JCN Open Access REVIEW

pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2022;18(2):127-139 / https://doi.org/10.3988/jcn.2022.18.2.127

Bayesian Interpretation of Essential Tremor Plus

Rodger J. Elble

Department of Neurology,
Southern Illinois University
School of Medicine,
Springfield, IL, USA

Essential tremor (ET) plus is a new tremor classification that was introduced in 2018 by a task force of the International Parkinson and Movement Disorder Society. Patients with ET plus meet the criteria for ET but have one or more additional systemic or neurologic signs of uncertain significance or relevance to tremor ("soft signs"). Soft signs are not sufficient to diagnose another tremor syndrome or movement disorder, and soft signs in ET plus are known to have poor interrater reliability and low diagnostic sensitivity and specificity. Therefore, the clinical significance of ET plus must be interpreted probabilistically when judging whether a patient is more likely to have ET or a combined tremor syndrome, such as dystonic tremor. Such a probabilistic interpretation is possible with Bayesian analysis. This review presents a Bayesian analysis of ET plus in patients suspected of having ET versus a dystonic tremor syndrome, which is the most common differential diagnosis in patients referred for ET. Bayesian analysis of soft signs provides an estimate of the probability that a patient with possible ET is more likely to have an alternative diagnosis. ET plus is a distinct tremor classification and should not be viewed as a subtype of ET. ET plus covers a more-comprehensive phenotyping of people with possible ET, and the clinical interpretation of ET plus is enhanced with Bayesian analysis of associated soft signs.

Keywords tremor; classification; essential tremor; dystonia; Bayesian analysis; dystonia.

INTRODUCTION

Essential tremor (ET) is a very common movement disorder,[1] but its true prevalence is difficult to determine because the condition has not been defined consistently by movement-disorder specialists.[2] ET is most commonly defined as a syndrome of tremor without any other neurologic signs; that is, ET is an isolated tremor syndrome.[3-5] However, some definitions have included dystonia,[2,6] and many experienced specialists disagree about the presence and diagnostic significance of subtle neurologic signs.[7,8] Therefore, misdiagnosis and conflicting diagnoses are common.[9-12]

A growing concern is that ET has become a "wastebasket" diagnosis that is applied loosely to patients with upper extremity action tremor and no other gross or diagnostic abnormalities.[12] An unanswered and largely unaddressed question is how to address clinical features or signs that are equivocally abnormal or questionably relevant to tremor. Such "soft signs" might either be clinical noise or be useful in identifying those patients that actually have a combined tremor syndrome, which is a syndrome of tremor and other neurologic signs (e.g., dystonia, ataxia, or parkinsonism).[8] This problem is the principal focus of this review.

A task force of the International Parkinson and Movement Disorder Society (MDS) concluded in 2018 that ET is a clinical syndrome that needs to be defined consistently in order to discover its underlying etiologies and effective treatments.[4,13] The MDS task force proposed a tremor classification scheme that is based on two axes of classification: 1) clini-

Received October 17, 2021
Revised December 20, 2021
Accepted December 20, 2021

Correspondence
Rodger J. Elble, MD, PhD
Department of Neurology,
Southern Illinois University
School of Medicine,
Springfield, Illinois 62794-9645, USA
Tel +1-217-545-7194
Fax +1-217-545-1903
E-mail relble@siumed.edu

cal features and 2) etiology. ET is defined as an axis-1 syndrome of bilateral upper extremity action tremor with a duration of at least 3 years, with or without tremor in other locations (e.g., head or voice), and no other neurologic signs such as dystonia, ataxia, or parkinsonism.[4] This definition of ET differs from the 1998 MDS consensus definition that included isolated head tremor as ET and had no requirement for a minimum symptom duration. The 2018 MDS definition and the widely used Tremor Investigation Group (TRIG) criteria differ only in the required duration of tremor (3 versus 5 years).[3]

Clinicians frequently encounter patients who fulfill the criteria for ET but have one or more clinical signs of an uncertain abnormality or relevance to the patient's tremor. Recognizing this problem, the MDS task force introduced a new tremor classification called ET plus. This axis-1 classification is applied when a patient has tremor with the characteristics of ET along with additional neurologic signs of "uncertain significance such as 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."[4] In addition, ET with tremor at rest is classified as ET plus, because true rest tremor is uncommon in ET and is usually associated with other neurologic signs that suggest a different tremor classification (e.g., dystonic tremor or parkinsonian tremor).[14]

Some tremor specialists have questioned the usefulness of the ET-plus classification. Detractors note that ET plus is not based on known differences in the underlying pathology or prognosis relative to ET.[15] However, the underlying pathology and prognosis of ET are both variable and controversial, and there is no reason to assume that ET and ET plus have either the same or different pathology or prognosis.[16] ET plus is not a subtype of ET; rather, it is a distinct classification that acknowledges the existence of other neurologic or systemic signs that might be abnormal or related to a patient's tremor.

Another objection is that the more-comprehensive phenotyping inherent in ET plus makes certain types of research studies more difficult.[17] It is admittedly easier to perform epidemiologic, genetic, and treatment studies with inclusion criteria that are more inclusive than the MDS definition of ET, but such an approach could make the results less valid and more difficult to interpret. Furthermore, while ET plus is a diagnostic placeholder rather than a final diagnosis,[18] this is also true for ET and all other axis-1 clinical syndromes.[16,19] It is now clear that ET—as defined by the MDS task force—is far less common than previously suggested. Signs of uncertain abnormality or relevance were not being adequately documented before the advent of ET plus, and ET plus is more common than ET.[20-22]

An important question is how to address signs of uncertain abnormality or relevance. Common examples are absent ankle reflexes in older patients, impaired tandem walking, and unusual limb posturing that could be dystonic. The purpose of this review is to demonstrate how Bayesian analysis can be used to estimate the probability that a patient with ET plus has a combined tremor syndrome, rather than ET.

METHODS

This scoping review[23] builds on previous systematic reviews of tremor classification.[4,5] PubMed was searched on October 1, 2021 using the following search expression: (essential tremor plus) AND (diagnosis). This search produced 20 additional relevant articles that reported soft signs in patients that otherwise met the new or old MDS criteria for ET. PubMed and Google were then searched for estimates of the sensitivity and specificity of these signs for a movement disorder other than ET (e.g., dystonia, ataxia, or Parkinson disease).

During the period from March 2011 to March 2020, the author used the Essential Tremor Rating Assessment Scale (Supplementary Materials 1 in the online-only Data Supplement) to quantify the distribution of tremor in 212 consecutive adult ET patients: 116 males and 96 females aged 64±15 and 69±13 years (mean±SD), respectively.[24] All patients met the TRIG and 2018 MDS criteria for ET and were referred to the author's clinic for tremor. These data were used to examine right/left asymmetry in upper limb tremor and to compute the relative severity of head tremor and voice tremor versus upper limb tremor in a clinic-based cohort of ET patients.

RESULTS

Probability of ET in patients referred for ET

Referral diagnoses of ET are reportedly incorrect in nearly 50% of patients, and the most common alternative diagnoses are Parkinson disease and dystonia.[10-12] In a cohort of 104 patients referred for ET, 47 received a different diagnosis by the main author, most commonly dystonia.[12] Half of 350 patients loosely diagnosed as ET in a large movement-disorders clinic had dystonia.[25] Thus, tremulous dystonia is the most common differential diagnosis for ET, but parkinsonian tremor, ataxic tremor, and myoclonic tremor are also common.

Clinical signs that are incompatible with ET

Any definitive sign of another movement disorder is incompatible with the 2018 MDS definition of the ET syndrome. ET is defined as a syndrome consisting of action tremor and

no other neurologic signs that could be pathophysiologically or etiologically related to the patient's tremor. The signs in Table 1 are relevant to the differential diagnosis of ET versus dystonia and Parkinson disease. The reasons for excluding these signs are summarized below.

