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# Essential tremor-plus: a controversial new concept

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## Abstract

In addition to redefining essential tremor (ET), the 2018 consensus statement of the Movement Disorder Society on tremor coined a new term: essential tremor-plus (ET-plus). This term is

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uncertainly defined as tremor with the characteristics of ET, with additional neurological signs of uncertain clinical significance. If ET-plus had been defined on the basis of a difference in underlying pathology or an appreciable difference in prognosis, it would have a valid, scientific rationale, as does the term Parkinson-plus. However, there is no such evidence, so the basis for the term is questionable. In fact, ET-plus might only represent a state condition (ie, patients with ET might develop these additional clinical features when the disease is at a more advanced stage). We caution against coining new terms that are not supported by a firm scientific basis and encourage research into the creation of essential tremor subsets that are defined with respect to differences in underlying causes or pathophysiology.

## Introduction

Essential tremor (ET) is among the most prevalent neurological disorders[1] and various practitioners, including internists, general neurologists, and movement disorder neurologists, care for patients with this condition. An issue of central importance for ET is its definition, [2] which has broad clinical implications, as well as implications for the design and interpretation of clinical, genetic, and epidemiological studies of this enigmatic, challenging, and highly prevalent disorder. A growing body of evidence suggests that ET is phenotypically heterogeneous,[2-6] and that previous classification schemes[7] did not use a consistent approach to tremor classification. This body of evidence provided a major rationale for revising the classification of tremor in 2018.[8] Essential tremor-plus (ET-plus), a newly suggested term coined in the consensus statement by the Movement Disorder Society on the classification of tremor,[8] is a tentatively and uncertainly defined entity that is separate from ET and is characterised by the presence of neurological signs other than action tremor (eg, impaired tandem gait, questionable distonic posturing, and memory impairment; panel 1).

The proposed nomenclature has already engendered comments and controversy,[9-12] because its adoption and use would result in a range of foreseeable problems. Numerically, the potential effect of this nomenclature is already apparent. A study reported that with the use of the proposed nomenclature, 110 (83%) of 133 patients with ET would have to have their disorder reclassified as ET-plus because of the presence of neurological signs other than tremor; 97 (88%) of the 110 patients had rest tremor, 20 (18%) had tandem gait impairment, 14 (13%) had memory impairment, and five (5%) had dystonic posturing.[13] In another study, 99 (39%) of 252 patients with ET would also have to have their diagnosis reclassified as ET-plus for similar reasons, with 62 (63%) of 99 patients having rest tremor, 21 (21%) having mild cervical dystonia, 38 (38%) having cerebellar signs, and 14 (14%) having mild bradykinesia.[10] Furthermore, lessons can be learnt from other examples of movement disorders in which plus terms were proposed. In the case of dystonia, for example, the term dystonia-plus was used in the past,[14] but a 2013 classification scheme suggested moving away from the use of this term; the reasons for which have been discussed elsewhere.[11,15]

In the consensus statement,[8] ET is defined as isolated tremor syndrome of bilateral, upper-limb action tremor of at least 3 years' duration, with or without tremor in other locations (eg, head, voice, or lower limbs), and absence of other neurological signs, such

as dystonia, ataxia, or parkinsonism (panel 1). ET-plus is defined as tremor with the characteristics of ET, with additional neurological signs of uncertain clinical significance, such as impaired tandem gait, questionable dystonic posturing, memory impairment, or other mild neurological signs of unknown clinical significance that do not suffice to make an additional syndrome classification or diagnosis. ET with tremor at rest would be classified as ET-plus (panel 1).[8] Patients with Parkinson's disease with a long-standing history of ET would be classified as having Parkinson's disease with antecedent ET.[16,17]

Although ET and ET-plus were combined in a single box in figure 3 of the consensus statement,[8] that was intended as a broad-sweeping and all-inclusive figure that consolidated the full range of tremor entities. In the pages that followed figure 3 of the consensus statement,[8] ET and ET-plus were clearly separated, each occupying its own box, and each defined using its own set of distinctive criteria. Although the term ET-plus was proposed as a placeholder to draw attention to the presence of heterogeneity within ET, and the term should not be taken too literally, as is often the case, new terms have a way of gaining acceptance, sometimes uncritically and without adequate discussion, and then being quickly adopted. Lines are already being drawn between what is being labelled as ET and what is being labelled as ET-plus, and the new nomenclatural terms are being applied both strictly and literally in a range of scientific and professional settings.

