EXPERT REVIEWS

Distinguishing essential tremor from Parkinson's disease: bedside tests and laboratory evaluations

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Mary Ann Thenganatt[1] and Elan D Louis*[1,2,3,4]

[1]*Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY, USA*
[2]*Taub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University, New York, NY, USA*
[3]*GH Sergievsky Center, College of Physicians and Surgeons, Columbia University, New York, NY, USA*
[4]*Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA*
**Author for correspondence:*
Tel.: +1 212 305 9194
Fax: +1 212 305 1304
EDL2@columbia.edu

Distinguishing essential tremor from Parkinson's disease can be challenging, both in the early stages of these diseases and as these diseases progress. Various tremor types (rest, postural, kinetic and intention) may be seen in both essential tremor and Parkinson's disease. Furthermore, with time, the two diseases may coexist within a single patient. Detailed clinical examination with attention to specific features of tremor (frequency, amplitude, pattern and distribution) and associated neurological findings may help distinguish patients with the two diseases. Laboratory testing may provide information that further aids in differentiating the two diseases. These tests include accelerometry and surface electromyography, spiral analysis, dopamine transporter imaging, olfactory testing and, eventually, postmortem histopathology. These tests have limitations and their diagnostic utility requires additional study.

Keywords: clinical • DAT-SPECT • diagnosis • essential tremor • laboratory • olfaction • Parkinson's disease • postmortem • tests

Essential tremor (ET) and Parkinson's disease (PD) are two of the most common adult-onset tremor disorders. The prevalence of PD increases with age and is estimated to be 1.8% in individuals who are 65 years of age and older [1]. The prevalence of ET, which also increases with age, has been estimated to be 4.6% in that age group [2]. Clinicians are often faced with the prospect of distinguishing ET from PD, which can be a diagnostic challenge in early stages of disease when clinical signs are subtle. Indeed, one study observed that one-third of patients who were diagnosed as ET were misdiagnosed, with PD being the most common true diagnosis [3]. Traditionally, ET has been considered a monosymptomatic disease characterized exclusively by action tremor. Yet over the past 10 years, this concept has been challenged, with the description of additional clinical features. Indeed, patients with ET and PD can have overlapping clinical features, and some patients may meet criteria for both diseases. The clinical features that may be used to diagnostically distinguish ET from PD will be the focus of this article. We will discuss bedside tests as well as laboratory tests that may help the practicing clinician to distinguish these two common tremor disorders.

'ET+PD': co-occurrence of two diseases

As alluded to above, patients with ET and PD may exhibit overlapping clinical features. To further complicate the matter, patients with ET may eventually meet criteria for an additional diagnosis of PD (i.e., 'ET+PD') [4]. Thus, the two disorders may coexist within the same individual, and having one seems to increase the risk of developing the other. Thus, one community-based study evaluated the risk of incident PD in 201 clinically diagnosed ET cases [4]. Three percent of ET cases developed PD compared with 0.7% of controls, after a median follow-up of 3.3 years (i.e., patients with ET had a fourfold to fivefold increased risk of developing PD compared with controls) [4]. In that study, the median latency between the onset of ET and subsequent PD was 8.0 years [4]. This propensity for disease co-occurrence adds a layer of complexity to the differential diagnosis of these two disorders.

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Types of tremor & tremor terminology

Before proceeding further, it is important to briefly delve into tremor nosology. There is a variety of tremor types that clinicians must consider when evaluating patients (Table 1). Rest tremor occurs when voluntary muscle activity is absent. Action tremor can be subdivided into postural, kinetic and intention tremors. Postural tremor occurs when holding a body part (e.g., arm, head, leg) motionless against gravity. Re-emergent tremor is a particular type of postural tremor; when the patient holds their arms extended, the tremor commences after a variable latency of one to several seconds. Kinetic tremor occurs with voluntary movement (e.g., pouring, writing). Intention tremor occurs with goal-directed movement (e.g., finger-nose-finger movement) and worsens as the body part (e.g., finger) approaches the target. Familiarity with the terms defined above is necessary in order to understand the diagnostic criteria, which have been proposed for both ET and PD.

Diagnostic criteria for ET & PD

Two sets of criteria are commonly used for the diagnosis of ET. For definite ET, the diagnostic criteria proposed by the Movement Disorder Society require the presence of persistent, bilateral postural tremor of the forearms [5]. Kinetic tremor may be present, but is not necessary for the diagnosis [5]. No other abnormal neurological signs may be present, except for Froment's sign, which is a cogwheel phenomenon without rigidity [5]. For definite ET, the criteria proposed by the Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET) require the presence of moderate (or greater) amplitude postural tremor as well as kinetic tremor, with the latter resulting in impairment of activities of daily living [6].