Unilateral upper extremity tremor

Strictly unilateral upper extremity action tremor was found in only 4.4% of patients in 17 families with autosomal dominant ET,[26] and in only 2 of 44 clinic patients (4.5%) examined with electrophysiology.[27] Tremor was mild in all of these patients with unilateral tremor, and none had tremor or other neurologic abnormalities elsewhere. The MDS task force concluded that isolated unilateral upper extremity action tremor was too uncommon to be included in the ET phenotype. Patients with this syndrome may ultimately develop a phenotype that is compatible with ET, but evolution to a dystonia syndrome or Parkinson syndrome is more likely.[28]

Isolated head and voice tremor

Isolated head tremor was included in the 1998 MDS criteria for ET, but this was excluded from the 2018 MDS criteria because focal head tremor is present in <5% of possible ET patients[29,30] and is commonly dystonic.[14,31] Isolated voice tremor is similarly uncommon[30] and is usually dystonic.[32] The interrater reliability for distinguishing between voice tremor versus dystonia is only fair to poor, even when the examination includes flexible laryngoscopy.[33,34]

The dystonic nature of isolated voice and head tremors is supported by studies of somatosensory temporal discrimination.[35] Patients with isolated head tremor or voice tremor may ultimately develop the ET syndrome, but dystonia should be strongly suspected when head or voice tremor is the most severe or initial aspect of the ET syndrome.

Approximately 85% of the elderly patients in a large population-based cohort in central Spain had upper extremity tremor without head or voice tremor, 1.6% had isolated head tremor, and none had isolated voice tremor.[36] Similar results were found in another population-based study.[37] Thus, isolated bilateral upper extremity action tremor is a common ET phenotype in the general population, whereas isolated head and voice tremors are rare and are not considered a form of ET.

Table 1. Clinical signs that are incompatible with ET

Clinical sign	Alternative diagnosis
Unilateral extremity tremor	D, PD
Isolated head or voice tremor	D
Vocal spasms, strain, or breaks	D
Extremity rest tremor	D, PD
Persistent head tremor at rest	D, PD
Bradykinesia	D, PD
Rigidity	D, PD
Sensory trick	D
Positional and task-specific tremors	D, PD

D, dystonia syndrome; ET, essential tremor; PD, Parkinson disease.

Vocal spasms, strain, and breaks

Vocal strain, spasms, and breaks are signs of dystonia. A dysphonia attribute inventory has been developed to facilitate accurate diagnosis,[34] and standardized clinical examinations are also available.[38] These voice characteristics are not compatible with ET, but vocal breaks due to severe tremor are difficult to distinguish from those caused by dystonia.[39]

Extremity rest tremor

A prospective clinic-based cohort of 473 patients with various types of adult-onset primary dystonia included 262 patients (55.4%) with tremor, which was head tremor in 196, upper limb tremor in 140, and both types of tremor in 98. The patients with upper limb tremor included 40.7% with rest tremor, which was unilateral in 67% and asymmetric in 93%.[14] These findings suggest that upper extremity tremor in adult-onset dystonia commonly has a rest component.

True rest tremor occurs in <15% of clinic-based ET patients[40] and in <5% of ET patients in population-based cohorts.[41] Therefore, rest tremor is uncommon in patients who otherwise fulfill the criteria for ET, and these patients are now classified as ET plus.[4] Postmortem studies have not produced consistent or diagnostic pathology findings in most cases of ET plus rest tremor,[42,43] and many of these patients are suspected as having dystonia.[44,45]

The presence or absence of rest tremor is frequently uncertain, especially in patients with severe ET who find it difficult to completely relax. Many clinicians examine rest tremor with the forearms resting in the lap in a semiprone posture.[14] This posture requires some voluntary activation of the forearm muscles and is therefore not ideal for assessing tremor at rest. The probability of a false-positive rest tremor is 20% in this posture, while it is 37% when the hands are hanging over the armrest.[46] In contrast, the probability of false positives is only 2% with the hand and forearm relaxed, pronated, and fully supported;[46] the sensitivities to rest tremor in these three postures are 95%, 97%, and 85%, respectively.

Extremity rest tremor occurs in ≥67% of patients with Parkinson disease[47] and in the rare tremor syndromes of Holmes tremor and myorhythmia.[48] Rest tremor in Parkinson disease subsides during voluntary muscle activation (posture or movement) and often re-emerges after a variable delay;[49] these characteristics are uncommon in dystonic tremor syn-

dromes.[14] The suppression of rest tremor by voluntary muscle activation has an estimated sensitivity and specificity of 92% and 69%, respectively, for parkinsonian rest tremor.[49]

Persistent head tremor at rest

Rest tremor should be identified when a patient is attempting to relax in a facilitating environment. A supine position with comfortable body support results in the highest specificity for extremity rest tremor,[46] and this is the best posture for determining the presence of rest tremor in the head and torso. Complete cessation of head tremor at rest was found in 55 of 60 ET patients, while 4 of the remaining 5 patients also had rest tremor in their upper limbs and would therefore be classified as ET plus on that basis alone.[50] In the same study, the head tremor in 13 of 19 patients with tremulous cervical dystonia persisted at rest. Head tremor rarely occurs in Parkinson disease except as a comorbid condition, but true Parkinson head tremor is likely to persist at rest.[51] Head tremor at rest, like rest tremor elsewhere, is not compatible with the current definition of ET.

Bradykinesia

Upper extremity bradykinesia is commonly assessed with repetitive finger tapping (index finger and thumb), hand opening/closing, and hand pronation/supination as widely and rapidly as possible. A clinic-based cohort of 90 ET patients included only 6 (6.6%) who exhibited slight slowness of upper extremity movement in clinical examinations.[52] However, a kinematic analysis of repetitive finger tapping revealed that the ET patients produced fewer movements within 15 seconds than did the controls, while exhibiting no decrement in amplitude or velocity with repetition (i.e., no sequence effect). Roughly half of the ET patients exhibited normal finger-tapping kinematics, and there was considerable overlap between the kinematic values for the ET patients, Parkinson patients, and healthy controls.[52] Nevertheless, another study found that ET patients performed repetitive pronation/supination more slowly than did controls,[53] and a third study identified mild slowing of wrist flexion in ET that overlapped considerably with the control values.[54] Therefore, it remains to be determined whether precise kinematic measures of bradykinesia can be useful in axis-1 phenotyping, and a standardized operational definition of bradykinesia is needed.[55] A clinical examination is currently the gold standard, and none of the ET patients in these kinematic studies were judged as having bradykinesia in clinical examinations.

Therefore, the finding of definite bradykinesia in a neurologic examination is not compatible with ET, and patients with questionable bradykinesia should be classified as ET plus. However, one dopamine transporter imaging study found poor diagnostic agreement regarding the presence or absence of Parkinson disease between two experienced movement-disorder specialists who assessed video examinations of 38 patients with ET, dystonic tremor, or tremor-dominant Parkinson disease (kappa coefficient=0.24, 95% confidence interval=0 to 0.48).[45] This disagreement was largely attributable to a high degree of discord in the identification and interpretation of bradykinesia. Abnormal dopamine transporter imaging is incompatible with ET, and is helpful but not infallible for distinguishing tremor-dominant Parkinson disease from ET and most dystonic tremor syndromes.[45]

Rigidity

Rigidity is incompatible with a diagnosis of ET. However, cogwheeling is frequently palpable in an upper limb when normal muscle tone is enhanced by the performance of voluntary repetitive movement with the contralateral limb.[56] Cogwheeling is simply palpable action tremor in an incompletely relaxed extremity during passive movements within the normal range of motion, and the presence of this sign does not distinguish ET from other forms of action tremor.[3]

Sensory trick

A sensory trick has been defined as "an episodic and specific maneuver that ameliorates dystonia in a manner that is not easily physiologically perceived as necessary to counteract the involuntary movement."[57] The existence of sensory tricks varies with the anatomical location of the dystonia, and they are more common in craniocervical dystonia (>40% of cases) than in upper extremity dystonia (20%).[31,57] It appears that dystonic tremor and dystonia without tremor respond similarly to sensory tricks, although this has not been studied systematically. Regardless, a response to a sensory trick is rarely seen in movement disorders other than dystonia, and this is therefore regarded as a sign of dystonia rather than of ET.[57-59]

Positional and task-specific tremors

Strictly positional[60] and task-specific tremors are rare, and are incompatible with the current definition of ET.[4] However, positional specificity and task specificity are not absolute in most patients, and they may change over time.[61] Identifying the associated neurologic signs (e.g., dystonia) is difficult when tremor is severe.[62] The degree of positional or task specificity that is incompatible with ET has not been defined. Task-specific forms of dystonia are well known,[63,64] and strictly positional and task-specific tremors are hypothesized to be a form of dystonia,[65-67] but they might also be a separate disorder.[68] These rare tremors may evolve into a combined tremor syndrome, so patients should be monitored for the

development of additional signs.[67]

Caveats

Interrater reliability is known to be poor in clinical assessments of dystonia, even among specialists.[69-71] There is considerable interrater disagreement about the presence of tremor[69] and the presence of dystonia.[71,72] Poor interrater agreement effectively reduces the sensitivity and specificity of a neurologic sign.[73] In a clinic-based cohort of 18 patients with dystonia, 9 patients with other movement disorders, and 2 healthy controls, the sensitivity and specificity in diagnosing dystonia were 66.7% and 95.2%, 75.2% and 76.3%, and 71.6% and 84.6% for movement-disorder experts, general neurologists, and residents, respectively.[71] Therefore, significant diagnostic uncertainty is common for a single clinical encounter.

