Title: The MDS Consensus Tremor Classification: the best way to classify patients with tremor at present

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Highlights

- In 2018, the new Consensus Statement on the Classification of Tremors was published
- Tremor is classified according to clinical manifestation and etiology (Axis 1 and 2)
- Essential tremor is considered as a syndrome
- The new category essential tremor plus is recognised
- Considering our current knowledge, this tremor classification is the best at present

Abstract

In 2018, the new Consensus Statement on the Classification of Tremors, by the Task Force on Tremor of the International Parkinson and Movement Disorder Society, was published. So far, the article has been cited more than 400 times in peer-reviewed international journals and commonly debated in conferences and meetings due to an enthusiastic welcome from the community.

Compared to the previous Consensus Statement (1998), the main novelties are: 1) the classification of tremor according to clinical manifestation (Axis 1) and etiology (Axis 2), and therefore the use of a syndromic approach; 2) the definition of essential tremor as a syndrome; 3) the recognition of the new category essential tremor plus, that derives from the uncertain significance of the *soft neurological signs* often associated with essential tremor.

In this paper, we summarise and explain the most important aspects of the new classification of tremors, highlighting the main novelties, their relevance, and application in clinical practice. Moreover, we discuss its possible weakness and reflect on the critical comments made so far.

We believe that this new tremor classification is comprehensive, rigorous, and consistent and, considering our current knowledge of tremor syndromes, it is the best we can do at present.

Introduction

Disease taxonomy plays an important role in defining the diagnosis, treatment, and underlying mechanisms of human diseases. The principle of the current clinical disease taxonomies, in particular the International Classification of Diseases (ICD), is primarily derived from the differentiation of clinical features. This requires the identification and clustering of symptoms into syndromes, with the challenge that clusters need to be fine enough to distinguish different underlying causes, but also flexible enough to allow meaningful statistical studies. This type of classification has been, however, criticised because of the rigid hierarchical structure and the poor attention given to disease etiology(1). For this reason, for instance, the modern ICD provides increasing detail about the cause, as well as pathology, or anatomical site of the disease(2).

Based on these principles, a new Consensus Statement on the Classification of Tremors, from the Task Force on Tremor of the International Parkinson and Movement Disorder Society (MDS), was published in 2018(3). The new Consensus Statement was promoted by the MDS with the intent to review and expand the outdated 1998 MDS Consensus Statement on Tremor, in view also of the new clinical and scientific progress in the field. So far, the article has been cited more than 400 times in peer-reviewed international journals and commonly debated in conferences and meetings due to an enthusiastic

welcome from the MDS community and yet some criticisms. Most importantly, the proposed classification system and the overcoming of previous rigid diagnostic barriers have encouraged fruitful discussions that will definitively bring novel ideas for future studies and new discoveries.

In this paper, we summarise and explain the most important aspects of the new classification of tremors, highlighting the main novelties, their relevance, and application in clinical practice.

1998 vs 2018 Consensus Statement on the Classification of Tremors

The 1998 Consensus Statement was a very popular and highly cited criteria of tremor classification(4). This was however variably based on presumed functional origin (e.g., cerebellar tremor syndromes), anatomical distribution (e.g., palatal tremor), presumed etiology (e.g., parkinsonian tremor), or on clinical features (e.g., primary writing tremor, orthostatic tremor, and isolated voice tremor)(4). This non-systematic approach was not designed for describing tremors with new and different etiologies, such as genetic forms, and in recognising syndromes. For this reason, in the new Consensus Statement it was decided to classify tremor according to 2 main axes: clinical manifestation (Axis 1) and etiology (Axis 2), an approach largely used in medicine and epidemiological studies (as mentioned above) and already used in other movement disorders(5). According to Axis 1, tremor can be further divided into two broad categories: *isolated* tremor, in which tremor is the only abnormal sign, and *combined* tremor, in which other abnormal signs are present. This approach is advisable in disorders with phenomenological and etiological heterogeneity like tremor; indeed, a tremor syndrome can have multiple etiologies and a particular etiology may produce different clinical syndromes. A clear example of this is essential tremor (ET), which thanks to the 2018 Consensus Statement is now recognised as a syndrome and not as an etiology. Moreover, a new category, namely ET plus, has been added to make the clinical features more precise. These aspects are the most innovative of the 2018 Consensus Statement and will be further discussed in the following paragraphs.