The UK Parkinson's Disease Society Brain Bank criteria require postmortem confirmation for the diagnosis of definite PD [7,8]. The diagnosis of probable PD requires bradykinesia and one of the following additional features: rigidity, 4–6-Hz rest tremor or postural instability (not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction) [7,8]. In addition, three supportive features are required [7,8]. The National Institute of Neurological Disorders and Stroke (NINDS) criteria for PD only include clinical criteria for possible PD, which require three out of four of the following features: rest tremor, bradykinesia, rigidity or asymmetric onset [9].

Based on the above criteria, one would think that there would be little clinical overlap between ET and PD, and that the diagnostic differentiation would be clear and straightforward. However, in practice, this is not always the case. Reasons for this difficulty will be discussed in detail below. In this discussion, we will continue to use the imprecise qualitative term 'clinical overlap', as published data on specificity and sensitivity of many of these clinical features in this setting (ET vs PD) do not exist.

Table 1. Tremor types (based on the activity state of the body region).

Tremor type	Definition
I. Rest	Occurs when voluntary muscle activity is absent
II. Action	Occurs with voluntary movement or sustained posture
a) Postural	Occurs when holding a body part motionless against the force of gravity
i) Reemergent	A particular type of postural tremor; when the patient holds their arms extended, the tremor commences after a variable latency of one to several seconds
b) Kinetic	Occurs with voluntary movement
c) Intention	Occurs with goal-directed movement and worsens as approaching the target

Bedside examination: distinguishing ET from PD

Although the aforementioned diagnostic criteria attempt to clearly delineate ET from PD, it is not uncommon for patients with ET to exhibit 'PD signs' and, conversely, for patients with PD to exhibit 'ET signs'. This overlapping of neurological signs is a source of diagnostic uncertainty. Clinicians should both be aware of this potential for overlap and look for the specific features that point to the correct diagnosis of ET or PD. Below, we address a number of common clinical misperceptions about these two diseases; these misperceptions fuel the diagnostic confusion. In doing so, we will review the neurological findings classically associated with PD and ET, as well as the subtle findings on examination that help to further distinguish the two disorders.

Misperception #1: 'Rest tremor = PD & not ET'

Rest tremor is a cardinal feature of PD, and resolves upon initiation of movement. When it is accompanied by bradykinesia and rigidity, PD is high in the differential diagnosis. The proportion of PD patients with rest tremor has been reported to be 90% in clinical series [10] and 76–100% in postmortem series [11,12]. Patients with PD may also have tremor-predominant PD, in which rest tremor occurs in the relative absence of other signs of akinesia and rigidity.

While rest tremor is highly suggestive of a diagnosis of PD, rest tremor may also be seen in some settings in certain ET patients, with different studies reporting prevalence values of 19, 19, 22 and 30% [13–16]. Rest tremor in ET typically occurs in the arm in contrast to PD, where it may occur in the arm, leg or both [12]. One study, at a tertiary referral center, reported rest tremor in 12/64 (19%) ET cases [13]. The rest tremor was bilateral in eight cases; it was also asymmetric in eight cases [13]. ET cases with rest tremor had longer disease duration than those without rest tremor (32.1 ± 24.5 vs 19.6 ± 16.8 years) [13]. ET cases with rest tremor also had more severe postural and kinetic tremor and were more likely to have head tremor than those without rest tremor [13]. Another study of nine ET cases with rest tremor reported a median disease duration of 42 years [15]. All cases had moderate to severe action tremor of the arms and cranial (head, jaw or voice) tremor [15]. Rest tremor was bilateral in seven cases, and in five cases, the side with more severe rest tremor was concordant with the side with more severe action tremor [15]. One study at a tertiary referral center compared 38 PD patients with 11 ET

patients with rest tremor [17]. The intensity of rest tremor was compared in two states: while walking and while seated [17]. In the majority of patients with PD, rest tremor increased in intensity while walking; in contrast, rest tremor decreased in intensity in all patients with ET while walking [17]. This study suggests that observing rest tremor in different states (while the patient is seated, while walking) may help in distinguishing patients with ET from patients with PD.

Clinical pearl #1: While rest tremor may be seen in 20–30% of patients with ET, it tends to occur in patients with more severe disease and disease of longer duration. In addition, it may differ qualitatively from the type of rest tremor that occurs in patients with PD.

Misperception #2: 'Action tremor = ET & not PD'

Action tremor is the hallmark feature of ET and can be further subdivided into postural, kinetic and intention tremors. Yet just as rest tremor may occur in patients with ET, conversely, action tremor may be found in patients with PD. Indeed, it is not uncommon to encounter patients with PD who have various forms of action tremor. Below, we discuss postural, kinetic and intention tremors separately.