The classification of ET plus was introduced to cover patients with signs that are questionably present or questionably abnormal. The MDS task force recognized that axis-1 syndromes should not be viewed as fixed or final, since ET and ET plus may evolve into other tremor syndromes. Signs of uncertain significance or relevance that lead to the classification of ET plus are reviewed below.

Signs of uncertain diagnostic significance

Uncertainties in clinical classifications commonly arise from clinical signs and symptoms whose diagnostic significance is uncertain. Examples of such soft signs are listed in Table 2. The signs in Table 1 are viewed as "soft" when their presence is uncertain or equivocal. The clinical signs in Table 2 are soft because they occur in normal people (and hence in ET) or because they are not understood well enough to be considered incompatible with ET. The signs in Table 2, like those in Table 1, will be variably recognized depending on their severity and clinical context (e.g., dystonia clinic versus general neurology clinic versus primary-care clinic) and also on the skills of the examiner.

Lower extremity action tremor

The possibility of lower extremity action tremor is acknowledged in the MDS criteria for ET, but the prevalence of lower extremity tremor in ET is reported to be 10%–30%, and this is very mild and asymptomatic in most cases.[25,30,37,40,74,77-79] In the author's clinic-based cohort of 212 ET patients, 72 (34%) had visible lower limb postural or kinetic tremor, as measured at the foot according to the Essential Tremor Rating Assessment Scale (TETRAS) examination.[24] Only 3 patients exhibited lower limb tremor >1 cm, and only 39 patients (18%) exhibited tremor while standing. No patient considered their lower extremity tremor to be disabling. Lower limb tremor is nearly twice as likely in other conditions such as ET plus, dystonia, Parkinson disease, and ataxia.[74] Therefore, the sensitivity and specificity of lower limb tremor for a dystonic tremor syndrome are estimated to be 50% and 70%, respectively, in a hypothetical cohort of ET patients and patients with tremulous dystonia.

The prevalence of lower extremity tremor in ET was 44% in one study, but 14% of the controls in this study were also judged as having lower limb tremor.[80] Irregular lapses in posture are commonly observed in the extended lower limbs of normal people and can be misinterpreted as tremor, which by definition is rhythmic. The interrater reliability for identifying lower extremity tremor is particularly poor in patients with suspected ET.[24]

Intention tremor

Intention tremor is a form of kinetic tremor (i.e., tremor produced by voluntary movement) in which the tremor amplitude increases markedly as the affected body part approaches its visual target.[4] Distinguishing simple kinetic tremor from intention tremor could be useful for improving the phenotyping of ET. Intention tremor was judged to be present in the lower limbs of 27% of patients in one ET cohort[79] and in the upper limbs of 38.5% of patients in another ET cohort.[81] Intention tremor is most common in patients with greater tremor severity.[81,82] Techniques for eliciting intention tremor need to be standardized and validated, and an operational definition of intention tremor (i.e., the required amplitude change) versus kinetic tremor is needed for neurologic examinations and electrophysiologic studies. The interrater reliability of distinguishing simple kinetic tremor from inten-

Table 2. Sensitivity and specificity of signs that suggest a dystonia syndrome

Sign*	Sensitivity	Specificity	Reference
Lower limb action tremor	0.5	0.7	Rajalingam et al.[74]
Irregular rhythm and jerkiness	?	?	See text
Highly asymmetric upper limb tremor	?	?	See text
Unusual postures (e.g., finger pointing)	0.20	0.90	Vives-Rodriguez and Louis[75]
Mirror dystonia	0.67	0.67	Sitburana et al.[76]
Muscular overflow contractions	0.28	0.96	Sitburana et al.[76]

*Cohort is assumed to consist of patients with essential tremor and dystonic tremor syndromes

tion tremor has not been investigated.

Irregular rhythm and jerkiness

Dystonic tremor is frequently described as jerky and irregular,[69] but these characteristics have not been operationally defined for dystonic tremor or any other form of tremor. There is no validated method for assessing these attributes in a neurologic examination, and the interrater reliability for these attributes was poor in a large cross-sectional study.[69] Furthermore, it has long been known that dystonic tremor can be either irregular or highly rhythmic.[83,84]

Motion transducers or EMG are needed for precise measurements of rhythm variability and for elucidating the cause(s) of jerkiness (e.g., dystonic contractions or myoclonus).[85-87] No form of tremor is perfectly rhythmic or sinusoidal, and the cycle-to-cycle variability (i.e., regularity) in the tremor frequency varies with the tremor amplitude.[88,89] A higher tremor amplitude is probably caused by greater entrainment of motor pathways, which is likely to increase the rhythmicity. It therefore seems unlikely that ET can be distinguished from other forms of tremor simply on the basis of rhythm variability (i.e., regularity).[90] Tremor amplitude must be controlled for when comparing different types of tremor based on rhythm regularity.

Asymmetric upper limb tremor

The MDS task force did not address the degree of asymmetry in upper extremity tremor that is compatible with ET. Asymmetry is common,[91] but the degree of asymmetry that should alert clinicians to an alternative diagnosis needs to be defined. The right-left difference in upper limb tremor in the author's clinic-based cohort of 212 ET patients was estimated using item 4 of the TETRAS examination, which consists of 0 to 4 point ratings of upper limb tremor in forward posture, wing posture, and finger-nose-finger movement (maximum score=12 for each upper limb).[24] The right-left difference was 0.0±1.4, indicating no significant right-left preference for asymmetry. Moreover, 95% of all patients had a difference of 1 point or less in the forward posture and finger-nose-finger assessment, and a difference of 1.5 points or less in the wing posture assessment. These results are comparable with those found with a different scale that uses scores from 0 to 3.[91]

Therefore, asymmetry of >1 point in a upper extremity tremor rating from 0 to 4 points is unusual for ET, and consistent asymmetry of >1 point across multiple upper extremity ratings should be viewed as a red flag for conditions such as dystonia and Parkinson disease, in which tremor asymmetry is common. This conclusion is supported by the finding that the somatosensory temporal discrimination threshold was increased in a cohort of patients with asymmetric and/or jerky upper limb tremor, suggesting that these patients were likely to have a form of dystonia.[92] However, the sensitivity and specificity of tremor asymmetry for ET versus dystonic tremor are presently unknown, and so this needs to be investigated in large patient cohorts.

Unusual postures

The significance of unusual posturing of the head and extremities is another area of diagnostic uncertainty. Subtle posturing is often viewed as a compensatory response to tremor. For example, hyperextension of the wrist while writing could be due to dystonia or represent an attempt to control severe tremor.[62] Postures such as a slight head tilt during conversation, spoon-shaped curvature of the extended hands,[93] and subconscious index finger pointing while standing or walking may indicate dystonia, but these behaviors are also exhibited by normal people.[75] In one clinical cohort, index finger pointing was observed in 20% of craniocervical dystonia patients, 16% of Parkinson patients, 10% of ET patients, and 3.8% of controls.[75] These data suggest that the sensitivity and specificity of index finger posturing are 20% and 90%, respectively, in a mixed population of people with ET and tremulous cervical dystonia. It seems likely that other forms of subtle or unusual body posturing have similar sensitivity and specificity, although confirmatory data are needed.

Mirror dystonia and muscular overflow

Mirror dystonia and muscular overflow contractions are considered to be supporting signs of dystonia,[59] but they have only modest sensitivity and specificity.[59] Blinded assessments of focal hand dystonia found mirror dystonia in 67% of patients and 39% of healthy controls (sensitivity=67%, specificity=61%).[76] Only 4% of the controls in that study exhibited overflow contractions (specificity=96%), but the prevalence rates (sensitivities) of ipsilateral and contralateral overflow contractions in patients were only 28% and 8%, respectively. Upper or lower limb mirror movements were found in 32.7% of ET patients and 23.7% of controls.[94] Therefore, the sensitivity and specificity of mirror movements in dystonia versus ET are both approximately 67%.

