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The relationship between essential tremor and Parkinson's disease

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ABSTRACT

Essential tremor (ET) and Parkinson's disease (PD) are the two most common tremor disorders encountered in a movement disorders clinic. Although distinct clinical-pathological entities, both disorders may share overlapping features in addition to rest and postural tremor, such as bradykinesia, rigidity, gait and balance impairment and some non-motor signs. A subset of patients may have a combination of long-standing ET with subsequent PD (ET-PD). There are several lines of evidence from clinical, epidemiologic, imaging, genetic and pathologic studies supporting a link between ET and PD, greater than by chance alone. In this review we will discuss the latest data supporting a relationship between ET and PD and the implications for possible pathogenic link and treatment.

1. Introduction

Collectively, essential tremor (ET) and Parkinson's disease (PD) represent the two most common tremor disorders in adults. The prevalence of ET is estimated to be 0.9% and this increases to 4.6% in individuals ≥65 years old [1]. The prevalence of PD is estimated to be 0.3%, increasing to 1% in individuals ≥60 years [2]. Although it has been suggested for decades that ET and PD are related beyond mere chance co-existence, this association is still considered controversial by some clinicians [3–5] (Fig. 1). In this review, we will discuss published data regarding the relationship between ET and PD in terms of clinical features, epidemiology, imaging, genetics and pathology.

2. Clinical features

Several studies have reported that patients with asymmetric, childhood-onset ET, when they later developed PD-related rest tremor, that tremor usually started on the same side as the more severe ET [6,7]. The relationship between pre-existing ET and subsequent PD is discussed further in the section on Epidemiology.

While ET is defined by the presence of action tremor and PD is characterized by rest tremor, it is well recognized that the two disorders often have both types of tremor and have other overlapping clinical features [4,8] (Table 1). Action tremor, both postural and kinetic, is not uncommon in PD and can be seen in up to 90% of PD patients [8]. Re-emergent tremor, a form of postural tremor that 'emerges' after a certain latency of maintaining the arms in a horizontal posture, is classically associated with PD. When compared with ET, the latency of re-emergent tremor is considerably longer in PD compared to those with ET, and may not become apparent for up to 2–3 min (or even longer) of postural holding. The mean frequency of the re-emergent tremor present when arms are held in outstretched or "wing-beating" position is typically similar to that of the rest tremor. Kinetic tremor can be seen in both disorders but, intention tremor, present when the limb approaches the target, is more common in ET than PD.

In addition to tremor, other overlapping clinical features between ET and PD include bradykinesia, rigidity (sometimes manifested by cogwheeling only), gait and balance disorder and a variety of non-motor features. Because of the overlapping clinical features, differentiating between PD and ET can be challenging, especially early on in the disease course [8].

Rest tremor can be seen in ET without necessarily invoking the diagnosis of PD and has been reported in up to 30% of ET patients [9]. One study identified 12/64 (18.8%) ET patients who had rest tremor and, compared to the 52 ET patients without rest tremor, they had a longer disease duration, greater tremor severity and more widespread distribution of tremor, including head tremor, which is almost never seen in patients with PD without co-existing ET [9].

While head tremor is classically associated with ET, and jaw tremor with PD, both types of cranial tremor have been occasionally described in either ET or PD. The rare occurrence of head

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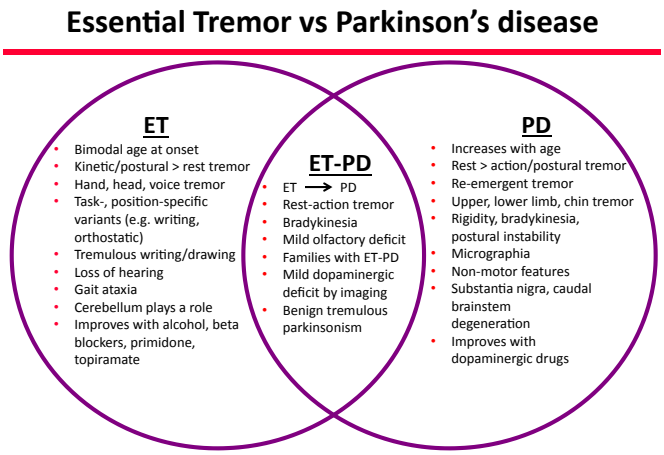

Fig. 1. The overlap between essential tremor and Parkinson's Disease. ET = essential tremor, PD = Parkinson's disease.

tremor was documented in five patients with clinically diagnosed PD [10]. The head tremor was present at rest and resolved with action; its frequency of 4–6 Hz was very similar to that of the limb tremor. Furthermore, the head tremor was responsive to levodopa, suggesting that, like other PD rest tremors, it was related to underlying dopaminergic deficiency. Jaw tremor, typically present in patients with PD, has been also described in ET, and has been associated with older age, the presence of voice and head tremor and greater severity of action tremor in the hands [11]. Furthermore, jaw tremor had a greater prevalence in ET patients with rest tremor 4/14 (28.6%) compared to those without rest tremor 15/193 (7.8%).