Other minor changes compared to the 1998 Consensus Statement can be identified. For instance, while in the 1998 Consensus Statement the only *isolated* tremor appears to be the *isolated voice tremor*, in the current Consensus Statement clinicians are encouraged to identify associated or concomitant signs and to divide tremors accordingly. Therefore, new categories were added, including *isolated segmental postural or kinetic tremor syndrome* (that involves also head tremor, that is not considered anymore sufficient for the diagnosis of ET) and *isolated rest tremor syndromes.* Another novelty is the proposal of the term *pseudo-orthostatic tremor* to describe tremor during standing that has a lower frequency than 13 Hz. For *dystonic tremor syndromes* (combined), the terminology of

dystonic tremor and tremor associated with dystonia was retained, while the category of *dystonia gene-associated tremor* was abandoned. Finally, among the combined tremors, *myorhythmia* was included and acknowledged as a very rare rhythmic movement disorder of cranial or limb muscles at rest or during action, often associated with brainstem or cerebellar signs.

Axis 1 and Axis 2: a syndromic approach

In clinical practice, the advantage and beauty of movement disorders it that the diagnosis relies on observation of the patients' signs, clinical assessment (including patients' medical history and symptoms, and neurological examination) and clinicians' expertise to define the disease phenotype. When approaching patients with movement disorders, the first step is to identify the dominant type of movement disorder and its clinical features(6). Secondly, it is important to recognise whether the dominant movement disorder occurs in isolation or if it is combined to other neurological and systemic signs. The specific combination of the symptoms and signs enable the recognition of the clinical syndrome, a process that relies on pattern recognition and that leads to the differential diagnosis. Sometimes the pattern is sufficient to suggest a diagnosis, other times tests are needed. Once the clinical syndrome is defined, its possible etiologies are explored (Box 1). Often, the clinical features of the dominant movement disorders (for instance type of onset) or the associated features (for instance systemic signs) can provide important clues about the underlying etiology or guide the work-up. Finally, the investigations can help to exclude or confirmed a specific etiology.

The classification of tremor based on Axis 1 and 2 simply follows the methodological approach that clinicians naturally use in daily practice (Box 2); therefore, it is the most recommended for diagnostic purpose.

The most important aspect of this classification is that encourages clinician to recognise and define syndromes, as a starting point to make the exact diagnosis and find the possible etiology. In the new Consensus Statement, 7 main syndromes are proposed, including *action or rest tremor, focal tremors, task and position specific tremors, orthostatic tremors, tremor with prominent additional signs, functional tremor, and indeterminate tremor syndromes*. These are further subdivided according to more specific features of the predominant presenting symptoms. For clinical and research purpose, each patient can be classified only into one of the syndromes listed; if they do not fit in anyone, the diagnosis of indeterminate tremor syndrome is made. Although the latter might be considered a sort of "mixed bag", its content is potentially "recyclable", since, if sufficiently established, new syndromes can emerge from it.