Other diagnostic considerations

Isolated bilateral upper extremity action tremor

Mild action tremor restricted to the hands is compatible with the classification of ET syndrome, but enhanced physiologic tremor (a.k.a., enhanced mechanical-reflex tremor) is an important and common differential diagnosis.[95] Enhanced physiologic tremor was three times more common than ET

in a population-based study performed in northern Italy.[95] The Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET) scale was designed with amplitude criteria to exclude enhanced physiologic tremor, but this approach may also exclude people with mild ET of comparable severity.[96] Electrophysiology is useful in distinguishing mild ET from enhanced physiologic tremor.[97,98] Applying 300−1000 gm mass loads to the hand reduces the frequency of enhanced physiologic tremor by more than 1 Hz, depending on the load, and this test is helpful in distinguishing mild ET from enhanced physiologic tremor.[99,100] Cervical dystonia is commonly associated with mild action tremor in the hands, and so patients presenting with mild upper extremity tremor should be examined carefully for subtle dystonia.[101]

In the author's clinic-based cohort of 212 ET patients, only 35 exhibited tremor in the upper limbs only, and only 5 of those patients had a total score for item 4 of the TETRAS examination of >10 (the maximum is 24). Therefore, ET presenting with isolated upper limb tremor is generally mild, and the presence of severe tremor restricted to the upper limbs should prompt a careful search for other diagnostic signs such as focal dystonia, ataxia, and parkinsonism.

Impaired tandem walking

The most common soft neurologic signs that lead to a diagnosis of ET plus are rest tremor, impaired tandem walking, memory impairment, mild peripheral neuropathy, and questionable dystonic posturing.[102-104] Impaired tandem walking is an exemplar soft sign in tremor classification. The first report of impaired tandem walking in 50% of ET patients led to the notion that ET "may be associated with signs other than tremor" and that "abnormal tandem in these patients supports the concept that cerebellar dysfunction may be the source of the tremor."[105] However, while tandem walking is very sensitive to impaired balance,[106] it is greatly influenced by normal aging and also by a wide variety of neurologic and nonneurologic conditions.[107] Therefore, while impaired tandem walking has high sensitivity for detecting cerebellar dysfunction, it also has very low specificity.

The first study of tandem walking in ET found that 50% of patients exhibited multiple missteps during a 10-step tandem walk; however, 28% of controls also exhibited this problem.[105] Therefore, the occurrence of impaired tandem walking can be assumed to be at least 28% in other axis-1 tremor syndromes, and is probably much higher in most (e.g., ataxia, dystonia, and parkinsonism), resulting in the specificity being 72% or lower for most diagnostic comparisons.

Another study found that 73% of controls with impaired tandem walking and 89% of ET patients with impaired tandem walking were aged ≥70 years.[105] In a similar study, impaired tandem walking was exhibited by only 7.4% of ET patients and 8.6% controls aged <70 years, but by 71% of ET patients and 22% of controls aged ≥70 years.[108] Thus, the interpretation of impaired tandem walking is severely confounded by the effects of aging.

ET and other forms of tremor emerge from oscillatory entrainment of the corticobulbocerebellothalamocortical loop. Tandem walking normalizes when ET oscillations in this loop are suppressed by ventrolateral thalamic deep brain stimulation[109] or by ethanol.[110] These observations indicate that dysfunction of the corticobulbocerebellothalamocortical loop in ET is largely a physiologic disturbance. This loop is critically important in the feedforward cerebellar control of movement, and hence it is reasonable that people with ET are more vulnerable to any additional cause of impaired balance such as chronic vestibulopathy, impaired vision, peripheral neuropathy, musculoskeletal disease, impaired cognition, or the adverse effects of normal aging.[107,111-113]

To summarize, impaired tandem walking is a common neurologic sign of impaired balance, and it should not be assumed to be etiologically related to ET. Impaired tandem walking has relatively little diagnostic utility in tremor classification when no other neurologic signs are present. Furthermore, tests of tandem walking need to be standardized in terms of how they are performed and scored.[107]

Electrophysiologic tests

There are no electrophysiologic abnormalities that are specific for ET. However, several electrophysiologic tests have been used to uncover differences in pathophysiology between dystonia and ET, and the results of such tests could be viewed as soft signs in the differential diagnosis.

The somatosensory temporal discrimination threshold is the shortest time interval between two tactile stimuli that are still discernible. The temporal discrimination threshold is increased in patients with tremor associated with dystonia, while it is normal in ET (sensitivity=90%, specificity=85%).[114] This test had a sensitivity of 60% and a specificity of 71.4% in a study comparing patients with asymmetric, jerky tremor (i.e., ET plus questionable signs of dystonia) with ET patients.[92]

A well-established test of sensorimotor learning that depends on normal cerebellar function is eyeblink reflex classical conditioning, which was found to be greatly reduced in ET, consistent with cerebellar impairment.[115] Such reduced conditioning was also found in patients with dystonic tremor syndromes[116] and in patients with inflammatory neuropathy with tremor, but not in patients with dystonia or inflammatory neuropathy without tremor.[115,117] However, a subsequent analysis of data from a larger cohort of dystonia patients re-

vealed that eyeblink reflex classical conditioning was normal in dystonic patients with or without tremor.[118] Like most electrophysiologic tests, eyeblink reflex classical conditioning varies greatly among patients and controls, but it possibly has some as-yet-undefined value in the classification of ET versus dystonia. Further investigations are needed to confirm this.

Increased R2 blink reflex recovery was observed in patients with a dystonic tremor syndrome but not in patients with ET (sensitivity=100%, specificity=100%).[116,119] Increased R2 blink reflex recovery was also seen in ET plus rest tremor versus ET (sensitivity=100%, specificity=100%).[44] R2 blink reflex recovery is increased in patients with parkinsonian rest tremor, but seems to differ from ET plus rest tremor recovery for interstimulus intervals of 100−150 ms.[120] These observations need to be confirmed in different laboratories and in larger patient cohorts. Confusing and conflicting observations are not uncommon in this field of electrophysiology; for example, one study found increased R2 blink reflex recovery in DYT1 dystonia but not in DYT6 dystonia.[121] Therefore, the sensitivity and specificity of increased R2 blink reflex recovery in distinguishing ET from dystonic tremor are probably less than 100% and may depend on the etiology of dystonia.

Bayesian analysis of soft signs

Soft signs, by definition, have insufficient sensitivity and specificity to be diagnostic when they are observed in isolation. However, multiple soft signs may be sufficient to change the diagnosis from ET plus to a more-specific combined tremor syndrome. Bayesian analysis is needed to interpret the significance of multiple soft signs.

Two groups of investigators independently found that the prevalence of craniocervical dystonia was roughly 30% in some pedigrees of ET.[122,123] For the sake of discussion, let us assume that any patient with an ET-like tremor has a 30% probability of dystonia and that we wish to know if one or more soft signs make a dystonia syndrome more likely than ET (i.e., probability of dystonia is >50%). We also wish to determine how many soft signs are needed to achieve a tremor classification with >90% certainty.

To illustrate this process, assume that an expert dystonia specialist examined a hypothetical patient with probable ET and noticed an index-finger-pointing posture during ambulation. Based on the available published data, the sensitivity and specificity of finger pointing for dystonia are estimated to be 20% and 90%, respectively, in a population of patients having either ET or dystonia (Table 2).[75]

The sensitivity and specificity of a test or sign can be used to compute the likelihood ratio (LR) or the likelihood of having a disease, given a positive result (LR+) or a negative result (LR-).[124] The positive and negative likelihood ratios (i.e., LR+ and LR-) are given in equations 1 and 2, and these equations are solved using the estimated sensitivity and specificity of the finger-pointing sign for dystonia versus ET. The pre-examination and postexamination odds (O_{pre} and O_{post}) and the postexamination probability (P_{post}) are computed using equations 3, 4, and 5 assuming a pre-examination probability (P_{pre}) of 0.3:[125]

$$LR+ = \frac{\text{Sensitivity}}{1-\text{specificity}} = \frac{0.2}{1-0.9} = 2, \quad (1)$$

$$LR- = \frac{1-\text{specificity}}{\text{Sensitivity}} = \frac{1-0.2}{0.9} = 0.89, \quad (2)$$

$$O_{pre} = \frac{P_{pre}}{1-P_{pre}} = \frac{0.3}{1-0.3} = 0.43, \quad (3)$$

$$O_{post} = O_{pre} \cdot LR = 0.43 \cdot 2 = 0.86, \quad (4)$$

$$P_{post} = \frac{O_{post}}{1+O_{post}} = \frac{0.86}{1+0.86} = 0.46. \quad (5)$$

Thus, the postexamination probability of dystonia is 0.46 if the expert finds finger-pointing posturing, and it is easily shown that the postexamination probability of dystonia would be 0.28 if no posturing had been found.