## Potential problems with the proposed nomenclature

The new nomenclature could create several problems (panel 2). First, the notion that ET is a monosymptomatic condition (ie, that ET is isolated, bilateral, upper-limb action tremor) is an increasingly outdated one, and there is a growing body of evidence that ET can present as a heterogeneous disorder.[2-6] Clinical heterogeneity is well described in almost all the movement disorders, and ET does not seem to be an exception. As with other chronic, progressive, neurological diseases that occur in later life (eg, Parkinson's disease and Huntington's disease), the core motor feature of ET, tremor, could be accompanied by additional motor and non-motor features. Even some of the people who were initially proponents of the notion that ET is monosymptomatic recognised that tremor could be accompanied by additional features.[18] The pathological mechanism of ET has long been thought to lie in an aberrant cerebello-thalamo-cortical loop,[19-23] and postmortem evidence has increasingly identified structural, degenerative changes in the cerebellum itself in patients with ET.[24-34] Given this pathological anatomy, it is not surprising that a mild gait ataxia can accompany ET.[35,36] Similarly, although dystonia was originally viewed as a disorder of the basal ganglia, evidence also suggests a role of the cerebellum in the pathogenesis of dystonia.[37,38] As such, in a disorder such as ET, which involves the cerebellum and its pathways, there might be some degree of dystonia. After all, dystonia is a feature of many spinocerebellar ataxias.[39-43] Thus, an abundance of evidence shows that ET is not merely an isolated action tremor.

Second, as ET progresses, action tremor typically evolves and worsens.[44,45] Over time, patients often also experience the progressive addition of tremors that occur under different activation conditions (eg, with intention[46] or at rest[47]) and in different bodily regions (eg, in the neck, jaw, or larynx).[48,49] The presence of these tremors, as well as the presence

of gait and balance difficulty, are associated with ET of a longer duration.[46,47,49,50] That is, patients with ET accumulate these additional clinical features during the course of their illness.[51,52] Thus, importantly, ET-plus might only represent a state condition (ie, patients with ET develop additional clinical features when they are at a more advanced stage in their disease) rather than a trait condition (ie, patients with additional clinical features representing a distinct and completely separate clinical subtype of ET).[51,53] The use of ET-plus nomenclature would set up the seemingly incongruous situation in which many patients with ET would develop a different condition, ET-plus, as their disorder progresses from mild and monosymptomatic to severe and polysymptomatic.

Third, along similar lines, if a patient with ET develops mild cognitive impairment or dementia, as happens quite often (eg, in one cross-sectional study, 25% of patients with ET with a mean age of 80·9 years also had dementia),[54-57] do they cease to have ET? By analogy, when a patient with Parkinson's disease develops mild cognitive impairment or dementia, the Parkinson's disease diagnosis is not typically removed and the diagnosis Parldnson's-plus (or mild cognitive impairment or dementia with antecedent Parkinson's disease) given instead. If the proposed nomenclature were adopted, when patients who were diagnosed with ET develop additional neurological signs, they would have to be told that they now have another condition, ET-plus. This condition would probably carry its own clinical billing code.

Fourth, as per the newly proposed nomenclature, ET-plus refers to tremor with other neurological signs of uncertain clinical significance that are not sufficient to make an additional syndrome diagnosis. A key concern about this definition is the absence of a quantifiable metric to gauge whether a sign qualifies for an additional diagnosis, leaving it up to the subjective assessment of the clinician. This absence of an objective diagnostic metric will contribute to either an underdiagnosis or an over-diagnosis of ET-plus.

Last, if ET-plus was defined on the basis of a difference in underlying cause or pathology, or on the basis of an appreciable difference in prognosis or pharmacotherapeutic profile, the term might have some scientific merit. However, none of these differences has been identified. Furthermore, we are not aware of any data that directly compare rate of progression or pharmacotherapeutic responsive phenotype in ET versus ET-plus, or of any data that compare rate of progression or pharmacotherapeutic responsive phenotype among patients with ET with each additional neurological sign versus patients without such a sign (eg, impaired tandem gait, dystonia, rest tremor, or cognitive dysfunction). Creating a new term that does not have such an underlying biological basis does not seem advisable.

## Research implications

The use of the term ET-plus also has implications for research. First, the proposed nomenclature will complicate efforts to assess the incidence and prevalence of ET. For example, when an investigator is doing a study of the incidence of ET-plus, would individuals who had ET at baseline be excluded, because they already have some form of ET, or would these patients be excluded because they did not have the precise outcome of interest (ET-plus) at baseline? The nomenclature would also add to the expense and burden

of doing prevalence studies. Most studies of the prevalence of ET include an initial screening phase, which is followed by a more detailed phase, including a neurological examination. During this examination, rest tremor, dystonia, ataxia, and cognitive difficulty would have to be carefully assessed if the new term was used. The proposed nomenclature would also complicate the ability to connect results between past and future studies. In past studies, the term ET comprised both ET and ET-plus. The separate prevalence estimates of ET and ET-plus would have to be added together in current studies to compare these estimates to the reported prevalence of ET from previous studies.

Second, the introduction of the term ET-plus will make it challenging to do longitudinal cohort studies, because the baseline condition itself will probably disappear during follow-up. If a patient with ET was enrolled who at the time of the baseline assessment had rest tremor (requiring the diagnosis ET-plus), but who at the first follow-up assessment did not display this often-transient neurological sign, would the diagnosis be changed at the first follow-up assessment from ET-plus back to ET? The implication is that ET-plus diagnoses might be reversible and unstable.

