From the pathogenesis standpoint, the cerebellar neurodegenerative model seems to have abundant evidence in its favor compared with the olivary model, which has largely fallen out of favor. From the standpoint of therapeutics, magnetic resonance–guided focused ultrasound (MRgFUS) thalamotomy has enriched the therapeutic armamentarium.

Summary

There has been considerable progress in the field of ET. We discuss five new things in this article, which include (1) new definition, (2) ET plus, (3) approach to the diagnosis of ET, (4) cerebellar degeneration, and (5) MRgFUS thalamotomy.

Essential tremor (ET) is one of the commonly observed movement disorders among adults.[1] Substantial progress in the research on ET has not only improved our understanding of its etiopathogenesis but also widened the clinical spectrum of a disease that once was considered a monosymptomatic illness. Given the fast progress in the field of ET, it is crucial to remain updated about various clinical and research aspects of this disease. Through this article, we highlight five new things in the field of ET, which would affect research and clinical practice in the future.

ET: A New Definition and Diagnostic Criteria

The tremor task force of the International Parkinson and Movement Disorders Society (IPMDS) proposed a new classification 3 years ago.[1] The introduction of a new definition for ET was one of the principal components of the new classification. Accordingly, ET is now defined as bilateral isolated action tremor of both upper limbs of at least 3-year duration with or without tremor involving other body parts such as the head, voice, and lower limbs (Table 1).[1] In addition, important exclusion criteria have been provided to exclude isolated focal tremor (voice and head) and task- and position-specific tremors from the clinical scope of ET. There are substantial advances in the new definitions and diagnostic criteria. Now, the clinical definition of ET is narrower and more precise. A 3-year embargo is a helpful addition to the inclusion criteria considering that it allows the only clinically stable patient to be

MedStar Georgetown University Hospital (AL), Washington, DC; and G.B. Pant Institute of Postgraduate Medical Education and Research (SP), New Delhi, India.

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Table 1 Summary of the Diagnostic Criteria for Essential Tremor as Suggested by the Tremor Taskforce of the International Parkinson's Disease and Movement Disorders Society (IPMDS)

Essential tremor
Body part affected: upper limbs (other parts such as the head, voice, and lower limbs may be affected) Laterality: bilateral Type of tremor: isolated action tremor Duration: >3 y Absence of: other neurologic signs, such as dystonia, ataxia, or parkinsonism.
Essential tremor plus
Features: must fulfill the criteria for essential tremor outline above Additional features: subtle or questionable dystonia, tandem gait impairment, and memory impairment Others: essential tremor with tremor at rest
What is not classified as "Essential tremor" and "Essential tremor plus"
Isolated focal tremor (head and voice) Task- and position-specific tremor

classified as ET and reduces the chances of subsequent development of other neurologic signs such as dystonia, parkinsonism, and ataxia. Also, the newly added exclusion criteria are very helpful to highlight what is not ET. A uniform definition of ET was an unmet need for a long time. Such a definition is important to have uniformity in the diagnosis, which caters to a long-term goal of having relatively homogeneous cohorts for future studies.

ET Plus: A New Category

There are several neurologic soft signs, which have been reported in association with ET, and these include mild tandem gait impairment, subtle/questionable dystonia, and memory impairment. These soft signs have questionable significance in clinical practice and are not sufficient or convincing enough to be recognized as nosologically distinct entities. As their presence compounds the clinical heterogeneity, the IPMDS task force suggested grouping patients with ET with the aforementioned neurologic soft signs of unclear significance into a category termed "ET plus." This categorization (ET and ET plus) has initiated a scientific debate since its introduction.[2]

Several movement disorder research groups have reclassified their patients with ET based on the new consensus criteria[1] and reported that a large proportion of patients who were previously labeled as ET now fall in the ET plus category.[3,4] We succinctly discuss the pros and cons of the introduction of this category.

