

Review

The Relationship Between Parkinson's Disease and Essential Tremor: Review of Clinical, Epidemiologic, Genetic, Neuroimaging and Neuropathological Data, and Data on the Presence of Cardinal Signs of Parkinsonism in Essential Tremor

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Abstract

Background: The possible relationship between essential tremor (ET) and Parkinson's disease (PD) has been controversial since the first description of PD. However, there is increasing evidence suggesting an overlap between these two disorders. The aim of this review is to examine the relationship between PD and ET, focusing on clinical, epidemiologic, genetic, neuroimaging, and neuropathological data, and the presence of cardinal parkinsonism symptoms in ET.

Methods: We conducted a PubMed search for articles published between 1966 and November 2011 regarding the relationship between ET and PD and the presence of postural tremor in PD patients; the presence of rest tremor, rigidity, and slowed movements in ET patients is reviewed.

Results: Clinical series, follow-up studies of ET patients, and case-control and genetic epidemiological studies indicate that ET is associated with increased risk for PD. Some neuroimaging studies and neuropathological reports suggest an association between the two diseases. ET patients show high prevalence of rest tremor, and at least seven studies described slowed movements (possibly related to cerebellar dysfunction and/or bradykinesia) in patients with ET.

Discussion: There is reasonable epidemiological and clinical evidence to support a link between ET and PD, although it is not clear what factors predict ET patient risk for developing PD or, more rarely, of PD patients developing ET. Future multicentric and multidisciplinary studies including epidemiological, clinical, neuroimaging, genetic, and neuropathological assessments are required to understand these associations.

Keywords: Essential tremor, parkinsonism, Parkinson's disease, rest tremor, bradykinesia

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Introduction

Essential tremor (ET) is probably the most common movement disorder and is characterized by a postural or kinetic 4–12-Hz tremor mainly involving the hands and forearms, although it can also affect the head, chin, and voice, as well as other locations.^{1,2}

A possible relationship between ET and Parkinson's disease (PD) has been debated for nearly 200 years. In 1817, James Parkinson,³ commented on the distinction between *paralysis agitans* and senile tremor (ET) in his seminal work *An essay on the shaking palsy*. However, in 1888 Gowers⁴ stated, “it is doubtful whether senile tremor is

essentially different from paralysis agitans,” and “some cases are met with a character intermediate between the two affections.” In 1949, Mjones⁵ suggested that ET was a “*forme fruste*” of PD, and Critchley⁶ stated that because both disorders were relatively common, the presence of ET or PD in family members and cases of concurrent PD might be due to chance. This has also been suggested by other authors.⁷ Recent systematic reviews describe epidemiological evidence supporting a link between ET and PD⁸ and evidence for overlap between these two disorders, particularly between ET and tremor-dominant PD.⁹

The aim of this review is to evaluate the current literature on the possible relationship between ET and PD, focusing on clinical, epidemiologic, genetic, and neuroimaging data. In addition, we considered studies of the presence of cardinal signs of PD (rest tremor, rigidity, and slowed movements/bradykinesia) in ET patients.

Search strategies

References for this review were identified by PubMed searches for papers published between 1966 and November 2011. The terms “essential tremor” and “Parkinson” were crossed with “Clinical,” “Epidemiology,” “Co-occurrence” or “Coexistence,” and “Family history.” The term “essential tremor” was also crossed with “rest tremor,” “rigidity,” “bradykinesia,” “slowing,” and “slow movements.”

Association between essential tremor and Parkinson's disease

Studies assessing PD frequency in clinical series of ET patients

In an epidemiologic study of ET in Papua, New Guinea, Hornabrook and Nagurney¹⁰ described the presence of rhythmic pill-rolling tremor with no other evidence of extrapyramidal dysfunction in seven patients, and indubitable signs of PD in 3 out of 175 patients diagnosed with ET; they reported that patients with ET had 35 times the risk of developing PD than individuals without ET. In a clinical series of 130 ET patients (19.2% with concomitant PD), Geraghty et al.¹¹ concluded that the risk of PD in this population was 24 times greater than expected. In the same clinic, Lou and Jankovic,¹² reported that 20% of 350 ET patients were thought to have parkinsonism. Our group reported that 8.7% of 357 patients who fulfilled diagnostic criteria for ET had concomitant PD (ET was present at least 2 years before PD diagnosis),¹³ and Koller et al.¹⁴ reported a frequency of concomitant PD in 6.1% of 678 ET patients.