Another advantage of this classification is that it is not rigid but dynamic and enables to change the diagnosis according to the evolution of the clinical features that can occur with time. Indeed, tremor body distribution and activation conditions might change eventually, while additional signs often develop after years (for instance, overt dystonia or ataxia associated to action tremor). If new clinical features appear, Axis 1 should be updated accordingly and another etiology (Axis 2) should be considered, if appropriate. In this case, it is suggested to mention the *antecedent* diagnosis (Box 3). An example is given in the Consensus Statement: for patients who "have ET for decades before developing dystonia", the authors "recommend that such patients be re-classified as having dystonic tremor with antecedent ET." This aspect has been criticised since it can potentially create a "dual-disease pitfall", as could happen for the debated ET evolving/co-occurring with Parkinson's disease (PD)(7). In their criticisms the authors stated that "most of these patients probably never had such a thing as "ET," if indeed such a thing as ET exists in etiologic form in some patients". Nevertheless, it is in this case that the syndrome concept proves useful. Making a diagnosis of tremor combined with parkinsonism with antecedent ET suggests that the clinical features that define Axis 1 can change and that one syndrome can evolve into another over time, while the etiology remains to be established. Therefore, since ET is not considered as a disease, but as a syndrome, the "dual-disease pitfall" no longer exists. The diagnosis of *tremor combined with parkinsonism with antecedent ET*, however, does not imply any causality; if ET may be a risk factor for PD, or may be part of PD, or their association is purely coincidental needs still to be clarified.

ET is a syndrome

In the last few years, the nature of ET, and whether this is a syndrome or due to a distinct etiology, has been largely debated among tremor experts(8-13). It was not different during the tremor Task Force since the authors of the Consensus Statement admitted that it was "extraordinarily" difficult to achieve an agreement on the definition of ET. Eventually, it was agreed that ET is a syndrome with widely endorsement from the MDS community, but not without disappointments.

Some of the experts that consider ET as a disease believe that the "syndrome" view derives from the clinical heterogeneity of ET; nevertheless they consider the clinical heterogeneity as a feature of the disease ET(13). In our opinion, this is an underestimation of the nosological problem. Clinical heterogeneity is common to different conditions (PD is a good example for it) and it is, therefore, not a discriminant for the "disease" and "syndrome" concepts. Simply, ET is not a disease because its etiologies are unknown, and it has no distinguished clinical and pathogenic features that would allow us to recognise it as a specific entity. ET is claimed to be the most common movement disorder and it

is familial in about 75% of the cases(14), yet after 25 years of extensive searching, its etiology is not identified. Only four genes with rare causative mutations have been discovered (FUS(15), NOTCH2NLC(16), HTRA2(17), TENM4(18)), but they are rarely found in ET patients. On the other side, the typical ET phenotype, namely bilateral action hand tremor with or without head/voice/lower limbs tremor, often familial, either in isolation or with subtle associated signs as a presenting symptom or during the course of the disease, is an extremely common manifestation of the central nervous system, and its causes are various (see table 1 in Fasano et al. 2018(7)). Pathophysiologically, ET is thought to be driven by oscillatory activity generated in the cerebello-thalamo-cortical network, which is however implicated in most forms of tremor and not specifically involved in ET(19-21). Finally, pathological studies have shown Purkinje cell pathology in some but not all ET patients, that are not pathognomonic(22-24); moreover, the post-mortem findings, when present, are not uniform across the ET cases, and even in those with cerebellar pathology the range of pathology severity is high(23, 25). This clinical and pathogenic heterogeneity is acknowledged also by the colleagues whom do not completely agree with the syndrome definition and for this reason they proposed that ET is not a single disease but rather a "family of diseases"(26), but with an unknown number of family members. According to them, ET is an umbrella name that describes a clinical phenotype with etiological and pathophysiological heterogeneity, i.e., different disease entities(26). Hence, the boundaries between "syndrome" and "family of diseases" seems very subtle and the dispute is likely merely semantic rather than conceptual.

Since ET often evolves into another syndrome, the new criterion requires at least a 3-year history of tremor and excludes isolated head and isolated voice tremor. The 3-year history is an arbitrary cut-off not supported by data, but it was thought to be a reasonable amount of time to reduce the chances of subsequent development of other neurological signs, which would imply a reclassification of the syndrome. Future studies to confirm this cut-off are however required and if evidence supporting this are not found, it might be discarded in the future.

Given the above, the term *essential* might sound obsolete and misleading(7). This introduces another criticism, i.e. that ET will continue to be a "diagnostic placeholder"(7), but this is inevitable until eventually specific common etiologies are recognised. This is common sense also for other fields in medicine (essential hypertension).