Third, doing genetic studies will become challenging when the presence of phenotypic heterogeneity within families (eg, the presence of rest tremor in one relative but not in others) is interpreted to mean that the family manifests two neurological conditions rather than one condition with variable expression.

Finally, the new designation would complicate experimental therapeutic studies. ET-plus and ET are not categories that are based on identified biological differences; hence, it is quite likely that the two proposed diagnostic designations will respond similarly to medications. If all trials must separate ET from ET-plus, then two parallel sets of trials will need to be done.

## Conclusions and future directions

The term ET-plus should be considered within the context of the consensus statement of the Movement Disorder Society in which it was coined.[8] Although that consensus statement is a useful expert commentary in some ways, it is not a document that is driven by data. The section on ET cites nine papers, only six of which contain original data, and only two of which were published in the past decade (ie, during the time in which most new data-driven studies have emerged).[9]

Other examples of terminology in the field of movement disorders can provide valuable lessons. Dystonia-plus syndromes are those in which the dystonia is accompanied by another movement disorder (eg, myoclonus or parkinsonism), and in which that other movement disorder is a major feature.[14] These syndromes are usually linked to specific genes,[14] which is not the case with ET-plus. Furthermore, the dystonia classification in 2013 suggested moving away from the use of the term plus.[11,15]

That the new classification proposed for ET is problematic is, in some ways, not a huge surprise, given that consensus classifications for other movement disorders (eg, for dystonia) have been problematic.[58] In a study of the validity of the 2018 consensus criteria for Parkinson’s disease, only 59% of patients who were diagnosed with Parkinson’s disease by

an expert neurologist met consensus criteria for clinically established Parkinson's disease.[59] The sensitivity of consensus criteria for clinical diagnosis of multiple system atrophy at the first clinical visit was also considered suboptimal—41% (possible multiple system atrophy) and 18% (probable multiple system atrophy).[60,61]

It is, however, important to acknowledge that clinicians are increasingly recognising phenotypic heterogeneity within ET, and that the concept of ET as a syndrome or family of diseases is evolving. During the analytical phase of research studies, in addition to presenting grouped data, investigators might wish to stratify patients with ET into potential subgroups on the basis of the presence of specific clinical features (eg, patients with or without rest tremor, dystonia, parkinsonism, or ataxia), or on the basis of the presence versus the absence of a family history, or on the basis of differences in age of tremor onset. Ideally, however, analytical subgroups should be defined by their genetic, physiological, or pathological bases, other biomarkers, or their pharmacotherapeutic response profile, but that is not possible yet. Until then, we caution against coining new terms that are not yet supported by a firm scientific basis.

## Declaration of interests

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**Panel 1:**

### Essential tremor versus essential tremor-plus

**Essential tremor**

- Isolated tremor syndrome of bilateral, upper-limb action tremor
- At least 3 years' duration
- With or without tremor in other locations (eg, head, larynx, or lower limbs)
- Absence of other neurological signs, such as dystonia, ataxia, or parkinsonism

**Essential tremor-plus**

- Tremor with the characteristics of essential tremor, with additional neurological signs of uncertain clinical significance, such as impaired tandem gait, questionable dystonic posturing, memory impairment, or other mild neurological signs of unknown clinical significance that do not suffice to make an additional syndrome classification or diagnosis
- Essential tremor with tremor at rest would be classified as essential tremor-plus

**Panel 2:**

### Problems with the proposed nomenclature

- Essential tremor (ET) itself is a heterogeneous condition and the creation of a second term does not seem necessary
- As ET progresses, patients often develop worsening tremor, spread of tremor, different forms of tremor, and other motor and non-motor features; therefore, essential tremor-plus (ET-plus) might only represent a state condition rather than a trait condition
- The development of other clinical features (eg, cognitive impairment) does not necessarily require a change in diagnosis; an analogy can be made with Parkinson's disease
- ET-plus refers to tremor with other neurological signs of uncertain clinical significance that do not suffice to make an additional syndrome diagnosis; this definition omits quantifiable metrics to gauge whether a sign qualifies for an additional diagnosis, leaving it up to the subjective assessment of the clinician
- ET-plus is not defined on the basis of a difference in underlying cause or pathology, or on the basis of an appreciable difference in prognosis or pharmacotherapeutic profile

### Search strategy and selection criteria

We searched PubMed for articles published in English, from its inception to April 30, 2019, using the search terms “ET-plus”, yielding four articles; “essential tremor-plus”, yielding no articles, and “essential tremor” and “diagnostic criteria”. The search yielded a total of 68 articles, and no articles were excluded based on quality or relevance. We cited those articles that provided relevant data or information, which added to our discussion.