Cleaves et al.¹⁵ described “mild extrapyramidal signs” in 4.5% of 237 ET patients, which were interpreted as consistent with normal aging. They also described a history of uncomplicated ET in 3% of 100 PD patients, suggesting a lack of association between PD and ET.

Clinical studies of patients with concomitant ET and PD

Shahed and Jankovic¹⁶ described the clinical features of 22 patients (17 males, 5 females) with childhood-onset ET who developed PD about 40 years later. Eighteen of them reported a family history of ET, and 13.6% described a family history of PD. In 10 of the 11 patients with asymmetric ET, PD symptoms began on the same side as the more severe ET. Rest tremor was the initial sign of PD in 71.4% of cases; rest tremor, bradykinesia, and rigidity were present in more than 90% of patients.

Minen and Louis¹⁷ studied the clinical features of 53 patients with combination of ET and PD who fulfilled diagnostic criteria for isolated ET prior to ET with PD. The latency from ET onset to the initial PD symptoms was less than 5 years in 38.5% of patients, and more than 20 years in 30.8%. All the patients had rest tremor, and most also had rigidity and limb bradykinesia as initial signs of PD. As previously reported by Shahed and Jankovic,¹⁶ the more severe ET corresponded

to the side with the more severe PD symptoms. These data suggest the possibility that a single pathological process underlies both ET and PD.

Studies assessing ET as a PD risk factor

In a retrospective study of medical records of all patients diagnosed with ET over a 45-year period (1935–1979) in Rochester, Minnesota, Rajput et al.¹⁸ found 266 incident cases. Six (2%) of these had an additional diagnosis of PD subsequent to the index date. Although this study did not include a control group, the authors hypothesized that the concurrent diagnosis of ET and PD was incidental based on the prevalence rate of PD.

In a retrospective hospital-based case-control study of 210 patients diagnosed with PD and 210 patients diagnosed with Parkinson-plus syndrome, Louis and Frucht¹⁹ found that PD patients were more likely to have had a prior diagnosis of ET than patients with Parkinson-plus syndrome (7.1% vs. 2.4%; odds ratio [OR]=3.16; 95% CI 1.13–8.85, $p=0.02$). This difference was even higher when the ET diagnosis was made by a neurologist at the clinic during the first visit.

Tan et al.²⁰ conducted a prospective case-control study in patients referred to a tertiary PD center and diagnosed by a movement disorders neurologist as having PD ($n=204$) for over 2 years. The control groups comprised patients with hemifacial spasm ($n=206$) who had been referred to the center in the same period, as well as healthy subjects ($n=190$). All of them were examined by the same movement disorders neurologist. They found a significantly higher frequency of PD in patients with a diagnosis of ET (5.9%) than in subjects with hemifacial spasm (1%, OR=6.4, 95% CI 1.5–22.7, $p=0.006$) or healthy subjects (0.5%, OR=11.8, 95% CI 1.9–71.3, $p=0.003$). ET diagnosis was made at least 3–5 years prior to the onset of PD or hemifacial spasm.

Benito-León et al.²¹ reported a prospective population-based study to estimate the incidence of PD in ET patients versus normal controls. The study sample included 3,813 elderly persons (65 years or older) who were examined by neurologists at baseline and 3.3 years later. The frequencies of incident parkinsonism and incident PD during that time interval were 5.8% (12 of 207 cases) and 3.0% (6 of 201) in ET cases, and 1.6% (56 of 3606) and 0.7% (24 of 3574) in controls, respectively (adjusted RR=3.47, 95% CI 1.82–6.59, $p<0.001$ for parkinsonism and RR=4.27, 95% CI 1.72–10.6, $p=0.002$ for PD).