The prevalence of postural tremor in patients with PD has been reported to be as high as 88–92% (the latter study only including PD patients with tremor) [18,19]. Studies have shown that the postural tremor in PD may be similar in frequency to the rest tremor in PD [19,20]. One hospital-based study, involving 11 PD cases and 10 ET cases, evaluated tremor using accelerometry [20]. Postural tremor amplitude was lower than that of rest tremor in six of 11 PD cases [20]. In that study, the postural tremor in PD cases had a mean amplitude that was 2.7-times higher than the postural tremor in ET cases [20]. Based on clinical experience, we have found that postural tremor of ET and PD may differ in several respects, although published data are lacking. First, the postural tremor in ET can involve oscillations around several joints, including the shoulder joint, elbow, wrist and fingers, whereas in PD, the more distal structures (especially fingers) are more typically involved. Indeed, the postural tremor of PD also can involve the more distal phalanges of the fingers, where a parkinsonian flexed posture may be present. Second, during arm extension, a flexion-extension tremor of the thumb, if it occurs, is more typical of PD, especially when other fingers are not exhibiting tremor. Third, the postural wrist tremor in ET typically involves a flexion-extension movement at the wrist; more often in PD, the tremor may include a component of wrist pronation-supination. Finally, the postural tremor of PD has been described as a re-emergent tremor, which occurs after a variable latency period after assuming an outstretched posture [21]. One study evaluated 18 PD cases, 20 ET cases and seven ET+PD cases at a tertiary referral center [21]. Twelve patients with PD had a re-emergent tremor, with a mean latency of 9.37 ± 10.66 s, and five patients with ET+PD had a re-emergent tremor, with a mean latency of 6.57 ± 8.24 s [21]. In contrast, only one patient with ET had a re-emergent tremor, with a latency of 1.29 s [21]. In patients with PD, the mean frequency of the re-emergent tremor was similar to that of their rest tremor (5.47 ± 1.24 vs 4.91 ± 1.32 Hz) [21]. Furthermore, the amplitude of the postural tremor in PD and ET+PD cases was higher than that of patients with ET as measured by acceleration at peak frequency (3.83 ± 6.82 and 11.20 ± 10.70 vs 0.52 ± 1.07 g^2) and root mean square amplitude (0.186 ± 0.115 and 0.28 ± 0.25 vs 0.051 ± 0.053 g) [21].

Kinetic arm tremor is another form of action tremor that is a classic feature of ET. One study evaluated kinetic and postural tremors in 50 ET cases ascertained from a tertiary referral center and 55 ET cases from a community [22]. All cases were evaluated using a clinical rating score, and a subset of cases was also evaluated by accelerometry [22]. Clinical rating scores were higher for kinetic than postural tremor in the clinic and community cases [22]. The electrophysiologic evaluation similarly demonstrated that the amplitude of kinetic tremor was six to seven times higher than that of the postural tremor in the clinic cases (mean amplitude during finger-nose-finger 2.91 ± 2.11 mm vs arm extension 0.51 ± 0.66; $p < 0.01$) and community cases (mean amplitude during finger-nose-finger 2.03 ± 1.12 mm vs arm extension 0.29 ± 0.25; $p < 0.01$) [22]. Kinetic leg tremor is also seen in ET (e.g., tremor observed during the toe–finger maneuver) and was clinically evaluated in 63 ET cases and 63 similarly aged controls [23]. Such tremor was observed in 44.4% of ET cases versus 14.3% of controls [23]. Kinetic leg tremor was associated with longer disease duration, advanced age of disease onset and the presence of head tremor [23]. While kinetic arm tremor is a classic feature of ET, it is also seen in patients with PD, and its prevalence was reported in one clinical series to be 48% [18]. One study evaluated tremor in 81 patients with PD, both clinically and with accelerometry [18]. In contrast to the situation in ET [22], the amplitude of kinetic tremor in PD was lower than that of the rest and postural tremors [18]. Another study evaluated kinetic tremor in 870 patients with PD by clinically grading tremor on spiral drawings [24]. Marked to severe kinetic tremor was seen in 47.1% of patients, and kinetic tremor was most frequently present in combination with postural and rest tremor [24].