These equations are incorporated into an Excel spreadsheet in online Supplementary Materials 2 (in the online-only Data Supplement). This spreadsheet can be used to examine the additive effects of multiple sequential tests/examinations. Useful tests have a high positive likelihood ratio (LR+) and a low negative likelihood ratio (LR-). Soft signs have LR+ and LR- values close to 1. As shown in Supplementary Materials 2 (in the online-only Data Supplement), an additional soft sign of dystonia is needed to increase the posttest probability to above 50%, and four soft signs might be required to reach a posttest probability of 90%.

The Bayesian analysis of clinical soft signs can be extended by applying electrophysiologic tests. For example, reduced somatosensory temporal discrimination in the above patient with finger pointing would produce an estimated probability of dystonia of 0.64 (Supplementary Materials 2 in the online-only Data Supplement); in other words, dystonic tremor would become more likely than ET.

Limitations of the Bayesian approach

A major limitation of the Bayesian approach is the paucity of data with which to estimate the sensitivity and specificity of various signs that are important for phenotyping patients. Data need to be obtained from age- and sex-matched con-

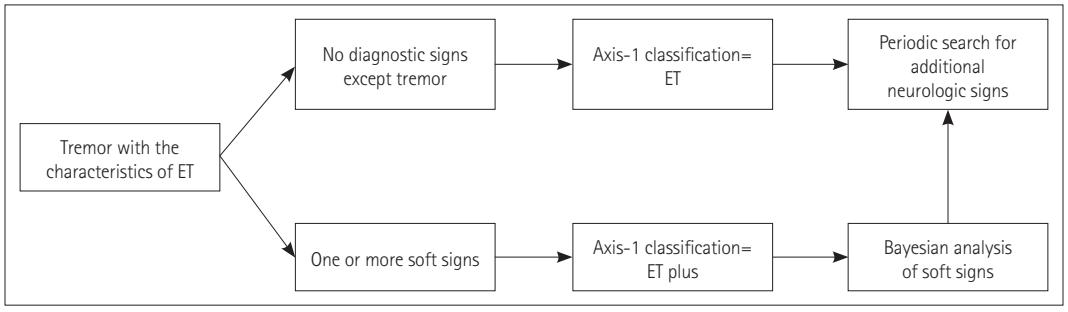

Fig. 1. Flow diagram for the clinical diagnosis and interpretation of essential tremor (ET) and ET plus. People fulfilling the criteria for ET are examined for any signs of uncertain abnormality or uncertain clinical significance (i.e., "soft signs"). People with one or more soft signs are classified as ET plus. Bayesian analysis can be used to estimate the probability of a combined tremor syndrome, based on the soft signs and any associated electrodiagnostic results (Supplementary Materials 2 in the online-only Data Supplement). Patients with ET and ET plus should be re-examined periodically for additional neurologic signs that could result in a different tremor classification (e.g., dystonic tremor syndrome).

trols. This limitation also applies to electrophysiologic tests, whose sensitivities and specificities have been derived only from small samples of patients and controls.[118]

Another limitation is that the baseline probability of ET always has some degree of statistical uncertainty stemming from the reliability of the patient's history and physical examination findings, the clinician's examination skills, and the diagnostic composition of the population from which the case was derived. Clinicians have different examination skills and clinical experience, and there is no infallible expert or gold-standard diagnostic biomarker for ET or syndromes that mimic ET, such as tremulous dystonia. Consequently, a range of baseline probabilities should be considered when applying a Bayesian analysis to soft signs.[126]

Moreover, interrater reliability affects the measured sensitivity and specificity of a test or physical examination item.[73] The measured sensitivity and specificity are reduced by poor interrater reliability,[71] and this must be considered when judging the true value of a particular diagnostic approach. All signs of dystonia, parkinsonism, ataxia, and other movement disorders have some degree of "softness" (i.e., reduced sensitivity and specificity) due to variation in the clinical skills of clinicians. Craniocervical dystonia appears to be the most likely type of dystonia to be associated with tremor resembling ET.[14,25,69,122] The interrater agreement is poor for diagnosing dystonia and tremor in the context of dystonia,[69,70] and agreement is particularly poor for signs of uncertain abnormality or clinical relevance (i.e., soft signs).[7,8]

DISCUSSION

Some authors have questioned the utility of soft signs and the concept of ET plus due to the poor interrater reliability.[8] However, the main purpose of ET plus is to acknowledge any diagnostic uncertainty in tremor classification and to promote a more-comprehensive phenotyping of patients with tremor. This approach should reduce any temptation to either dismiss soft signs as irrelevant or accept soft signs as diagnostic of a combined tremor syndrome. Diagnostic certainty is not achievable in most patients, especially those with ET since there is no diagnostic biomarker. Bayesian analysis can be used to estimate the probability that ET plus is a combined tremor syndrome rather than ET. However, it should also be remembered that the tremor classification may change over time in an individual patient based on the results of periodic re-examination (Fig. 1).

The clinical significance of a soft sign depends on the estimated pretest probability of ET versus some other tremor syndrome, and also on the sensitivity and specificity of the soft sign for the alternative diagnosis versus ET. The presence of only a single soft sign may mean that the probability of an alternative diagnosis remains below 50%. However, two or more soft signs that are congruent with an alternative diagnosis will probably increase the diagnostic probability to >50%, making the alternative more likely than ET. Three congruent soft signs with sensitivity and specificity values of 75% will increase the initial probability of an alternative classification from 0.3 to 0.92 (Supplementary Materials 2 in the online-only Data Supplement), making the diagnosis of ET untenable. A recent clinic-based study found that 67% of ET plus patients had only one soft sign.[104]

A systematic, comprehensive neurologic examination is required for the axis-1 classification of tremor, and the Standardized Tremor Elements Assessment was developed for this purpose.[7] Guidelines for examining people with possible dystonia have also been proposed.[127] Ultimately, accurate sensitivity and specificity estimates are needed for the items in these assessments.

Many investigators will choose to include patients with only one soft sign in studies of ET if the soft sign has low sensitivity and specificity for an alternative tremor classification. Common examples of such soft signs are impaired tandem

walking, mild cognitive impairment, and impaired hearing. Some soft signs may be considered exclusionary for reasons other than the diagnosis. For example, a drug study might exclude patients with mild cognitive impairment if cognitive side effects are anticipated, and functional neurosurgery studies might exclude patients with impaired tandem walking due to the risk of impaired balance following surgery. In contrast, postmortem, genetic, and epidemiologic studies might be justified in including any patient with ET or ET plus, and use post-hoc analyses to generate testable hypotheses regarding the relevance of particular soft signs. When viewed from these perspectives, ET plus becomes a useful axis-1 classification that permits an unambiguous definition of ET and a more-comprehensive phenotyping of patients.

One or more follow-up examinations will often reveal the significance of soft signs in ET plus. Soft signs may become "hard signs" (e.g., dystonia), and patients may develop additional hard or soft signs that lead to a more-definitive tremor syndrome. The rationale for the Bayesian approach is strongest when invasive procedures with significant risks are being considered (e.g., deep brain stimulation and focused ultrasound ablation) and when patients are evaluated in research studies that require comprehensive phenotyping.

Finally, this review has focused on the common differential diagnosis of ET versus dystonic tremor to illustrate the value of ET plus and Bayesian analysis in clinical decision-making. This approach is also applicable to other differential diagnoses in tremor classification. Clinical diagnosis frequently requires a Bayesian analysis of clinical data,[128] and ET plus is a new tremor classification that arguably requires Bayesian methods for its optimum use and interpretation.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.18.2.127.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

ORCID iD

Rodger J. Elble https://orcid.org/0000-0003-2928-4214

Conflicts of Interest

R. Elble is an employee of SIU Medicine. He has served as a consultant for Cadent, Cydan, ES Therapeutics, Jazz, Neurocrine Biosciences, Novartis, Osmotica, Praxis Precision Medicines, and Sage regarding clinical trials for the treatment of essential tremor. He is also a consultant for Applied Therapeutics regarding clinical trials for galactosemia. He has served on advisory boards for the International Essential Tremor Foundation and the Neuroscience Research Foundation of Kiwanis International, Illinois-Eastern Iowa District.