Additional parkinsonian signs such as bradykinesia have been also described in ET patients [12]. One study compared 61 ET patients and 122 controls, and found significant impairment in ET patients in terms of repetitive finger movements and visual reaction time, indicating that some ET patients may have an element of underlying bradykinesia [12].

Gait and balance impairment has been described in ET patients including reduced cadence and speed, as well as difficulties with tandem gait and postural instability [13]. Overall, the gait pattern in ET patients differs from that seen in PD patients and suggests underlying cerebellar dysfunction. A study involving 30 ET cases and 25 controls, evaluated balance during normal and tandem gait [13]. During normal gait, there was increased step width that correlated with midline tremor severity. During tandem gait, ET cases demonstrated greater missteps and postural sway and decreased gait velocity. Furthermore, several measures of gait impairment correlated with advancing age.

Although prior studies of the ET-PD relationship assumed that ET precedes PD, in many cases ET may emerge in a patient who already has the cardinal symptoms of PD. We find the following features helpful in diagnosing ET in patients with pre-existing PD: family history of ET, family history of alcoholism, no latency when testing for re-emergent tremor, and the presence of head, voice and writing tremor, including ET-like drawing of a spiral.

3. Epidemiology

There have been several studies demonstrating an association between ET and PD greater than expected in the general population [14–16] (Table 2). In one of our earlier studies we evaluated 130 patients with ET, and identified 25 (19%) subjects with parkinsonian features consistent with an additional diagnosis of PD [14]. Other studies of the prevalence of PD in ET cohorts have reported lower values of 6.1% of 678 ET patients [17] and 8.7% of 357 patients [18]. A prospective, case-control study in Singapore found a higher prevalence of ET in PD patients (12/204, 5.9%) compared to diseased controls with hemifacial spasm (2/206, 1%) and healthy controls (1/190, 0.5%) [15]. A regression analysis, adjusted for age and gender, found that PD patients had a greater odds of having ET compared to diseased (OR = 5.43, 95% CI 5 = 1.16, 25.39, $P < 0.001$) and healthy controls (OR = 10.87, 95% CI = 1.39, 85.15, $P < 0.001$). Furthermore, 25% of the ET-PD patients had a family history of ET. ET-PD patients had an older age at onset of PD, less severe PD and were on lower doses of levodopa compared to PD patients without ET. One of the most important epidemiological studies addressing the ET-PD relationship was a population-based cohort study of 3813 subjects ≥age 65 in central Spain which found that ET patients were 4 times more likely to develop PD compared to controls [16]. After a median of 3.3 years, six (3.0%) of 201 ET cases developed incident PD vs. 24 (0.7%) of 3574 controls (adjusted RR 4.27, 95% CI 1.72 to 10.61; $p = 0.002$). The mean latency between the onset of ET and subsequent PD was 8.7 years.

PD patients, particularly those with tremor-dominant PD, have a greater frequency of a family history of ET compared to controls. A population-based study in Olmsted County, Minnesota demonstrated an increased risk of ET in family members of PD ≤66 years of age (hazard ratio = 2.24; 95% confidence interval (95% CI) = 1.26–3.98; $p = 0.006$) [19]. Amongst 2684 first-degree relatives of 411 PD patients referred to Mayo Clinic, the risk of a family history of ET was greater in PD patients who were men, who had a younger onset of PD and with a tremor-dominant or mixed form of PD. A prospective, case-control study of 303 PD probands and 249 controls in Greece, found a greater frequency of ET in family members of PD patients compared to controls (OR:3.64, $p < 0.001$) [20]. Again, the odds of having ET were greater when the proband

Table 1
Clinical features. ET = Essential Tremor, PD = Parkinson's Disease, UPSIT = University of Pennsylvania Smell Identification Test.