Intention tremor (e.g., during the finger-nose-finger maneuver) can occur in patients with ET, with the prevalence variably reported to be 38.5, 46.8 and 59.0% [25–27]. One study evaluating 117 ET cases at a tertiary referral center found that cases with intention tremor had a longer disease duration compared with those without intention tremor [25]. In that study [25], ET cases with intention tremor had a higher overall action tremor score, and a greater proportion had voice and rest tremor. The severity of intention tremor correlated with disease duration [25]. Another study, which evaluated tremor in 79 outpatients with ET, used both clinical rating scales and accelerometry [26]. ET cases with intention tremor were older, and more often had head and trunk tremor than ET cases without intention tremor [26]. Furthermore, ET patients with intention tremor had significantly increased hypermetria compared with controls, as measured by vertical overshoot of the wrist (10.1 ± 4.8 vs 1.0 ± 0.8 mm; $p < 0.05$) [26]. Intention tremor in ET is not limited to the arms. One study described intention tremor of the head in 9.0% of clinically diagnosed patients with ET evaluated at a tertiary referral center [28]. The intention tremor involved the neck or chin and was noted in goal-directed activities such as

drinking from a cup or eating from a spoon [28]. The ET cases with intention head tremor had significantly more severe intention tremor of the arms compared with those without intention head tremor [28]. Intention tremor has less commonly been reported in PD patients. In one study, the prevalence of intention tremor was reported as 23% in patients with PD [18]. The amplitude of the intention tremor was lower than that of the postural and rest tremors in those patients with PD [18].

Clinical pearl #2: Although action tremor is the hallmark feature of ET, it is commonly found in patients with PD as well. When evaluating kinetic tremor in a particular patient, comparing it to other tremor types within that patient may help distinguish PD from ET. Thus, kinetic tremor is generally of greater amplitude than postural tremor in ET whereas the converse has been reported in PD. Intention tremor with limb dysmetria is more suggestive of ET than PD. Some of the clinical features of action tremor may similarly suggest one disorder or another. Thus, a postural tremor whose frequency is similar to the 4- to 6-Hz rest tremor of PD is suggestive of PD. A postural tremor with a significant latency (re-emergent tremor) is also more characteristic of PD.

Misperception #3: 'The tremor of ET is bilateral & symmetric'

Action tremor in patients with ET is usually, though not always, bilateral, and it is typically asymmetric [29,30]. In a community-based study of 54 patients with ET, the use of clinical rating scales revealed on average a 1.32-fold side–side difference, and quantitative computerized tremor analysis revealed on average a 1.71-fold (range: 1.00–4.33-fold) side–side difference in arm tremor severity [29]. Unilateral arm tremor is less common, reportedly occurring in 2, 4.4 and 10% of ET cases, with values varying depending on the criteria used [3,31,32]. One study evaluated unilateral arm tremor in 412 ET cases from 133 kindreds with presumed autosomal dominant ET [32]. Inclusion criteria required unilateral kinetic or postural tremor for at least 5 years, without dystonic posturing or bradykinesia/rigidity [32]. Only subjects with a first-degree relative with definite ET were included [32]. Eighteen (4.4%) patients were identified as having isolated unilateral arm tremor without tremor affecting other body segments [32]. Out of the 18 patients, 13 had a combination of postural and kinetic tremor and 5/18 had only unilateral postural tremor [32]. Isolated unilateral postural tremor should raise the suspicion of PD, and the patient should be followed closely for the development of additional signs suggestive of PD.

Clinical pearl #3: Action tremor in ET is often but not necessarily bilateral. Small to moderate side–side differences are the rule rather than the exception.

Misperception #4: 'Head tremor occurs in ET but not in PD'

Head tremor is observed in patients with ET, with the reported prevalence being dependent on the ascertainment of the cases. One study noted head tremor in 12% of patients in the community, 37% in a tertiary referral center and 54% in a brain repository [33]. Two studies evaluating factors associated with head tremor found that women with ET were four to six times more likely to have head tremor than men with ET [34,35]. The head tremor of ET is typically a postural tremor that resolves at rest (i.e., it disappears while patients are supine [36]). Yet head tremor is not unique to ET. Head tremor has also been described in PD patients; one study reported head tremor in 17% of clinically diagnosed PD cases [18]. Head tremor was described in detail in five clinically diagnosed PD cases [37]. The head tremor was present at rest (i.e., it persisted while they were supine), had a frequency similar to the 4–6-Hz rest tremor of the limbs and responded to levodopa [37]. None of the cases had voice tremor.

Clinical pearl #4: Head tremor often occurs in patients with ET but can on occasion also be seen in patients with PD. The head tremor of ET is typically one that resolves at rest (i.e., while supine), in contrast to what has been reported in PD.

Misperception #5: 'Jaw tremor = PD'

Jaw tremor is a type of cranial tremor that is classically associated with PD. It typically occurs when the mouth is closed (i.e., at rest). However, jaw tremor can also occur in ET cases. One study evaluated jaw tremor in ET and found a prevalence of 8% in a population-based sample, 10% in a tertiary referral sample and 18% in a brain repository sample [38]. The jaw tremor was predominantly a postural tremor (occurring during voluntary mouth opening) or kinetic tremor (occurring while speaking) [38]. Jaw tremor, was associated with older age, increased severity of arm tremor and the presence of head and voice tremor [38]. Jaw tremor was also more frequently associated with rest tremor of the arms [38], which raises the possibility of the future development of PD in those patients.