Funding Statement

This work was supported by a grant from the Neuroscience Research Foundation of Kiwanis International, Illinois-Eastern Iowa District.

REFERENCES

1. Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. *Mov Disord* 2010;25:534-541.
2. Chouinard S, Louis ED, Fahn S. Agreement among movement disorder specialists on the clinical diagnosis of essential tremor. *Mov Disord* 1997;12:973-976.
3. Findley LJ. Classification of tremors. *J Clin Neurophysiol* 1996;13:122-132.
4. Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, et al. Consensus statement on the classification of tremors. From the task force on tremor of the International Parkinson and Movement Disorder Society. *Mov Disord* 2018;33:75-87.
5. Deuschl G, Bain P, Brin M. Consensus statement of the movement disorder society on tremor. *Mov Disord* 1998;13 Suppl 3:2-23.
6. Jankovic J. Essential tremor: a heterogenous disorder. *Mov Disord* 2002;17:638-644.
7. Becktepe J, Govert F, Balint B, Schlenstedt C, Bhatia K, Elble R, et al. Exploring interrater disagreement on essential tremor using a standardized tremor elements assessment. *Mov Disord Clin Pract* 2021;8:371-376.
8. Fearon C, Espay AJ, Lang AE, Lynch T, Martino D, Morgante F, et al. Soft signs in movement disorders: friends or foes? *J Neurol Neurosurg Psychiatry* 2019;90:961-962.
9. Quinn NP, Schneider SA, Schwingenschuh P, Bhatia KP. Tremor--some controversial aspects. *Mov Disord* 2011;26:18-23.
10. Jain S, Lo SE, Louis ED. Common misdiagnosis of a common neurological disorder: how are we misdiagnosing essential tremor? *Arch Neurol* 2006;63:1100-1104.
11. Schrag A, Münchau A, Bhatia KP, Quinn NP, Marsden CD. Essential tremor: an overdiagnosed condition? *J Neurol* 2000;247:955-959.
12. Amlang CJ, Trujillo Diaz D, Louis ED. Essential tremor as a "waste basket" diagnosis: diagnosing essential tremor remains a challenge. *Front Neurol* 2020;11:172.
13. Elble RJ. Essential tremor is a useful concept? No. *Mov Disord Clin Pract* 2017;4:663-665.
14. Erro R, Rubio-Agusti I, Saifee TA, Cordivari C, Ganos C, Batla A, et al. Rest and other types of tremor in adult-onset primary dystonia. *J Neurol Neurosurg Psychiatry* 2014;85:965-968.
15. Louis ED, Bares M, Benito-Leon J, Fahn S, Frucht SJ, Jankovic J, et al. Essential tremor-plus: a controversial new concept. *Lancet Neurol* 2020;19:266-270.
16. Elble RJ. Do we belittle essential tremor by calling it a syndrome rather than a disease? No. *Front Neurol* 2020;11:586606.
17. Louis ED. "Essential tremor plus": a problematic concept: implications for clinical and epidemiological studies of essential tremor. *Neuroepidemiology* 2020;54:180-184.
18. Vidailhet M. Essential tremor-plus: a temporary label. *Lancet Neurol* 2020;19:202-203.
19. Emamikhah M, Aghavali S, Moghadas F, Munhoz RP, Lang AE, Alavi A, et al. Spinocerebellar ataxia 40: another etiology underlying essential tremor syndrome. *Mov Disord Clin Pract* 2021;8:944-946.
20. Bellows ST, Jankovic J. Phenotypic features of isolated essential tremor, essential tremor plus, and essential tremor-Parkinson's disease in a movement disorders clinic. *Tremor Other Hyperkinet Mov (N Y)* 2021;11:12.
21. Pandey S, Bhattad S. Questionable dystonia in essential tremor plus: a video-based assessment of 19 patients. *Mov Disord Clin Pract* 2019;

6:722-723.
22. Rajalingam R, Breen DP, Lang AE, Fasano A. Essential tremor plus is more common than essential tremor: insights from the reclassification of a cohort of patients with lower limb tremor. *Parkinsonism Relat Disord* 2018;56:109-110.
23. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol* 2018;18:143.
24. Elble R, Comella C, Fahn S, Hallett M, Jankovic J, Juncos JL, et al. Reliability of a new scale for essential tremor. *Mov Disord* 2012;27:1567-1569.
25. Lou JS, Jankovic J. Essential tremor: clinical correlates in 350 patients. *Neurology* 1991;41:234-238.
26. Phibbs F, Fang JY, Cooper MK, Charles DP, Davis TL, Hedera P. Prevalence of unilateral tremor in autosomal dominant essential tremor. *Mov Disord* 2009;24:108-111.
27. Elble RJ. Physiologic and essential tremor. *Neurology* 1986;36:225-231.
28. van de Wardt J, van der Stouwe AMM, Dirkx M, Elting JWJ, Post B, Tijssen MA, et al. Systematic clinical approach for diagnosing upper limb tremor. *J Neurol Neurosurg Psychiatry* 2020;91:822-830.
29. Louis ED, Dogu O. Isolated head tremor: part of the clinical spectrum of essential tremor? Data from population-based and clinic-based case samples. *Mov Disord* 2009;24:2281-2285.
30. Findley LJ, Gresty MA. Head, facial, and voice tremor. *Adv Neurol* 1988;49:239-253.
31. Masuhr F, Wissel J, Müller J, Scholz U, Poewe W. Quantification of sensory trick impact on tremor amplitude and frequency in 60 patients with head tremor. *Mov Disord* 2000;15:960-964.
32. Patel A, Frucht SJ. Isolated vocal tremor as a focal phenotype of essential tremor: a retrospective case review. J Clin Mov Disord 2015;2:4.
33. Daraei P, Villari CR, Rubin AD, Hillel AT, Hapner ER, Klein AM, et al. The role of laryngoscopy in the diagnosis of spasmodic dysphonia. *JAMA Otolaryngol Head Neck Surg* 2014;140:228-232.
34. Ludlow CL, Domangue R, Sharma D, Jinnah HA, Perlmutter JS, Berke G, et al. Consensus-based attributes for identifying patients with spasmodic dysphonia and other voice disorders. *JAMA Otolaryngol Head Neck Surg* 2018;144:657-665.
35. Conte A, Ferrazzano G, Manzo N, Leodori G, Fabbrini G, Fasano A, et al. Somatosensory temporal discrimination in essential tremor and isolated head and voice tremors. *Mov Disord* 2015;30:822-827.
36. Benito-León J, Bermejo-Pareja F, Morales JM, Vega S, Molina JA. Prevalence of essential tremor in three elderly populations of central Spain. *Mov Disord* 2003;18:389-394.
37. Larsson T, Sjogren T. Essential tremor: a clinical and genetic population study. *Acta Psychiatr Scand Suppl* 1960;36:1-176.
38. Barkmeier JM, Case JL, Ludlow CL. Identification of symptoms for spasmodic dysphonia and vocal tremor: a comparison of expert and nonexpert judges. *J Commun Disord* 2001;34:21-37.
39. Aronson AE, Hartman DE. Adductor spastic dysphonia as a sign of essential (voice) tremor. *J Speech Hear Disord* 1981;46:52-58.
40. Whaley NR, Putzke JD, Baba Y, Wszolek ZK, Uitti RJ. Essential tremor: phenotypic expression in a clinical cohort. *Parkinsonism Relat Disord* 2007;13:333-339.
41. Louis ED, Hernandez N, Michalec M. Prevalence and correlates of rest tremor in essential tremor: cross-sectional survey of 831 patients across four distinct cohorts. *Eur J Neurol* 2015;22:927-932.
42. Louis ED, Asabere N, Agnew A, Moskowitz CB, Lawton A, Cortes E, et al. Rest tremor in advanced essential tremor: a post-mortem study of nine cases. *J Neurol Neurosurg Psychiatry* 2011;82:261-265.
43. Rajput A, Robinson CA, Rajput AH. Essential tremor course and disability: a clinicopathologic study of 20 cases. *Neurology* 2004;62:932-936.
44. Nisticò R, Pirritano D, Novellino F, Salsone M, Morelli M, Valentino P, et al. Blink reflex recovery cycle in patients with essential tremor associated with resting tremor. *Neurology* 2012;79:1490-1495.
45. Bajaj NP, Gontu V, Birchall J, Patterson J, Grosset DG, Lees AJ. Accuracy of clinical diagnosis in tremulous parkinsonian patients: a blinded video study. *J Neurol Neurosurg Psychiatry* 2010;81:1223-1228.
46. Wilken M, Bruno V, Rossi M, Ameghino L, Deuschl G, Merello M. Sensitivity and specificity of different hand positions to assess upper limb rest tremor. *Mov Disord* 2019;34:575-579.
47. Pasquini J, Ceravolo R, Qamhawi Z, Lee JY, Deuschl G, Brooks DJ, et al. Progression of tremor in early stages of Parkinson's disease: a clinical and neuroimaging study. *Brain* 2018;141:811-821.
48. Baizabal-Carvallo JF, Cardoso F, Jankovic J. Myorhythmia: phenomenology, etiology, and treatment. *Mov Disord* 2015;30:171-179.
49. Papengut F, Raethjen J, Binder A, Deuschl G. Rest tremor suppression may separate essential from parkinsonian rest tremor. *Parkinsonism Relat Disord* 2013;19:693-697.
50. Agnew A, Frucht SJ, Louis ED. Supine head tremor: a clinical comparison of essential tremor and spasmodic torticollis patients. *J Neurol Neurosurg Psychiatry* 2012;83:179-181.
51. Roze E, Coêlho-Braga MC, Gayraud D, Legrand AP, Trocello JM, Fénelon G, et al. Head tremor in Parkinson's disease. *Mov Disord* 2006;21:1245-1248.
52. Bologna M, Paparella G, Colella D, Cannavacciuolo A, Angelini L, Alunni-Fegatelli D, et al. Is there evidence of bradykinesia in essential tremor? *Eur J Neurol* 2020;27:1501-1509.
53. Duval C, Sadikot AF, Panisset M. Bradykinesia in patients with essential tremor. *Brain Res* 2006;1115:213-216.
54. Montgomery EB Jr, Baker KB, Lyons K, Koller WC. Motor initiation and execution in essential tremor and Parkinson's disease. *Mov Disord* 2000;15:511-515.
55. Paparella G, Fasano A, Hallett M, Berardelli A, Bologna M. Emerging concepts on bradykinesia in non-parkinsonian conditions. *Eur J Neurol* 2021;28:2403-2422.
56. Findley LJ, Gresty MA, Halmagyi GM. Tremor, the cogwheel phenomenon and clonus in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1981;44:534-546.
57. Ramos VF, Karp BI, Hallett M. Tricks in dystonia: ordering the complexity. *J Neurol Neurosurg Psychiatry* 2014;85:987-993.
58. Dagostino S, Ercoli T, Gigante AF, Pellicciari R, Fadda L, Defazio G. Sensory trick in upper limb dystonia. *Parkinsonism Relat Disord* 2019;63:221-223.
59. Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VS, et al. Phenomenology and classification of dystonia: a consensus update. *Mov Disord* 2013;28:863-873.
60. Schaefer SM, Hallett M, Karp BP, DiCapua DB, Tinaz S. Positional tremor and its treatment. *Mov Disord Clin Pract* 2017;4:768-771.
61. Lee A, Furuya S, Altenmüller E. Epidemiology and treatment of 23 musicians with task specific tremor. *J Clin Mov Disord* 2014;1:5.
62. Elble RJ, Moody C, Higgins C. Primary writing tremor. A form of focal dystonia? *Mov Disord* 1990;5:118-126.
63. Stahl CM, Frucht SJ. Focal task specific dystonia: a review and update. *J Neurol* 2017;264:1536-1541.
64. Frucht SJ. The definition of dystonia: current concepts and controversies. *Mov Disord* 2013;28:884-888.
65. Latorre A, Rocchi L, Batla A, Berardelli A, Rothwell JC, Bhatia KP. The signature of primary writing tremor is dystonic. *Mov Disord* 2021;36:1715-1720.
66. Erro R, Ciocca M, Hirschbichler ST, Rothwell JC, Bhatia KP. Primary writing tremor is a dystonic trait: evidence from an instructive family. *J Neurol Sci* 2015;356:210-211.
67. Pita Lobo P, Quattrocchi G, Jutras MF, Sangla S, Apartis E, Vidailhet M, et al. Primary writing tremor and writer's cramp: two faces of a