Cohen et al., 2003 [9]	12/64 (18.8%) ET patients had rest tremor that was associated with longer disease duration, greater tremor severity and presence of head tremor.
Louis et al., 2006 [11]	Although jaw tremor is typically associated with PD, jaw tremor was identified in ET patients in 7.5% of a population sample, 10.1% in a tertiary referral center, and 18.0% in brain repository sample. Jaw tremor in ET was associated with older age, more severe hand action tremor, head and voice tremor and the presence of rest tremor.
Roze et al., 2006 [10]	Head tremor is typically found in patients with ET but it was reported in 5 cases of PD and was dopa-responsive and had similar frequency to tremor in limbs (4–6 Hz).
Jimenez-Jimenez et al., 2010 [12]	ET patients had greater motor impairments in repetitive finger movements and visual reaction time compared to controls.
Hoskocova et al., 2013 [13]	Compared to controls, ET subjects had slower tandem gait, more missteps during tandem and greater postural sway. During normal gait, increased step width in ET patients correlated with midline tremor severity.
Minen and Louis 2008 [7]	ET-PD patients had a male predominance similar to PD. The side of greatest PD severity corresponded to side of greatest ET severity.
Simoes et al., 2012 [22]	ET-PD patients had less widespread tremor compared to ET patients and required fewer ET medications. ET-PD and PD patients had similar UPDRS, Hoehn and Yahr and Schwab and England Scores.

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Table 2
Epidemiologic studies. ET = Essential Tremor, PD = Parkinson's Disease.

Geraghty et al., 1985 [14]	25/130 (19%) ET patients had a diagnosis of PD. The prevalence of PD in this group of ET patients was 24 times greater than expected in a population ≥age 60.
Koller et al., 1994 [17]	6.1% of ET subjects in specialty, university and private practice locations had an additional diagnosis of PD, more than expected in the general population.
Shahed et al., 2005 [21]	Out of 225 ET-PD patients at a tertiary movement disorders center, 22 had onset of ET prior to age 20. PD symptoms began on the side with more severe ET-tremor.
Rocca et al., 2007 [19]	In a population-based study, risk of ET was increased in relatives of patients with PD onset ≤66 years hazard ratio [HR] = 2.24; 95% confidence interval [95% CI] = 1.26–3.98; p = 0.006. In the referral-based sample, the risk of ET was greater in relatives of younger onset PD subjects and in relatives of tremor-dominant or mixed PD compared to akinetic-rigid. The risk of ET was also greater in male relatives
Tan et al., 2008 [15]	ET was more frequent in PD subjects (12/204, 5.9%) than diseased (2/206, 1%) or healthy controls (1/190, 0.5%).
Benito-Leon et al., 2009 [16]	In this population-based cohort study 12 (5.8%) of 207 ET cases developed parkinsonism vs. 56 (1.6%) of 3606 controls (adjusted relative risk (RR) 3.47, 95% CI 1.82 to 6.59; p < 0.001). Six (3.0%) of 201 ET cases developed PD vs. 24 (0.7%) of 3574 controls (adjusted RR 4.27, 95% CI 1.72 to 10.61; p = 0.002).
Spanaki and Plaitakis, 2009 [20]	ET present more often in 1st degree relative of PD patients compared to controls (OR:3.64, p < 0.001). The risk of ET was greater when proband had tremor-dominant or mixed PD (OR: 4.48). 12 subjects had ET-PD.

had tremor-dominant or mixed PD (OR: 4.48).

The characteristics of ET-PD patients have been evaluated in several studies. One study evaluated a group of 22 ET-PD patients with childhood-onset ET [21]. Of the 11 patients with asymmetric ET, 10 reported onset of PD on the side with more severe ET (90.9%, $X^2 = 0.66$, p = 0.024) and change in tremor was the first sign of PD reported in 68.2% of patients. Another study compared the clinical characteristics of 53 patients with ET-PD compared to 53 PD and 150 ET patients [7]. The mean latency from reported onset of ET to first sign of parkinsonism on examination was 14.0 ± 15.0 years (median 6.0 years, range 0.5–52.0 years). The percentage of males affected in the ET-PD group was identical to that of the PD group (67.9% male), but was greater than that in the pure ET group (50.0% male, P = 0.02). The first sign of PD was rest tremor in 100% of the ET-PD subjects and the laterality of PD severity corresponded to the more severely affected side with ET. A 2012 retrospective study, reviewed the motor phenotypes of 18 ET-PD patients compared with 20 ET and 30 PD patients of similar age and disease duration [22]. Compared to ET patients, ET-PD patients had less widespread postural and kinetic tremor (2/17 [11.8%] vs. 11/17 [64.7%]; p = 0.001), had less evidence of cerebellar dysfunction (nystagmus, intention tremor or dysmetria) (1/15 [6.7%] vs. 6/18 [33.3%], p = 0.06), and were on fewer ET medications. There was no significant difference in UPDRS, Hoehn and Yahr, or Schwab and England scores (p > 0.14) between ET-PD and PD patients.