Studies assessing family history of postural tremor or ET as a possible risk factor for PD

Roy et al.²² carried out a prospective study of 50 kindreds with familial PD, 50 kindreds with ET, and 50 kindreds originating from spouses of previous patients, and described a parkinsonism related to dominant ET in 34 kindreds (10% of all parkinsonians). In a subsequent publication, the same authors suggested that the presence of familial aggregations in 10–15% of PD cases was due to the existence of two well-defined familial subsets, one of which was termed “ET-related parkinsonism”.²³

Table 1 summarizes case-control studies and genetic epidemiological studies (family studies) assessing family history of postural tremor

or ET as a possible risk for PD. Although study design varied considerably, most of them suggested that family history of postural tremor or ET increases the risk for developing PD,^{15,25,29,30,32–35,38} although some authors did not confirm this^{24,27,28} or did not show increased frequency of PD in families with ET.⁴⁰ It is of note that although Cleaves et al.¹⁵ reported a lack of association between ET and PD, analysis of their data showed a significant association between family history of ET and risk for PD (Table 1).

Two family studies showed a significantly higher frequency^{31,38} and two others showed a non-significant trend towards a higher frequency^{37,39} of ET in relatives of PD patients than in relatives of controls. In one of these studies, the authors found a significantly increased risk for ET in relatives of PD patients, with onset of PD ≤ 66 years in a population-based sample and in relatives of PD patients with onset of PD ≤ 57 years in a hospital-based sample.³⁷ Costello et al.³⁹ found increased risk for ET in relatives of tremor-dominant PD cases.³⁹

After examining 543 individuals affected by definite ET or probable PD from 158 kindreds in which at least two individuals were classified as having definite ET, Hedera et al.⁴¹ identified 22 individuals with probable PD (20 of them with tremor-predominant PD) without ET from 21 different kindreds, suggesting a relationship between ET and tremor-predominant PD.

Functional imaging studies suggesting an association between ET and PD

Functional imaging study findings regarding a possible relationship between ET and PD are controversial. Although a number of imaging studies indicated clear differences between ET and PD in terms of basal ganglia involvement,^{42–44} other studies suggested some degree of overlap. In a study involving 11 patients with isolated rest tremor (nine of them with concomitant postural tremor) using ¹¹F-DOPA positron emission tomography, Brooks et al.,⁴⁵ showed reduced putamen uptake. They also found a 13% reduction of the mean putamen ¹¹F-DOPA uptake in patients with familial ET and a 10% reduction in patients with sporadic ET compared with controls. Some single-photon emission computed tomography (SPECT) studies using dopamine transporter (DAT) ligands, such as ¹²⁵I-beta-CIT or ¹²³I-ioflupane, have shown mild striatal dopaminergic deficits in patients with ET compared with controls, although it was less marked than in PD patients.^{46,47}

A recent report by Coria et al.⁴⁸ involving 167 patients with isolated action tremor employed a DAT-SPECT method and showed reduced striatal uptake in 68.3% of patients. Onset of tremor after 50 years and asymmetrical tremor distribution were predictive variables of nigrostriatal denervation, whereas gender; family history; and the presence of intentional, cephalic, or voice tremors were not.

Neuropathological data suggesting an association between ET and PD

At least two studies have suggested a pathological link between ET and PD. Yahr et al.⁴⁹ reported a multigenerational family comprised

of 36 members, including identical twins with early-onset ET who developed parkinsonism symptoms at age 50, which was proven to be PD at autopsy. Louis et al.⁵⁰ found Lewy bodies “far in excess of that reported in normal aging” confined to the locus coeruleus in a subgroup of ET patients.