The introduction of the ET plus category ensures that there is a pure or isolated ET group as defined above.[1] This, in turn, facilitates clinical homogeneity, which is crucial for research on ET. This was an unmet need for a long time and could have potentially affected many old clinical trials that recruited a proportion of patients with ET who would probably be reclassified as ET plus, based on the new criteria. If we assume that some or all the patients with ET plus transition to other movement disorders (dystonic tremor [DT], spinocerebellar ataxia type 12 [SCA12], and ANO3 variation) after a few years, the inclusion of those patients as ET in clinical trials targeting ET-specific pathophysiologic substrates would not be scientifically ideal. Therefore, a relatively accurate clinical diagnosis, as facilitated by the new definition, is crucial for future clinical trials. Moreover, a homogeneous cohort would be ideal for studies exploring the genetic substrates of ET, which has remained a gray area, although a plethora of clinical and epidemiologic studies have reported autosomal dominant transmission of the disease in half of the patients.[5]

Although the new classification is advantageous from a pure or isolated ET standpoint, the label ET plus has been the point of several scientific debates.[2,6] Because of the marked variability in disease progression and tremor characteristics, and due to the growing evidence for the existence of a repertoire of nonmotor symptoms, ET is now unequivocally recognized as a clinically heterogeneous disease or a family of diseases.[7,8] Hence, for a disease with such phenotypic heterogeneity, an additional diagnostic label ET plus has surfaced several controversies. Moreover, the additional clinical features based on which the term ET plus has emerged are subtle, of unclear clinical significance, and may have interrater variabilities.[9,10] Although it needs to be confirmed by additional studies, a recently published postmortem study did not find any significant histopathologic abnormalities in the cerebellum of patients with ET and ET plus.[11] Three possibilities need to be explored through large longitudinal studies. Those possibilities are that (1) the neurologic soft signs (subtle dystonia, memory impairment, parkinsonism, and rest tremor) described in the context of ET plus are an additional clinical feature of ET, (2) the neurologic soft signs are the forme fruste of some other neurologic diseases, and (3) the neurologic soft signs are just incidentally found features with questionable clinical significance. Hence, with time, we will know whether ET plus is a plus point, and until then, this group can be described as a temporary label or diagnostic placeholder.[6]

Clinical Assessment of ET: The Changing Dynamics

Tremendous progress in the field of tremor has changed the landscape of differential diagnoses of this common yet complex movement disorder. Although the new definition of ET is a straightforward one, it is contingent on the fact that there are no other identifiable etiologies of tremor.[1] As several neurologic diseases may mimic the clinical phenotype of ET, the tremor task force described ET as a syndrome. However, this syndrome vs disease issue is controversial, and it is discussed in detail elsewhere.[12,13] A wide variety of conditions, that is, neurodegenerative, genetic, metabolic, toxin and drug exposures, infections, and structural brain

lesions, may result in tremor, and such underlying conditions should be ruled out before labeling the tremor as ET.[1] The conditions that may present with isolated action tremor resembling that in ET are DT, SCA12, and DYT 24 (ANO3 variation). In these conditions, the onset of action tremor of the upper limbs may precede the onset of clinically significant dystonia (in DT and DYT 24) and ataxia (in SCA12) by a few months or years. Hence, a careful follow-up evaluation exploring these associated features is crucial. It is important to remember that for a clinical diagnosis of ET, isolated action tremor should be present for a minimum of 3 years. If it is <3 years, the term isolated action tremor is preferred. As subtle dystonic components may not be visible to the naked eyes, whenever in doubt, surface electromyogram and accelerometery may be used to accurately evaluate the tremor characteristics. Rarely, patients with ET may develop parkinsonian signs, which may amount up to a diagnosis of Parkinson disease (PD) (ET-PD overlap) or maybe of uncertain significance (ET plus). Such cases warrant detailed assessments in the lines of PD (levodopa challenge and dopamine transporter imaging) for the accurate phenotyping of tremor. The presence of a family history of tremor along with additional neurologic signs/symptoms (dystonia, ataxia, parkinsonism, and cognitive impairment) should prompt appropriate genetic testing.[14]

Pathogenesis of ET: Growing Evidence for Cerebellar Involvement

The exact neuropathologic substrate of ET is yet to be fully understood. However, several postmortem studies have provided valuable insights into the same. For a long period, the inferior olivary nucleus was considered the primary site of abnormality in ET because of its intrinsic rhythmic property. However, over the last few years, several lines of evidence have pointed against the olivary model of ET.[15] Instead, there is a growing body of evidence in favor of a cerebellar model of neurodegeneration in ET.[16,17] The pathologic abnormalities in the ET brains have largely been observed in the Purkinje cells. Abnormalities in several anatomic components of the Purkinje cells such as dendrites (swelling, pruning, and loss of spines), cell bodies (empty baskets and heterotopias), and axons (thickened axonal profile, torpedos, acriform axons, increase in recurrent collaterals, branching, and axonal sprouting) have been described in ET brains.[17] Other cerebellar neurons such as the climbing fibers and basket cells may also have abnormal changes in the brains of patients with ET compared with the controls.[18] These studies have also documented a reduced number of gamma aminobutyric acid receptors in the dentate nucleus in the ET brains.[17,18] However, surprisingly, a recent postmortem study did not find any difference in the neuronal density in the dentate nucleus of ET and control brains.[19] It is postulated that the histopathologic abnormalities in the Purkinje cells usually represent the early and middle stage of the cascade of neurodegeneration, whereas remodeling of the basket cells and reorganization of the climbing fibers are parts of the later events in the degeneration cascade. In addition to these postmortem studies, several neuroimaging studies also indicate the putative involvement of cerebellar structures in the pathogenesis of ET.[20]