ET plus

Maybe the most radical change compared to the previous Consensus Statement, is the construct of *ET plus* that derives from the uncertain significance of the *soft neurological signs* often associated with ET. These are mildly impaired tandem gait, questionable dystonic posturing, memory impairment, or other mild neurologic signs of unknown significance "that do not suffice to make an additional syndrome classification or diagnosis". ET with rest tremor is now classified as ET plus too. This is because the significance of resting tremor associated with ET is still not clear, and it has been proposed to be a form of dystonic tremor(27), a precursor of parkinsonism(28), or be an advanced stage of ET(29).

The "plus" makes a distinction, but, as the definition states, it does not formally make a different syndrome. At present, we are not able to say if ET and ET plus are part of a continuum or two separated syndromes. The "artificial" distinction between the two has been proposed with the intent to clarify this question. In fact, there is a precedent example of a similar argument in the past literature that concerns the issue of essential myoclonus and myoclonus dystonia(30). Clinical classification of patients with myoclonus and dystonia was subject to considerable debate and the literature was often confusing and contradictory until the discovery of mutations in the *epsilon-sarcoglycan gene* in patients with familial myoclonus dystonia has improved the ability to assign a specific genotype in some patients. Since then, the terms (hereditary/familial) essential myoclonus has been rarely used. Similarly, in the future, the nature of ET and ET plus will be clear if a common etiology will be discovered.

Although according to some experts also the category of ET plus is a "placeholder" and "merely represent ET of long duration"(7, 31), we believe that only recognising all deviations from ET that are of questionable significance, instead of taking them for granted as being part of ET, we will be able to clarify their relevance. In this regard, there are two main problems: 1) are these *soft signs* present in the normal population? and, therefore, can them be regarded as normal? 2) if not, do they suggest an alternative diagnosis compared to ET? A definitive answer is not available to both questions yet, but recent studies have in part investigated the problem.

First, it has become clear that ET plus is more common than ET. Retrospectively reclassifying a pre-existing cohort of ET diagnosed according to the 1998 Consensus Statement, it was found that of 252 patients only 33% remained as ET according to the new classification, while 40% were newly diagnosed as ET plus (25% reclassified as indeterminate tremor and 2% as isolated focal tremor); moreover, the authors found that ET plus patients were older at tremor onset(32). Similarly, in another study, of 133 patients only 20% continued to fulfil the criteria for ET, while 80% were reclassified as ET plus; again, ET-plus patients were significantly older at tremor onset and those with resting tremor (the most

common soft sign found in the cohort) were significantly older and had longer disease duration(33). Because of the correlation between the *plus* signs and age and disease duration, it has been proposed that ET plus is a state condition rather than a trait condition(29), in which the "state" could be a more advanced stage of ET or represents a transition to other disease, such as PD or dystonia. However, in a larger cohort of patients (300, of which the majority - about 70% - were re-diagnosed as ET plus) the duration of the tremor did not significantly differ between ET and ET plus, although ET plus patients were significantly older than ET (34). On the other side, ET and ET plus have been found to have similar pathology and response to treatment, but this conclusion should be taken with caution. According to one study of cerebellar pathology, these two entities do not differ on the cerebellar pathology metrics; however, it should be noted that tremor cases were grouped only by presence of rest tremor or intention tremor separately, the post-mortem analysis was performed in a single region of the cerebellar cortex and most importantly the significance of these abnormalities is still debated(35). Regarding treatment, one study showed that VIM deep brain stimulation (DBS) can induce comparable tremor reduction in ET and ET plus, although ET plus had higher stimulation parameters and a more dorsal location of active electrode contacts, that could not be explained by the authors because of the retrospective nature of the study (36). This result, however, does not imply that ET and ET plus have the same etiology since VIM DBS improves dystonic tremor too(37). Therefore, these two studies on DBS treatment and cerebellar pathology do not distinguish ET and ET plus, but do not even reject the hypothesis that they are different disorders.