Rest tremor and rigidity in essential tremor

It is possible that the controversy over the relationship of PD and ET is compounded by the difficulty distinguishing the two disorders. In fact, differential diagnosis between ET and tremor-predominant PD is often challenging because the typical tremor of PD occurs at rest but may be present with sustained posture, whereas the typical ET tremor is postural and/or kinetic but can also be present at rest in severe cases.^{51,52} A cardinal parkinsonian sign such as cogwheeling rigidity may also be seen in ET.^{53–55}

Rest tremor has been described in approximately 19% of ET cases,^{56,57} and occurs more frequently in patients with tremors that are more severe or of longer duration.⁵⁶ On the other hand, the reported prevalence of action tremor in PD patients is higher than 90%,^{58,59} although only 2% of PD patients fulfilled criteria for definite ET in one of these studies.⁵⁹

The significance of rest tremor in ET is uncertain. In a clinicopathological study conducted over 32 years of 20 cases with an initial clinical diagnosis of ET, Rajput et al.⁶⁰ reported that six of these cases developed clinical parkinsonism (rest tremor, rigidity, and bradykinesia) (two with progressive supranuclear palsy, one with Lewy body pathology, one with basal ganglia status cribosus, and two without neuropathological changes in which parkinsonism was attributed to neuroleptic drugs), and another six developed rest tremor (none of them had substantia nigra or basal ganglia pathology). The authors recognized some limitations to their study, such as the lack of detailed family history in all cases and the inclusion of selected cases (referral of complicated cases to their Movement Disorders Clinic) that could not be regarded as representative of ET cases in the general population. Their final conclusion was that the risk of PD in ET cases was comparable with that of the general population and that the presence of neuropathological changes of progressive supranuclear palsy in two cases was incidental comorbidity.

In another post-mortem study of nine ET cases with isolated rest tremor, Louis et al.⁶¹ used alpha-synuclein immunohistochemistry found an increased number of torpedoes and a decreased number of Purkinje cells in the cerebellar cortex; mild changes in the caudate, putamen, and globus pallidus; and sparse neuronal loss in the substantia nigra pars compacta (similar to that found in nine age-matched ET cases without rest tremor) without evidence of Lewy bodies or Lewy neurites in these structures (two cases presented Lewy bodies in the dorsal vagal nucleus and the locus coeruleus). These data suggest that isolated rest tremor in ET is not due to Lewy body pathology in the substantia nigra compacta and raises the possibility of a relationship with degenerative changes in the cerebellum observed in ET.

Table 1. Case–Control Studies and Genetic Epidemiological Studies Assessing Family History of Postural Tremor or ET as a Risk Factor for PD

Authors	Methodology/ Study Design	PD Patients	Controls	OR (95% CI) or HR (95% CI)	p-Value
		n (% with postural tremor)	n (% with postural tremor)		
Marttila et al. ²⁴	Population-based case–control study	444 (5.8%)	444 (8.1%)	0.71 (0.41–1.22)	0.188
Lang et al. ²⁵	Hospital-based case–control study	159 (17%)	104 (5.8%)	3.34 (1.25–9.41)	0.007
Marttila and Rinne ²⁶	Hospital-based case study	52 (2.03%) (All early onset PD)	No control group (expected frequency 1.67%)	–	–
Cleeves et al. ¹⁵	Hospital-based case–control study	100 (15%)	100 (6%)	2.80 (1.03–7.45)	0.036
Semchuk et al., 1993, 1995 ^{27,28}	Population-based case–control study	125 (?)	250 (?)	2.37 (1.20–4.69) 1.37 (0.67–2.80) after multivariate analysis	<0.05 n.s.
Morano et al. ²⁹	Hospital-based case–control study	74 (14.9%)	148 (4.7%)	3.52 (1.19–10.62)	0.009
Vieregge et al. ³⁰	Hospital-based case–control study	66 (13.6%)	72 (4.2%)	3.62 (0.84–17.86)	0.049
Jankovic et al. ³¹	Hospital-based family study	1874 parents and siblings or 391 PD patients (5.1%)	448 parents and siblings or 104 controls (2.2%)	2.37 (1.19–4.86)	0.008
De Michele et al. ³²	Hospital-based case–control study	100 (17%)	200 (5.5%) (1 spouse and 1 neurological control for each PD case)	3.1 (1.5–6.3)	0.002
De Michele et al. ³³	Hospital-based case–control study	116 (16.4%)	232 (5.6%) (1 spouse and 1 neurological control for each PD case)	3.30 (1.48–7.41)	0.001
Taylor et al. ³⁴	Hospital-based case–control study	140 (11.2%)	147 (3.4%)	3.97 (1.17–13.50)	0.007
Zorzon et al. ³⁵	Hospital-based case–control study	136 (6.6%)	272 (1.1%)	10.8 (2.6–43.7)	0.002
Kang et al. ³⁶	Population-based cases study	162 (15.4%)	–	–	–
Rocca et al. ³⁷	Population-based family study	981 first-degree relatives of 162 PD patients Total series 4.8% PD onset ≤66 years 5.8%	838 first-degree relatives of 147 controls (3.5%)	1.51 (0.95–2.41) 2.24 (1.26–3.98)	0.158 0.006