A New Therapeutic Option: Magnetic Resonance–Guided Focused Ultrasound Thalamotomy

Optimal treatment of ET has remained an unmet need. The commonly used medications (primidone, propranolol, and topiramate) in ET may not be effective in ameliorating tremor in all patients and may be associated with bothersome adverse effects.[21] Two types of surgical interventions for the treatment of medication refractory tremor in ET have been used in clinical practice. The common target is the thalamus, and the 2 categories of surgical interventions are (1) ablative surgeries and (2) deep brain stimulation (DBS) of the ventral intermediate (Vim) nucleus of the thalamus. The ablative surgeries may be invasive (using radiofrequency ablation) or noninvasive (using gamma knife and magnetic resonance–guided focused ultrasound [MRgFUS]).[21,22]

MRgFUS was introduced less than a decade ago to the world of tremor therapeutics (approved by the US Food and Drug Administration in 2016). In a large multicenter trial on 76 patients with ET, MRgFUS reduced the tremor scores by 47% at 3-month follow-up evaluation compared with sham intervention.[22] At 1-year follow-up, the reduction in the tremor scores was 40%. The commonly reported adverse effects were paresthesia and balance disturbances. Subsequently, a 3-year follow-up of 52 of these studies reported sustained benefit of MRgFUS in ameliorating hand tremor in ET.[23] Importantly, there were significant improvements in the scores reflecting the quality of life and disability due to tremor. A recently published multicenter single-arm study from Japan reported a significant and sustained tremor-

Table 2 Comparative Summary of the Key Features of MRgFUS and Vim-DBS

Features	MRgFUS	Vim-DBS
Invasive	No	Yes
Hardware implantation	No	Yes
Use of general anesthesia	No	Yes
Risk of infections	No	Yes
Need of frequent monitoring	No	Yes
Need of battery replacement	No	Yes
Irreversible effects	Yes	No
Available for patients with contraindications for MRI	No	Yes

Abbreviations: DBS = deep brain stimulation; MRgFUS = magnetic resonance–guided focused ultrasound; Vim = ventral intermediate nucleus of the thalamus.

FIVE NEW THINGS

- Revised inclusion criteria have been proposed for essential tremor that define the clinical syndrome and exclude other tremor syndromes such as isolated focal tremors of voice and head and task- and position-specific tremor.
- A new category "Essential tremor plus" has been added to define tremor with the characteristic of essential tremor and additional neurologic signs of uncertain significance such as possible dystonic posturing, impaired tandem gait, and memory impairment.
- In addition to the clinical assessment, ancillary testing (electrophysiology, neuroimaging, and genetic testing) may be required in a small subgroup of patients mimicking the presentation of essential tremor and essential tremor plus.
- The pathophysiologic features of essential tremor are controversial; however, there is growing evidence for cerebellar dysfunction.
- MRgFUS is emerging as an excellent therapeutic option for medically refractory and disabling essential tremor.

suppressing effect of MRgFUS on 35 patients with ET after 1-year follow-up.[24] Although Vim-DBS has been the most established surgical intervention for the medication refractory ET, in the future, MRgFUS may get wide acceptance due to a host of advantageous features, prominent of which are noninvasiveness and lack of hardware infections (Table 2). Also, future developments in the field of MRgFUS include the possibility of applying neuroimaging like tractography-based targeting and performing bilateral ablations.[25] However, there are certain limitations, which include its high cost, permanent lesioning effect, and lack of long-term data. Head-to-head trials of MRgFUS and Vim-DBS are warranted to determine which of these surgical interventions would be the best for patients with ET.

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Appendix Authors

Name	Location	Contribution
Abhishek Lenka, MBBS, PhD	MedStar Georgetown University Hospital, Washington, DC	Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Sanjay Pandey, DM	G.B Pant Institute of Postgraduate medical education and research, New Delhi, India	Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

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