One of the main challenges related to ET plus is the recognition of the soft signs, which can be difficult and susceptible to a wide range of inter-observer variability. According to one study, two independent raters were able to achieve absolute agreement in only 61.2% of the cases when classifying tremors in line with the Axis 1 syndromes; a further analysis revealed that the main discordance was on the judgment on the presence or absence of dystonia(38), that is a consequence of the lack of clinical and biological diagnostic markers for it (39, 40). For this reason, questionable dystonia is subject to clinical interpretation bias, as also suggested by another study. Using a new clinical tool for assessing clinical signs that are important in Axis1 classification called the Standardized Tremor Elements Assessment, 3 tremor-focussed and 1 dystonia-focussed movement disorder specialists rated 59 videos of patients with upper limb action tremor syndromes(41). Maybe not surprisingly, the overall agreement was modest, with the poorest agreement on the items related to dystonia. While the tremor specialists were more likely to rate posturing of the trembling upper extremity and abnormal posturing of the head as soft signs, the dystonia specialist was more confident in rating them as definitely dystonic. The reason for it is that the fine line between questionable and definitive dystonia cannot be

objectively defined but it depends on the clinician's training and experience and the possible existence of "normal" posturing, that so far has been poorly investigated.

Limitation and future directions

Despite the numerous strengths detailed above, the current Consensus Statement is not without limitations. These include the ambiguity of the term "essential" for ET, the differentiation of ET in ET and ET plus based on uncertain clinical features and not supported by data, the unknown clinical meaning and the poor definition of some of the soft signs (for instance questionable dystonia). Nevertheless, these weaknesses are the consequence of our limited knowledge of tremor in its different forms.

Compared to other movement disorders, the diagnosis of tremor can be easily made, if not clinically, with the help of electrophysiology. Tremor recording, by the means of surface EMG or accelerometer, can confirm the diagnosis of tremor in a definitive manner. Tremor analysis can give information about the tremor pattern (for example, alternating tremor), frequency and amplitude which in some cases can guide the differential diagnosis. For instance, the frequency and its changes can support the diagnosis of some forms of tremor such as orthostatic tremor and enhanced physiological tremor (during the loading test); other features, such as variable and distractable pattern, irregularities in the tremor frequency and amplitude, an increase in the amplitude of the tremor when weights are added, can be seen in functional tremor. On the other hand, there are no pointers that can distinguish most forms of action tremor, due to overlap in tremor frequencies and lack of specific EMG pattern. In a recent study, however, a new tool, called Tremor Stability Index (TSI), that can potentially differentiate tremors based on frequency analysis, was used. According to the result, dystonic tremor patients exhibit higher variability of peak frequency and greater instability of tremor burst intervals over time (higher TSI) compared to ET or tremor associated with dystonia(42). Other tests that can differentiate ET from dystonic tremor have been proposed, including the blink recovery cycle(43) and increased somatosensory temporal discrimination threshold(44). However, to date, none of these has been validated and used in clinical practice. This is true also for other techniques, including neuroimaging which, although it has shown that network-level connectivity is an important feature that differs substantially between dystonic tremor and ET(45), it should be further explored to implement appropriate diagnostic strategies.

Our poor understanding of the etiologies of ET and the lack of biological or clinical markers for dystonia are the crucial points of the debate around the Consensus Statement. For instance, we tend to assume

that some tremor characteristics, including jerkiness, asymmetry, irregularity in amplitude and rhythm, mild posturing of the head or limbs, are supportive of dystonic tremor although these are not definitive features of it. Others, such as “geste antagonist”, “null point” or “overflow”, are acknowledged dystonic features, but their sensitivity and specificity is unknown, so they are not included in the definition of dystonic tremor syndromes. An example of this problem is unilateral upper limb tremor with a jerky appearance that by definition is an indeterminate tremor, but it shares electrophysiological similarities with dystonic tremor(44); whether asymmetry and jerkiness are sufficient to classify a tremor as dystonic is still not known. Future studies are certainly needed to clarify the importance of these clinical signs, including the *soft* ones.