Table 1. Continued

Authors	Methodology/ Study Design	PD Patients	Controls	OR (95% CI) or HR (95% CI)	p-Value
		n (% with postural tremor)	n (% with postural tremor)		
Rocca et al. ³⁷	Hospital-based family study	2684 first-degree relatives of 411 PD patients Total series 5.92% PD onset ≤57 years 7.3%	838 first-degree relatives of 147 controls (3.5%)	1.96 (1.35–2.86)	0.0004
Spanaki and Plaitakis ³⁸	Population-based case–control study	303 (8.6%)	249 (3.2%)	2.83 (1.19–6.92)	0.015
Spanaki and Plaitakis ³⁸	Population-based family study	1483 first-degree relatives of 303 PD patients (2.8%)	1315 first-degree relatives of 249 controls (0.80%)	1.75–7.77	0.0001
Costello et al. ³⁹	Population-based family study	2980 first-degree relatives of 372 PD patients Total series 1.5% Relatives of tremor-dominant case 1.7% Relatives of younger case 1.4%	2981 first-degree relatives of 404 controls (1.0%)	1.44 (0.90–2.29) 1.69 (0.90–2.88) 2.03 (0.93–4.44)	0.13 0.05 0.08

Abbreviations: CI, confidence interval; ET, essential tremor; HR, hazard ratio; n.s., not significant; OR, odds ratio; PD, Parkinson's disease

Slowed movements in essential tremor

The question of whether patients with ET also have slowed movements as part of their clinical manifestations is still a matter of debate. Moreover, whether the presence of slowed movements is due to bradykinesia or uncoordination is unclear. To date, only a few studies have attempted to investigate this issue.

The first study attempting to evaluate motor performance in ET was carried out by Elble et al.⁶² The authors analyzed the timing of rapid wrist flexion in 10 ET patients with moderate to severe disability and 10 healthy age- and sex-matched controls. They found similar mean reaction time and motor time in both study groups. They also reported that although initial agonist muscle activation occurred in phase with rhythmic bursts of tremor on electromyographic recordings, the onset of rapid wrist flexion occurred when the momentum of ET opposed the volitional movement. The authors suggested that ET altered motor control, which impaired fine motor tasks in patients with advanced disease.

Deuschl et al.⁶³ analyzed reaching movements with kinematic methods in 26 ET patients (18 with and 8 without intention tremor),

12 age-matched healthy subjects, and 12 patients with cerebellar diseases of various origins. The subjects were asked to reach out and grasp a plug with their thumb and index finger. The target distance was adjusted to their height, and the movements were recorded with a camera system. Movement paths and speed were calculated. They found a significant increase in the curvature index when approaching the target in patients with cerebellar disease and in patients with ET (especially in those with kinetic tremor) and a weak but significant correlation between the curvature index of the target period and the clinical rating of kinetic tremor. They also found a significant slowing of the total reach-to-grasp movement in patients with cerebellar disease, ET patients with kinetic tremor, and, to a lesser degree, in ET patients without kinetic tremor, compared with controls.