Clinical pearl #5: Jaw tremor may occur in either ET or PD, although in ET it is more typically a postural or kinetic tremor rather than a rest tremor.

Misperception #6: 'Bradykinesia = PD'

Bradykinesia is a cardinal sign of PD. Although bradykinesia is not traditionally associated with ET, there have been several studies that report the contrary. One study quantified rapid alternating pronation-supination movements in 10 ET cases, 20 mild to moderate PD cases (10 with predominant rigidity and 10 with tremor-predominant PD) and 10 controls [39]. *Post hoc* analysis demonstrated that rapid alternating movement cycle duration was statistically longer in ET cases compared with controls, and similar to PD cases [39]. Another study, involving 61 ET cases and 122 controls, evaluated performance in four timed tests involving hand movements, as well as walking and visual reaction time [40]. ET cases compared with controls had longer mean finger tapping times (right 7.6 ± 2.4 vs 6.4 ± 2.5 s, $p < 0.001$; left 10.0 ± 3.8 vs 6.9 ± 2.9 s, $p < 0.001$) and mean visual reaction times (right 564.6 ± 223.0 vs 393.7 ± 114.2 ms, $p < 0.001$; left 516.7 ± 224.5 vs 348.1 ± 96.5 ms, $p < 0.001$) [40]. Another study reported reduced arm swing in 18/136 (13.2) clinically diagnosed ET cases [41]. While a small proportion of ET cases may exhibit slower movement times than controls, a reduction in

amplitude and cessation of movement (pauses or freezing) during rapid successive movements has not been demonstrated in ET.

Clinical pearl #6: Slower movement times may be observed in some patients with ET, yet other features of bradykinesia (reduction in amplitude or freezing) have not been demonstrated in ET.

Common clinical conundrums

As noted above, although published diagnostic criteria attempt to clearly delineate ET from PD, patients with these two disorders often exhibit the same neurological signs. Furthermore, the neurological examination evolves over time within individual patients with these diseases, and patients may codevelop ET and PD. These issues may all result in diagnostic confusion. There are a number of difficult clinical situations during which confusion commonly occurs, and these will be highlighted in this section.

Clinical situation #1: ET+PD or just PD?

Clinical summary

A 60-year-old man develops a mild, right-greater-than-left postural arm tremor and an even milder right arm kinetic tremor. The postural tremor involves a pronation-supination movement of the forearm and also involves the fingers. Five years later, the patient develops right-sided rest tremor, rigidity and bradykinesia.

Commentary

This patient eventually meets the criteria for a clinical diagnosis of PD. The initial action tremor was postural greater than kinetic and involved pronation-supination at the wrist, which is more characteristic of the postural tremor in PD than ET. That tremor was likely an early manifestation of PD rather than ET. Hence, the diagnosis all along was likely to have been just PD.

Clinical situation #2: PD or PD+ET?

Clinical summary

A 65-year-old man with rest tremor and rigidity in the right arm is diagnosed with PD. Five years later, he develops a postural tremor of his right arm, which occurs after a latency of 10 s and a frequency similar to his 4-Hz rest tremor.

Commentary

A re-emergent tremor with similar frequency to the patient's rest tremor is consistent with a diagnosis of PD. There are no additional features to suggest ET.

Clinical situation #3: ET or ET+PD?

Clinical summary

A 40-year-old woman with a family history of ET develops a kinetic tremor and, a few years later, a postural head tremor. Her tremor worsens considerably such that she has severe and debilitating tremor by the age of 65 years. At 70 years of age, she also develops a tremor at rest with no other features of parkinsonism.

Commentary

This patient likely only has ET with isolated rest tremor, a feature that can develop in ET cases with longstanding and severe disease.

Clinical situation #4: ET+PD?

Clinical summary

A 45-year-old woman develops a bilateral action tremor than progressively worsens over the ensuing 15 years. Kinetic tremor is more severe than the postural tremor and she subsequently develops a postural head tremor. At 60 years of age, she develops a rest tremor in the right arm accompanied by bradykinesia (slow rapid alternating movements with loss of amplitude).

Commentary

The bilateral, progressive action tremor of long duration suggests ET and the subsequent development of a postural head tremor supports the diagnosis. The patient subsequently develops two parkinsonian signs, satisfying criteria for a clinical diagnosis of PD. The patient thus has a combination of ET+PD.

Laboratory evaluation: distinguishing ET from PD

Aside from the neurological examination, other investigations may aid the clinician in distinguishing ET from PD. One caveat is that studies of the sensitivity and specificity of many of these tests are lacking and further research is needed to develop a diagnostic gold standard.