same coin? *Mov Disord* 2013;28:1306-1307.
68. Lee A, Schoonderwaldt E, Chadde M, Altenmüller E. Analysis of dystonic tremor in musicians using empirical mode decomposition. *Clin Neurophysiol* 2015;126:147-153.
69. Shaikh AG, Beylergil SB, Scorr L, Kilic-Berkmen G, Freeman A, Klein C, et al. Dystonia and tremor: a cross-sectional study of the dystonia coalition cohort. *Neurology* 2021;96:e563-e574.
70. Logroscino G, Livrea P, Anaclerio D, Aniello MS, Benedetto G, Cazzato G, et al. Agreement among neurologists on the clinical diagnosis of dystonia at different body sites. *J Neurol Neurosurg Psychiatry* 2003;74:348-350.
71. Beghi E, Regio V, Papantonio A, Bentivoglio AR, Fasano A, Fogli D, et al. Reliability of clinical diagnosis of dystonia. *Neuroepidemiology* 2014;43:213-219.
72. Lalli S, Albanese A. The diagnostic challenge of primary dystonia: evidence from misdiagnosis. *Mov Disord* 2010;25:1619-1626.
73. Omurtag A, Fenton AA. Assessing diagnostic tests: how to correct for the combined effects of interpretation and reference standard. *PLoS One* 2012;7:e52221.
74. Rajalingam R, Breen DP, Chen R, Fox S, Kalia LV, Munhoz RP, et al. The clinical significance of lower limb tremors. *Parkinsonism Relat Disord* 2019;65:165-171.
75. Vives-Rodriguez A, Louis ED. Index finger pointing (likely a subtle form of hand dystonia): prevalence across movement disorders. *Front Neurol* 2018;9:542.
76. Sitburana O, Wu LJ, Sheffield JK, Davidson A, Jankovic J. Motor overflow and mirror dystonia. *Parkinsonism Relat Disord* 2009;15:758-761.
77. Gerstenbrand F, Klingler D, Pfeiffer B. Essential tremor: phenomenology and epidemiology (author's transl). *Nervenarzt* 1982;53:46-53.
78. Tallón-Barranco A, Vázquez A, Javier Jiménez-Jiménez F, Ortí-Pareja M, Gasalla T, Cabrera-Valdivia F, et al. Clinical features of essential tremor seen in neurology practice: a study of 357 patients. *Parkinsonism Relat Disord* 1997;3:187-190.
79. Kestenbaum M, Michalec M, Yu Q, Pullman SL, Louis ED. Intention tremor of the legs in essential tremor: prevalence and clinical correlates. *Mov Disord Clin Pract* 2015;2:24-28.
80. Poston KL, Rios E, Louis ED. Action tremor of the legs in essential tremor: prevalence, clinical correlates, and comparison with age-matched controls. *Parkinsonism Relat Disord* 2009;15:602-605.
81. Louis ED, Frucht SJ, Rios E. Intention tremor in essential tremor: prevalence and association with disease duration. *Mov Disord* 2009;24:626-627.
82. Deuschl G, Wenzelburger R, Löffler K, Raethjen J, Stolze H. Essential tremor and cerebellar dysfunction clinical and kinematic analysis of intention tremor. *Brain* 2000;123:1568-1580.
83. Blitzer A, Lovelace RE, Brin MF, Fahn S, Fink ME. Electromyographic findings in focal laryngeal dystonia (spastic dysphonia). *Ann Otol Rhinol Laryngol* 1985;94:591-594.
84. Yanagisawa N, Goto A, Narabayashi H. Familial dystonia musculorum deformans and tremor. *J Neurol Sci* 1972;16:125-136.
85. Beylergil SB, Singh AP, Zee DS, Jinnah HA, Shaikh AG. Relationship between jerky and sinusoidal oscillations in cervical dystonia. *Parkinsonism Relat Disord* 2019;66:130-137.
86. Shaikh AG, Zee DS, Jinnah HA. Oscillatory head movements in cervical dystonia: dystonia, tremor, or both? *Mov Disord* 2015;30:834-842.
87. Shaikh AG, Jinnah HA, Tripp RM, Optican LM, Ramat S, Lenz FA, et al. Irregularity distinguishes limb tremor in cervical dystonia from essential tremor. *J Neurol Neurosurg Psychiatry* 2008;79:187-189.
88. Panyakaew P, Cho HJ, Lee SW, Wu T, Hallett M. The pathophysiology of dystonic tremors and comparison with essential tremor. *J Neurosci* 2020;40:9317-9326.
89. Vaillancourt DE, Slifkin AB, Newell KM. Regularity of force tremor in Parkinson's disease. *Clin Neurophysiol* 2001;112:1594-1603.
90. di Biase L, Brittain JS, Shah SA, Pedrosa DJ, Cagnan H, Mathy A, et al. Tremor stability index: a new tool for differential diagnosis in tremor syndromes. *Brain* 2017;140:1977-1986.
91. Louis ED, Wendt KJ, Pullman SL, Ford B. Is essential tremor symmetric? Observational data from a community-based study of essential tremor. *Arch Neurol* 1998;55:1553-1559.
92. Gövert F, Becktepe J, Balint B, Rocchi L, Brugger F, Garrido A, et al. Temporal discrimination is altered in patients with isolated asymmetric and jerky upper limb tremor. *Mov Disord* 2020;35:306-315.
93. Kim CY, Louis ED. "Spooning": a subtle sign of limb dystonia. *Tremor Other Hyperkinet Mov (N Y)* 2018;8:607.
94. Louis ED, Rios E, Henchcliffe C. Mirror movements in patients with essential tremor. *Mov Disord* 2009;24:2211-2217.
95. Wenning GK, Kiechl S, Seppi K, Müller J, Högl B, Saletu M, et al. Prevalence of movement disorders in men and women aged 50-89 years (Bruneck Study cohort): a population-based study. *Lancet Neurol* 2005;4:815-820.
96. Louis ED, Ottman R, Ford B, Pullman S, Martinez M, Fahn S, et al. The Washington Heights-Inwood Genetic Study of essential tremor: methodologic issues in essential-tremor research. *Neuroepidemiology* 1997;16:124-133.
97. Louis ED, Pullman SL. Comparison of clinical vs. electrophysiological methods of diagnosing of essential tremor. *Mov Disord* 2001;16:668-673.
98. Elble RJ, Higgins C, Elble S. Electrophysiologic transition from physiologic tremor to essential tremor. *Mov Disord* 2005;20:1038-1042.
99. Elble RJ, Deuschl G. Tremor. In: Brown WF, Bolton CF, Aminoff MJ, editors. *Neuromuscular Function and Disease: Basic, Clinical, and Electrodiagnostic Aspects*. Vol 2. Philadelphia: W.B. Saunders, 2002;1759-1779.
100. Longardner K, Undurraga FV, Nahab FB, Hallett M, Haubenberger D. How do I assess tremor using novel technology? *Mov Disord Clin Pract* 2019;6:733-734.
101. Deuschl G, Heinen F, Guschlbauer B, Schneider S, Glocker FX, Lücking CH. Hand tremor in patients with spasmodic torticollis. *Mov Disord* 1997;12:547-552.
102. Pandey S, Bhattad S, Hallett M. The problem of questionable dystonia in the diagnosis of 'essential tremor-plus'. *Tremor Other Hyperkinet Mov (N Y)* 2020;10:27.
103. Huang H, Yang X, Zhao Q, Ning P, Shen Q, Wang H, et al. Clinical characteristics of patients with essential tremor or essential tremor plus. *Acta Neurol Scand* 2020;141:335-341.
104. Pandey S, Bhattad S. Soft signs in essential tremor plus: a prospective study. *Mov Disord Clin Pract* 2021;8:1275-1277.
105. Singer C, Sanchez-Ramos J, Weiner WJ. Gait abnormality in essential tremor. *Mov Disord* 1994;9:193-196.
106. Stolze H, Klebe S, Petersen G, Raethjen J, Wenzelburger R, Witt K, et al. Typical features of cerebellar ataxic gait. *J Neurol Neurosurg Psychiatry* 2002;73:310-312.
107. Margolesky J, Singer C. How tandem gait stumbled into the neurological exam: a review. *Neurol Sci* 2018;39:23-29.
108. Lim ES, Seo MW, Woo SR, Jeong SY, Jeong SK. Relationship between essential tremor and cerebellar dysfunction according to age. *J Clin Neurol* 2005;1:76-80.
109. Fasano A, Herzog J, Raethjen J, Rose FE, Muthuraman M, Volkmann J, et al. Gait ataxia in essential tremor is differentially modulated by thalamic stimulation. *Brain* 2010;133:3635-3648.
110. Klebe S, Stolze H, Grensing K, Volkmann J, Wenzelburger R, Deuschl G. Influence of alcohol on gait in patients with essential tremor. *Neurology* 2005;65:96-101.
111. Dowd H, Zdrodowska MA, Radler KH, Cersonsky TEK, Rao AK, Huey ED, et al. Prospective longitudinal study of gait and balance in a cohort of elderly essential tremor patients. *Front Neurol* 2020;11:

581703.
112. Rao AK, Louis ED. Ataxic gait in essential tremor: a disease-associated feature? *Tremor Other Hyperkinet Mov (N Y)* 2019;9:1-12.
113. Rao AK, Gillman A, Louis ED. Quantitative gait analysis in essential tremor reveals impairments that are maintained into advanced age. *Gait Posture* 2011;34:65-70.
114. Tinazzi M, Fasano A, Di Matteo A, Conte A, Bove F, Bovi T, et al. Temporal discrimination in patients with dystonia and tremor and patients with essential tremor. *Neurology* 2013;80:76-84.
115. Kronenbuerger M, Gerwig M, Brol B, Block F, Timmann D. Eyeblink conditioning is impaired in subjects with essential tremor. *Brain* 2007;130:1538-1551.
116. Antelmi E, Di Stasio F, Rocchi L, Erro R, Liguori R, Ganos C, et al. Impaired eye blink classical conditioning distinguishes dystonic patients with and without tremor. *Parkinsonism Relat Disord* 2016;31:23-27.
117. Schwingenschuh P, Saifee TA, Katschnig-Winter P, Reilly MM, Lunn MP, Manji H, et al. Cerebellar learning distinguishes inflammatory neuropathy with and without tremor. *Neurology* 2013;80:1867-1873.
118. Sadnicka A, Rocchi L, Latorre A, Antelmi E, Teo JT, Parees I, et al. The final blink: intact eyeblink conditioning in isolated dystonia. *medRxiv* [Preprint]. 2021 [cited 2021 Jul 30]. Available at: https://doi.org/10.1101/2021.07.26.21260809.
119. Nisticò R, Pirritano D, Salsone M, Valentino P, Novellino F, Condino F, et al. Blink reflex recovery cycle in patients with dystonic tremor: a cross-sectional study. *Neurology* 2012;78:1363-1365.
120. Nisticò R, Salsone M, Vescio B, Morelli M, Trotta M, Barbagallo G, et al. Blink reflex recovery cycle distinguishes essential tremor with resting tremor from de novo Parkinson's disease: an exploratory study. *Parkinsonism Relat Disord* 2014;20:153-156.
121. Sadnicka A, Teo JT, Kojovic M, Pareés I, Saifee TA, Kassavetis P, et al. All in the blink of an eye: new insight into cerebellar and brainstem function in DYT1 and DYT6 dystonia. *Eur J Neurol* 2015;22:762-767.
122. Hedera P, Phibbs FT, Fang JY, Cooper MK, Charles PD, Davis TL. Clustering of dystonia in some pedigrees with autosomal dominant essential tremor suggests the existence of a distinct subtype of essential tremor. *BMC Neurol* 2010;10:66.
123. Louis ED, Hernandez N, Alcalay RN, Tirri DJ, Ottman R, Clark LN. Prevalence and features of unreported dystonia in a family study of "pure" essential tremor. *Parkinsonism Relat Disord* 2013;19:359-362.
124. Attia J. Moving beyond sensitivity and specificity: using likelihood ratios to help interpret diagnostic tests. *Aust Prescr* 2003;26:111-113.
125. Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. *BMJ* 2004;329:168-169.
126. Bianchi MT, Alexander BM, Cash SS. Incorporating uncertainty into medical decision making: an approach to unexpected test results. *Med Decis Making* 2009;29:116-124.
127. Defazio G, Albanese A, Pellicciari R, Scaglione CL, Esposito M, Morgante F, et al. Expert recommendations for diagnosing cervical, oromandibular, and limb dystonia. *Neurol Sci* 2019;40:89-95.
128. Gleason PM, Harris JE. The Bayesian approach to decision making and analysis in nutrition research and practice. *J Acad Nutr Diet* 2019;119:1993-2003.