Montgomery et al.⁶⁴ analyzed auditory reaction times and movement velocities of rapid wrist flexion and extension movements in the dominant hand of 34 ET patients, 46 idiopathic PD patients with mild disease, and 56 controls. They found no significant differences in reaction times between patients with ET and control subjects except in the extension-bounded task. Patients with ET and PD exhibited

longer reaction times and slower motion velocities than normal controls. In this study, the tremors were mild in amplitude and unlikely to interfere with motor performance.

Ozekmekçi et al.⁶⁵ quantitatively assessed movement times around the metacarpophalangeal, wrist, elbow, and shoulder joints in 17 patients with ET and 14 age-matched normal controls. Patients with intention (kinetic) tremor were excluded. They compared mean movement time for repetitive movements: after an imperative auditory stimulus, patients tapped as quickly as possible for 15 seconds using the index finger of the right (dominant) hand on two pushbuttons situated at different distances. They measured the time elapsed between two consecutive taps on the left and right pushbuttons for 15 seconds and the number of taps on the left key for 15 seconds. They observed slight slowing during repetitive movements around the shoulder and metacarpophalangeal joints in patients with ET compared with controls, although it did not reach statistical significance.

Farkas et al.⁶⁶ studied 34 ET patients (all of them had postural tremor, and 14 of also had kinetic tremor) and 41 controls. They measured the regularity and the maximum frequency of auditory-paced repetitive movements (finger-tapping and pronation–supination) at slow and fast stimulus rates in both hands. They found higher variability (assessed by standard deviation) of rhythmic finger-tapping and alternating pronation–supination hand movements in ET patients compared to controls. They suggested that ET patients were unable to synchronize repetitive movements to extrinsic timing cues during both slow and fast movement. The authors concluded that in ET, event-based timekeeping and the transition between slow and fast working modes of rhythm production was impaired, which resulted in a deterioration in rapid repetitive movement accuracy.

Héroux et al.⁶⁷ studied 30 ET patients and 28 age- and sex-matched controls. They assessed bilateral upper-extremity function using the Box and Block Test, the Purdue Pegboard Test, and the “test for evaluation of upper-limb performance in aged people”. They found that subjects with ET performed worse than controls in unilateral and bilateral tasks except in the Purdue Pegboard Test for the dominant side. In addition, they did not find a correlation between dominant-hand tremor severity and performance on the dominant-side Box and Block Test, Purdue Pegboard Test, or the “test for evaluation of upper-limb performance in aged people” scores for the control group or ET subjects with and without ET-type hand tremor, but these values were highly correlated in subjects with ET-type tremor in the non-dominant hand. These results indicated that the subjects with ET-type tremor in the non-dominant hand who had more severe tremor tended to take longer to complete the unilateral “test for evaluation of upper-limb performance in aged people” task (positive correlation) and placed fewer pegs and transferred fewer blocks during the Purdue Pegboard Test and Box and Block Test (negative correlations). In a subsequent study of 21 ET patients, the same group described significant correlations between “test for evaluation of upper-limb performance in aged people” scores and kinetic tremor scores and between the “test for evaluation of upper-limb performance in aged people” scores and loaded postural tremor scores.⁶⁸

Duval et al.⁶⁹ examined rapidly alternating pronation–supination movements with the largest excursion possible for 7 seconds on the most affected hand of 10 ET patients, 10 PD patients with mild–moderate stages of the disease, and 10 age- and sex-matched controls. They described slower pronation–supination movements in patients with ET than controls, which were at similar rates to those of patients with mild to moderate PD.