Neurophysiological evaluation

Quantitative analysis of tremor can include accelerometry and surface electromyography (EMG). Two measures obtained with accelerometry are tremor frequency and amplitude. One study evaluated 22 PD and 20 ET cases with accelerometry and surface EMG, with limbs in various positions [42]. When tremor frequencies were pooled from all positions, more than 95% of PD cases exhibited frequencies in the 4–6-Hz range, and 95% of ET cases exhibited frequencies in the 5–8-Hz range [42]. Hence, while the ranges differed somewhat, there was considerable overlap [42]. Mean tremor amplitude was not significantly different between PD and ET in most positions [42]. Only when the arm was fully at rest was there a clear difference (i.e., in ET cases the tremor completely disappeared) [42]. Surface EMG measures muscle activity during tremor and may identify patterns of synchronous versus reciprocal, alternating activity of antagonist muscles. Studies involving surface EMG have identified both patterns in PD and ET cases, and thus do not distinguish the two diseases. One EMG study evaluated rest and postural tremor in 110 patients with PD [43]. Rest tremor was characterized by alternating EMG activity in all patients, but this was not the case with postural tremor, for which some patients had synchronous activity while others had alternating activity [43]. A study evaluating EMG patterns in ET cases found synchronous activity in 59% of ET cases in all limb positions and alternating activity in 41% of cases [44]. One other study compared these patterns of muscle activity in ET and PD cases; there was too much variability to make a definite conclusion [42].

Archimedes' spiral analysis can be accomplished by qualitative visual inspection at the bedside or quantitative computer analysis. One study evaluated the spirals of 27 ET cases by visual inspection and with computerized spiral analysis [45].

Two examiners (a neurologist and nurse practitioner) visually determined if the tremor waveform aligned along a single axis [45]. The neurologist identified a single axis in either hand in 79.3% of the cases and the nurse practitioner identified an axis in 75.9% of the cases [45]. In 95% of the right hand spirals with an axis, the axis corresponded to the numbers 2 and 3 on the face of a clock; 83.3% of the left hand spirals with an axis corresponded to 10–12 o'clock (a 90° angle to the right hand axis) [45]. Computerized spiral analysis detected a single axis in spirals of either hand in 96.6% of the cases [45]. By contrast, in PD multiple spiral axes are often present in each hand, yet the diagnostic validity (sensitivity, specificity, and positive-predictive value) of this evaluation is not known. Tremor severity, spiral diameter and spiral density can also distinguish ET and PD [46]. One study evaluated spirals in 103 PD cases and 41 ET, cases and found that tremor severity (0–10 rating scale) and spiral diameter were significantly greater in ET cases (mean diameter at five turns:4.4 vs 3.6 cm; $p < 0.01$) [46]. Spiral density, measured by the total number of turns divided by the horizontal spiral diameter, was significantly greater in PD cases (mean: 7.3 vs 3.3 completed turns per dm^2; $p < 0.013$) [46]. However, the diagnostic validity of this assessment, as a discriminator of ET versus PD, requires additional study.

Neuroimaging

The dopamine transporter (DAT) is a presynaptic protein that is used as a biomarker for dopaminergic nigrostriatal neurons. Single-photon emission tomography (SPECT) with cocaine derivative tracers binding to DAT can thus be used as a measure of dopamine deficiency. Several studies have evaluated the utility of a DAT-SPECT scan in distinguishing PD and ET [47–50]. A large, multicenter European DAT-SPECT study of 158 cases with parkinsonism (idiopathic PD, multiple system atrophy, progressive supranuclear palsy), 27 ET cases and 35 controls, found that the institutional reading correctly classified 97.5% of parkinsonism cases, 100% of ET cases and 97.1% of controls [48]. Yet another multicenter study demonstrated that visual inspection of DAT-SPECT scans had a sensitivity of 98% and a specificity of only 83% for distinguishing parkinsonian syndromes (PD and progressive supranuclear palsy) from individuals without a parkinsonian syndrome (ET cases and healthy controls) [49]. Five out of 14 (35.7%) ET cases in that study were misclassified as having a parkinsonian syndrome, indicating the diagnostic limitations of the method [49]. There have been additional studies that have demonstrated DAT-SPECT scans with decreased radiotracer uptake in ET cases as well. A study compared DAT-SPECT scans in 32 patients with ET, 47 patients with tremor-predominant PD and 31 controls [51]. ET cases had decreased uptake compared with control subjects although not as severe as that seen in PD cases, leading the investigators to conclude that some patients with ET may have mild abnormalities of striatal DATs [51]. In a follow-up study involving this cohort, a subset of cases had two DAT-SPECT scans at least 3 years apart [52]. Compared to the original study, there was no significant difference in mean uptake between ET and control subjects at baseline or follow-up, and no loss of uptake in ET cases over time; however, there was considerable overlap of contralateral caudate uptake values between PD and ET cases [52]. These studies [49,51,52] indicate that DAT-SPECT scans may be abnormal in ET, although not as severely as seen in PD, and point to some of the potential diagnostic limitations of this method when attempting to distinguish ET from PD. Indeed, the follow-up study discussed above indicated that 30% of ET cases would have been misclassified as PD based on the initial scan and 5% based on the follow-up scan [52].