4. Imaging

Although single-photon emission tomography (SPECT) scans using ligands that bind to the presynaptic dopamine transporter (DAT) have been used to distinguish ET from parkinsonian disorders, a few studies have demonstrated reduced DAT uptake in ET cases as well. One study evaluated DAT-SPECT in 32 ET cases, 47 tremor-dominant PD and 31 controls [23]. While ET patients had a greater uptake compared to PD (50% putamen and 21% caudate, p < 0.001), ET cases had a lower uptake compared to controls (15% putamen and 21% caudate, p < 0.05). A follow-up scan in a subset of ET patients 3 years later did not demonstrate a loss of uptake over time and there was no significant difference in uptake between ET cases and controls at follow-up [24]. However, there was overlapping ET and PD uptake abnormalities in the caudate nucleus. In one study, 39 ET patients with and without parkinsonian features and 13 healthy controls underwent detailed examination by a movement disorders neurologist and 123-I ioflupane SPECT (DaTscan), analyzed by two independent radiologists "blinded" to the clinical diagnosis using semi-quantitative calculation of striatal binding ratios in different volumes of interest [25]. The study found evidence of minimal dopaminergic deficit in the caudate nucleus of ET patients. Although this pattern is different from that of PD, in which the putamen is more involved than the caudate, it suggests that some ET patients have a subtle dopaminergic deficit.

5. Genetics

Although ET is widely accepted to be a genetic disorder, no specific disease-causing gene or genes have been identified. In contrast, PD is largely a sporadic disorder, although several PD-causing gene mutations have been found. Furthermore, families in which some members have ET and others have PD have been described [26]. The leucine-rich repeat and Ig domain containing 1 gene (*LINGO1*) has been associated with ET and some studies have also suggested an association with PD. A review of the studies evaluating *LINGO1* suggests that there is stronger evidence for a link between *LINGO1* and ET than with PD [27]. Variants of *LINGO2*, a homolog of *LINGO1*, have also been associated with ET and PD in North American and Asian populations. More recently, whole exome sequencing of a six-generation Turkish kindred with ET and PD identified HTRA2 p.G399S associated with both conditions [28]. ET developed in individuals who were either heterozygous or homozygous for the allele. Homozygosity was associated with earlier age at onset and greater severity of postural and kinetic tremor. Parkinsonian signs developed in middle-aged individuals who were homozygous for the allele. The significance of this allele remains to be determined. These and other recently reported gene mutations or variants found to be associated with ET, such as *TENM4, NOS3, KCNS2, HAPLN4* and *USP46*, should be also explored in patients with PD.

6. Neuropathology

Although highly controversial, a pathological link between ET and PD has been suggested by the finding of Lewy bodies in a proportion of ET cases. A case control study involving 33 ET brains and 21 controls found Lewy bodies in 8/33 (24.2%) ET brains compared to 2/21 (9.5%) controls [29]. Six ET cases had Lewy bodies located predominantly in the locus coeruleus; the two other cases had more widespread Lewy bodies and were given an additional diagnosis of PD. ET cases with Lewy bodies were older (average 5.6 years) than ET cases without Lewy bodies. Other pathologic studies have not demonstrated an increased frequency of Lewy bodies in ET subjects, and some have argued that this finding represents an incidental Lewy body disease. The investigators in the Sun Health Research Institute and Body Donation Program examined 23 brains from ET patients both pathologically and chemically and concluded that "The hypothesis that ET represents early PD was not supported, as striatal dopaminergic markers were not reduced compared with

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control subjects" [30]. The interpretation of their data, however, seems to be flawed for several reasons. First, the mean age in the pathological series was 86.2 years and the mean duration of tremor was 11.1 years, suggesting that the mean age at onset of ET in their patients was about 75 years, which is substantially later than the usual mean age at onset of ET of 25 years. Furthermore, patients with prior history of a movement disorder, including those with parkinsonian features, were excluded, thus, by definition, clinical, pathological, or biochemical evidence of PD could not be demonstrated in this selected ET population.

7. Conclusion

The evidence supporting a link between ET and PD continues to accumulate. Greater understanding of this association will allow clinicians to better counsel their ET patients regarding their risk for developing PD. Identifying clinical characteristics that increase the risk for this progression from ET to PD may help in the development of potential disease-modifying therapies.

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