Our group⁷⁰ studied 61 unselected and unrelated patients fulfilling criteria for definite ET and 122 age and sex-matched healthy controls. Evaluation included four timed tests (right and left pronation–supination, finger-tapping, movement between two points, and walking test) and three computer-based tests. The timed tests used correlate with bradykinesia and functional impairment in PD⁷¹ and Huntington’s disease⁷² and have been used to study age-related motor performance decline in normal subjects.^{73,74} Tests performed on a personal computer included repetitive key pressing speed (frequency), visual reaction time, and movement time, which were all performed with both upper extremities. The subjects were instructed to perform the tasks as quickly as possible. We also tried to establish whether the results of these tests correlated with tremor severity. Compared to controls, ET patients showed significantly higher values for right and left finger-tapping and right and left visual reaction times. Left and right pronation–supination, movement between two points, movement time, and the walking test were similar in ET patients and controls. Tremor severity, assessed with two different rating scales, was not correlated with the altered values. We hypothesized that patients with ET have impaired motor performance, at least in some tasks, which probably means that patients with ET may have some degree of bradykinesia. In addition, we suggested that these findings could explain why ET patients are prone to develop drug-induced parkinsonism^{75,76} and why a percentage of ET patients develop PD over time. It is possible that these are all due to an underlying dopaminergic deficit.

Costa et al.⁷⁷ analyzed non-linear dynamics of repetitive movements in 18 ET patients, 33 mild–moderate PD patients, and 31 control subjects. For this purpose, they recorded accelerometer signals during finger-tapping and unbounded forearm movements between two points with the forearm and hand pronated and fingers extended. They asked the study subjects to execute both movements as quickly and widely as possible. They measured the interpeak intervals, interpeak interval variability, and the beat decay of auto-mutual information (BD-AMI). For the finger-tapping test, the interpeak intervals were similar in ET patients, PD patients, and controls, whereas interpeak interval variability and BD-AMI were significantly higher in ET and PD patient groups than in controls. For forearm movements, the interpeak intervals, interpeak interval variability, and BD-AMI were significantly higher in ET and in PD patients than in controls; the last two were also higher in ET patients than in PD patients. Interpeak interval variability and BD-AMI for forearm movements were also influenced by tremor severity in ET patients. The results of this study indicate slowness in execution of repetitive oscillatory movements in ET patients to a similar degree as observed

in patients with mild–moderate PD, which cannot fully be explained by tremor.

The findings of studies on motor performance in ET are difficult to interpret due to several factors, such as the lack of methodological homogeneity, the low number of participating patients in some, and the exclusion of patients with kinetic tremor in others. However, most studies suggest the presence of some degree of slowing for different types of movements in patients with ET,^{63,64,66,67,69,70,77} which were comparable to those observed in patients with mild–moderate PD.^{64,69,77}

There are at least two possible explanations (i.e., cerebellar dysfunction and true bradykinesia) for the slower movements in patients with ET. The possible role of cerebellar dysfunction is supported by the following evidence.

- (a) The observation by Deuschl et al.⁶³ that slowness of goal-directed movements was similar in ET (especially in patients with intention tremor) and cerebellar disease.
- (b) The description by Farkas et al.⁶⁶ that event-based timekeeping and the transition between the slow and fast working mode of rhythm production was impaired and caused rapid repetitive movement accuracy to deteriorate.
- (c) The correlation between “test for evaluation of upper-limb performance in aged people” scores and kinetic tremor scores described by Norman et al.⁶⁸
- (d) The description by Costa et al.⁷⁷ of higher interpeak interval variability and BD-AMI in ET patients than in PD patients.

Bradykinesia encompasses slowness, decreased movement amplitude, and dysrhythmia arrest in motion.⁷⁸ The presence of true bradykinesia in ET patients has also been supported by the results of some of the previously mentioned studies.

- (a) Montgomery et al.⁶⁴ suggested that the tendency of ET patients toward increased auditory reaction times and decreased movement velocities to the same degree as mild PD patients suggests bradykinesia–akinesia. These authors acknowledged the possibility that the presence of tremor could interfere with motor performance, but the observed tremors were mild. The lack of correlation between tremor scale scores in one report⁷⁰ and the lack of significant differences in the mean interpeak interval between PD patients with and without tremor and between ET patients with varying degrees of tremor severity in another study⁷⁷ seem to be in agreement with this statement.
- (b) Duval et al.⁶⁹ suggested that the similarly decreased movement velocities in performing rapid repetitive movements by ET patients and mild to moderate PD could also reflect bradykinesia.
- (c) Our group⁷⁰ found impairment in rapid repetitive finger movements (assessed by finger-tapping and frequency) and visual reaction time in ET patients compared with controls, but pronation–supination, movement between two-points, and movement time was similar to the control group. Although we did not analyze a subgroup of PD patients, some authors who reported similar findings, reported a worse performance for the

finger-tapping task than for forearm pronation–supination in PD patients.⁷⁹ Increased reaction time is often reported in PD.^{80,81} We hypothesize that these findings suggest that patients with ET have some degree of bradykinesia. We did not analyze the possible influence of kinetic tremor severity on motor performance, although global scores of two tremor rating scales did not correlate with motor task scores.