Response to treatment

Clinicians sometimes use the symptomatic response to treatment to support a suspected diagnosis (i.e., the notion of the 'diagnostic-therapeutic trial'). The response of parkinsonian rest tremor to anticholinergic agents, dopamine agonists and levodopa is well documented. For example, tremor response to several medications was evaluated in one study involving nine patients with PD [53]. Trihexyphenidyl (8 mg daily) reduced mean rest tremor amplitude, assessed by accelerometry, by 59.4 ± 11.8%, and carbidopa-levodopa (25/100 three times daily) reduced mean rest tremor amplitude by 54.6 ± 9.8% [53]. Another study evaluated the efficacy of dopamine agonists and levodopa in 85 patients with PD; each of the patients had a rest tremor score >3 in one limb on the Unified Disease Parkinson's Disease Rating Scale Part III (UPDRS III) [54]. Treatment response was defined as a sustained (≥3-month) decrease of at least two points in the UPDRS rest tremor score in one limb [54]. Thirty-six (42.4%) patients were in the responder group and 49 (57.6%) were in the nonresponder group [54]. The treatments for the tremor of ET are also well documented and were the subject of a recent practice parameter; they include several β-adrenergic blocking agents [55]. Yet clinicians should be cautious when using treatment response to β-adrenergic blocking agents to distinguish ET from PD. For example, the effect of nadolol, a β-adrenergic blocking agent, was assessed in eight patients with PD in a double-blind, placebo-controlled crossover study [56]. Accelerometer readings showed a progressive reduction in tremor amplitude with increasing nadolol dosage [56]. The maximum benefit was noted at 240 mg/day, when resting tremor improved 50% [56]. Physician ratings confirmed these accelerometric findings [56]. The results suggest that response to β-adrenergic blockade may not differentiate between ET and PD.

Genetics

During the past 10 years, there has been increasing interest in the search for susceptibility genes for PD and ET. A number of genetic forms of PD have been identified, including both autosomal dominant and recessive forms [57]; however, genetic testing is not used for diagnostic purposes and is not used to distinguish PD from ET. Indeed, the genetic causes of ET are not as well-defined. Linkage studies have identified three genetic loci in ET families [58]. In 2009, a genome-wide association study reported an association between a variant in the *LINGO1* gene and ET [59]. While further studies also demonstrated this association, not all studies have been confirmatory [58]. Interestingly, in several

studies, variants in the *LINGO1* gene have also been associated with PD as well [58].

Studies of olfaction

Numerous studies have demonstrated olfactory dysfunction in PD [60–62]. Olfactory dysfunction has also been identified in patients with ET in some but not other studies. One study of 37 ET cases and 37 controls found the mean University of Pennsylvania Smell Identification Test (UPSIT) score to be lower in cases versus controls [63]. Furthermore, 27% of ET cases had severe microsmia or anosmia [63]. There was no correlation between UPSIT score and tremor severity or disease duration [63]. An expansion of this study including 97 ET cases and 92 controls again found a lower UPSIT score in ET cases than controls [64]. One study involving 723 subjects compared olfaction in PD, ET and control groups [62]. Subjects with clinically probable PD had significantly lower UPSIT scores compared with the controls but there was no significant difference in UPSIT scores between ET cases and controls [62]. Another study evaluated olfaction in 59 ET cases, 64 tremor-predominant PD cases and 245 controls [65]. PD cases had a mean UPSIT score that was 13.8 points lower compared with the ET group as a whole [65]. An UPSIT score of 25 had a sensitivity of 83% and specificity of 94% for distinguishing tremor-predominant PD from ET and controls [65]. Based on the above studies, olfactory impairment may be present in ET, as well as occasional microsmia, but not to the same extent as seen in PD. The diagnostic utility of olfactory testing in distinguishing ET from PD remains to be fully explored.

Postmortem study

Postmortem pathological findings are instructive and can supplement clinical information; however, they should not be interpreted in isolation. The pathological hallmark of PD is neuronal loss in the substantia nigra pars compacta and the presence of neuronal inclusion bodies composed of the presynaptic protein α-synuclein. These inclusions can be thread-like Lewy neurites or globular Lewy bodies. Braak staging describes initial Lewy body formation in the dorsal motor nucleus of cranial nerves IX/X, the intermediate reticular zone and anterior olfactory nucleus [66]. The pathological changes ascend the brainstem, eventually in Stage 3 of the disease affecting the substantia nigra pars compacta, corresponding to the manifestation of motor signs [66]. The pathological changes may continue to spread to the anteromedial temporal mesocortex and neocortex [67].