Conclusion

The current Consensus Statement on tremor proposes a new classification based on clinical features (Axis 1) and etiology (Axis 2) and has the purpose to encourage clinicians to recognise syndromes and classify tremor according to them. The most important and also debated novelty is the acknowledgement of ET as a syndrome and the conception of the new entity ET plus. This is an important step forward for the understanding of the clinical significance of the so-called soft signs, which previously were often overlooked and condense as part of ET. Indeed, the broad definition of ET and the inclusion of an “assortment” of various type tremors in research studies are likely the causes of the inconclusive results and our limited understanding of the pathophysiology and etiology of this condition. We believe that a deeper and unbiased phenotyping, as suggested by the current classification, will help to clarify the nature of this syndrome and for instance whether the presence of a specific sign is predictive of a response to a certain treatment, or if it implies a specific etiology or pathophysiological mechanism. Moreover, it will possibly lead us to the discovery of ET subtypes or new syndromes.

The lack of biological or clinical markers for some forms tremor and related signs can create diagnostic uncertainty, as it happens for dystonia. This is a crucial aspect on which future research should invest; if successful, it will help to overcome some of the current classification and diagnostic flaws. If new markers or pathophysiological mechanisms are discovered, other Axes could be added to improve the classification of specific forms of tremor.

In conclusion, this new tremor classification is comprehensive, rigorous, and consistent and, considering our current knowledge of tremor syndromes, it is the best we can do at present.

Boxes:

Box 1. Summary of the clinical approach used for the diagnosis of movement disorders

MD: movement disorder

Box 2. Example 1 of Axis 1 and Axis 2 classification

18 years old male with a 1-year history of bilateral hands tremor, present during action. Patient has no family history for tremor or other neurological conditions, but he reports a history of asymptomatic hepatomegaly. On examination he has postural and kinetic tremor, and no associated neurological and systemic signs apart from hepatomegaly. According to Axis 1 the tremor diagnosis is isolated segmental postural or kinetic tremor syndrome. The current presentation does not point towards a specific diagnosis, but the history of asymptomatic hepatomegaly and the early onset of the tremor syndrome might suggest a metabolic disorder such as Wilson's disease. Therefore, ancillary tests are requested including Slit Lamp assessment for Kayser-Fleisher ring and blood tests for copper and ceruloplasmin levels. Keyser-Fleisher ring (which was not visible on naked eye) is confirmed and blood tests reveal low level of serum ceruloplasmin. Also, urinary analysis shows increased 24-hour urinary excretion of copper. The diagnosis is then confirmed by molecular testing. According to Axis 2, the etiological cause is Wilson's disease.

Box 3. Example 2 of Axis 1 and Axis 2 classification

50-year-old woman with 1-year history of bilateral hand tremor during action. The patient has no past medical history, but a strong family history for tremor. On examination she has postural and kinetic tremor and no associated neurological or systemic signs. Surface EMG recording of the tremor is performed, revealing rhythmic EMG burst with a frequency (calculated by Fourier analysis) of 9-10Hz, that does not change with weight. According to Axis 1, considering the 1-year history of isolated action tremor, the diagnosis is *indeterminate tremor syndrome*. No causes for the tremor are found and according to Axis 2, the tremor is classified as *idiopathic familial*. After 3 years, the tremor is more severe and spreads to the voice and head. According to Axis 1, the diagnosis is now *ET syndrome*, while Axis 2 is not changed. After another year, she develops a strained voice and slight head tilt defined as questionable dystonia. Considering these new features, along Axis 1 the diagnosis becomes *ET plus syndrome with antecedent ET*, while Axis 2 remains unchanged. Finally, after another year, she develops clear dysphonia and cervical dystonia. Genetic testing confirms ANO3 mutation as cause of her tremor. Therefore, the final diagnosis is *dystonic tremor syndrome with antecedent ET* (Axis 1) and the etiology is ANO3 mutation (Axis 2).

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Declaration of interest

A.L. none

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