Conclusions and future directions

Despite the fact that ET and PD are distinct clinical entities and the lack of consensus regarding a possible relationship between ET and PD, there is considerable evidence supporting the overlap between these two disorders, including the following:

- (a) the high frequency of concomitant PD in patients with ET in some clinical series;^{9–14}
- (b) the description that in patients with concomitant ET and PD the greater ET severity corresponds to the side with more severe PD;^{16,17}
- (c) the increased risk of ET patients for developing PD described in three studies with different designs;^{19–21}
- (d) the high frequency of family history of postural tremor of ET in PD patients found in the majority of case–control studies^{15,25,29,30,32–35,38} and genetic epidemiological studies;^{31,37–39}
- (e) the descriptions of mild abnormalities of striatal DAT and a significant presynaptic dopaminergic deficit in ET patients found in some functional imaging studies;^{45–48}
- (f) neuropathological reports describing Lewy pathology in ET patients;⁵⁰
- (g) the high frequency of rest tremor in ET patients^{56,57} and the presence of cogwheel rigidity in patients with ET;^{53–55}
- (h) the description of slowed movements in patients with ET (reasonably related to both cerebellar dysfunction and some degree of bradykinesia) reported in several studies that assessed motor performance with different methodologies.^{63,64,66,67,69,70,75}

It has been suggested that the lack of disease-specific markers for ET and PD, short follow-up, insufficient clinical information, and various methodological problems may lead to misdiagnosis and could contribute to discrepancies in reported associations between the two disorders.⁹ The diagnosis of PD in patients who previously met diagnostic criteria for ET is not difficult, but investigations into the association between ET and PD usually require the presence of ET for at least 5 years before the onset of cardinal PD symptoms. However, the diagnosis of ET in patients previously diagnosed with PD is complicated by the fact that postural tremor is usually associated with PD. We agree with Fekete and Jankovic⁹ that the appearance of head, voice, or writing tremor in a patient with PD (especially if this patient has a family history of ET) may indicate the possibility of comorbid ET.

We suggest that the ideal study to address the relationship between ET and PD should fulfill the following conditions:

- (a) Patients diagnosed with definite and “pure” ET according to standardized criteria⁸² and with a family history of ET, regardless of the duration of the disease, should be included.
- (b) A multicenter and prospective design with long-term follow-up.
- (c) Patients should undergo periodic clinical evaluations, including rating scales for tremor^{83,84} and the Unified Parkinson’s Disease Rating Scale (UPDRS).⁸⁵
- (d) Patients should undergo DAT-SPECT studies at the beginning and at end of the follow-up period, and there should be further study if a diagnosis of associated PD is made.
- (e) Blood DNA should be obtained from patients for future genetic studies attempting to link ET and PD. To date, neither linkage studies nor case–control association studies have been able to conclusively identify any gene responsible for ET. The results of a meta-analysis on the association between the *LINGO1* gene single nucleotide polymorphisms rs9652490 and rs11856808 and ET risk showed no association of the rs9652490G allele and a weak association of the rs11856808T allele with the risk for ET, although both variants showed a weak association with the risk for developing familial ET (Jiménez-Jiménez et al.⁸⁶). However, other meta-analyses have shown a lack of association between these *LINGO1* gene variants and the risk for PD.⁸⁷
- (f) Neuropathological examination of the brains of patients who died during the study interval would be desirable. The neuropathological features of patients conclusively diagnosed with ET and ET-PD should be compared with those of PD patients and controls.

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