The study of the pathological changes in ET is in its infancy relative to that of PD. Few quantitative controlled studies have been performed. Studies at the Essential Tremor Centralized Brain Repository have indicated that the majority of ET cases have postmortem changes in the cerebellum, with these changes including a reduction in the number of Purkinje cells, an increase in the number of Purkinje cell dendritic and axonal swellings, and reactive changes in the basket cell axonal processes [68–70]. A smaller proportion of the brains have brainstem Lewy bodies, predominantly in the locus coeruleus, thus expressing a different pattern than that seen in PD [68]. The presence of Lewy bodies has been found in some but not all postmortem studies of ET [71]. As can be seen from the above data, the postmortem features of PD and ET are quite different. However, they do not aid in the diagnosis during life.

Conclusion

Distinguishing ET from PD is important in terms of selecting the appropriate therapy as well as counseling patients about disease progression. When a patient meets all of the diagnostic criteria for ET or PD, separating the two diseases is relatively straightforward. When signs of both diseases occur, particularly when there is a combination of tremor types, diagnosis becomes more difficult. It is important to be aware of the various bedside features than can help the examining clinician to distinguish the two diseases from one another. The role of laboratory tests can further distinguish the two groups, although no single ancillary test is able to do that to perfection.

Expert commentary

When a clinician is faced with distinguishing between ET and PD, they must primarily rely on clinical examination. As the same types of tremor may occur in both disorders, the clinician should be aware of patterns suggestive of ET versus PD and categorize accordingly. Nonetheless, this is still a best estimate; clinical features may evolve or new signs may develop and the diagnosis may need to be revised accordingly. A diagnosis of ET PD should only be assigned when a patient fulfills the clinical criteria for each individual diagnosis. When there is diagnostic uncertainty, objective testing may provide useful information. These tests mentioned above have not been rigorously studied in controlled settings and should be taken into consideration along with the overall clinical picture. While there are no standardized published values, patterns suggestive of ET versus PD are described. DAT-SPECT imaging may be helpful in distinguishing parkinsonism from ET but the clinician must be aware of overlapping values and the limitations of qualitative results in particular. With more experience and research involving ancillary testing, their diagnostic accuracy will increase. Long-term follow-up of clinical cases including postmortem evaluation can help ascertain the accurate diagnosis. Accurately distinguishing between ET and PD enables the clinician to recommend appropriate symptomatic therapies.

Five-year view

Further research into objective diagnostic tests for ET and PD can lead to earlier and more accurate diagnosis. Controlled studies of neurophysiologic testing involving accelerometry, surface EMG and spiral analysis may serve to better define the diagnostic utility of these tests. These measures may become more readily accessible outside of research laboratories both in terms of technical complexity and cost. Further experience with DAT-SPECT imaging is needed to establish standard quantitative values distinguishing ET from PD. Continued postmortem analysis of ET brains will lead to a greater understanding of the neuropathology of that disease and, hopefully, the development of disease-modifying therapies.

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Key issues

- Rest tremor may be seen in as many as 20–30% of patients with essential tremor (ET), although it tends to occur in patients with more severe disease and longer disease duration.
- Action tremor can be seen in patients with ET and patients with Parkinson's disease (PD). Kinetic tremor tends to be of greater amplitude than postural tremor in ET. Postural tremor similar in frequency to a 4–6-Hz rest tremor is suggestive of PD. A postural tremor with a significant latency upon assuming an outstretched position (re-emergent tremor) is suggestive of PD.
- Head tremor often occurs in ET but has also been described on occasion in PD, where it persists at rest. Jaw tremor may occur in ET or PD; jaw tremor in ET is more typically a postural or kinetic tremor rather than a rest tremor.
- Bradykinesia has been described in patients with ET; however, decrementing amplitude and freezing as seen in PD has not been described in ET.
- As clinical features evolve, the diagnosis may need to be altered, as there may be a coexisting diagnosis of PD and ET within the same patient.
- Neurophysiology involving accelerometry, surface electromyography and spiral analysis can provide objective measures of tremor with certain patterns suggestive of ET versus PD.
- Dopamine transporter imaging may help distinguish between PD and ET, but this imaging modality has its diagnostic limitations.
- Olfactory testing can be abnormal in both PD and ET, thus limiting the diagnostic utility of this test.
- The pathological hallmark of PD is neuronal loss in the substantia nigra pars compacta and neuronal inclusion bodies composed of α-synuclein. Studies of ET pathology to date have mainly demonstrated cerebellar changes, and a smaller proportion of cases have brainstem Lewy bodies predominantly in the locus coeruleus.

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