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Essential Tremor-Parkinson's Disease: A Double Whammy

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Abstract

Background—Surprisingly little has been written about the combined clinical entity, essential tremor-Parkinson's disease (ET-PD), which is the result of a double disease hit. We carefully quantified tremor burden using a wide range of measures (tremor severity, tremor-related disability, tremor-related quality of life) and furthermore, studied additional motor and non-motor features in ET-PD.

Methods—In this prospective, clinical-epidemiological study, we performed a standardized, structured clinical evaluation of 27 ET-PD patients, comparing them to age-matched samples of 35 PD and 109 ET patients.

Results—The number of hours/day shaking was lowest in PD (median = 3.0), intermediate in ET (median = 10.0) and highest in ET-PD (median = 14.0) ($p < 0.001$). All measures of mobility and balance (Berg Balance test, Activities-specific Balance Confidence Scale, Timed Up and Go test)

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worsened across groups in a stepwise manner from ET to PD to ET-PD ($p < 0.05$). Mini-mental state test scores worsened ($p = 0.002$) and daytime sleepiness increased ($p = 0.002$) across groups from ET to PD to ET-PD.

Conclusions—The ET-PD patient seems to be more than just a PD patient with a little more kinetic tremor. Aside from a significantly greater tremor burden, ET-PD patients exhibited more cognitive and sleep problems and more mobility and balance problems than patients with isolated PD.

Keywords

essential tremor; Parkinson's disease; clinical

1. Introduction

Although controversial, there is evidence that patients with essential tremor (ET) are increased risk of developing Parkinson's disease (PD) [1,2,3]. Despite this, there are few studies examining this combined clinical entity, ET-PD, which seems to be the result of a double neurological hit (i.e., a “double whammy”). Although of value, each of the three reported ET-PD case series ($n = 22$ [2], $n = 53$ [4], $n = 54$ [5]) were retrospective chart reviews.

Clinically, patients with ET-PD may manifest a multiplicity of tremors, including PD-associated rest tremor and the rest tremor that can accompany advanced ET, action tremor associated with both ET and PD, and intention tremor. Hence, tremor-related burden has the potential to be quite high. However, existing studies have provided surprisingly limited details about the effects of tremor on function and/or quality of life in ET-PD. In this prospective, clinical-epidemiological study, we performed a standardized, structured clinical evaluation of 27 ET-PD patients, comparing them to age-matched samples of 35 PD and 109 ET patients enrolled in the same study. The primary goal was to quantify tremor burden in the combined condition (i.e., ET-PD) using a broad range of measures that assessed tremor severity, tremor-related disability, and tremor-related quality of life. Furthermore, we wished to ask, what does it mean for a patient to have both ET and PD? Is this merely PD with more kinetic tremor? Are there any broader effects of this double hit and if so, what are they? With this in mind, our second goal was to study ET-PD more broadly, assessing several clinical features (both motor and non-motor) aside from tremor, which have neither been assessed in this condition nor compared across this grouping of conditions (ET, PD, ET-PD).

2. Methods

2.1. Participants

Participants were enrolled in a prospective clinical-epidemiological study of movement disorders at the Neurological Institute, Columbia University Medical Center (CUMC) (2009 – 2014) [6]. The study assessed the role of environmental toxins in disease etiology; it also assessed a wide range of clinical features. ET, PD and ET-PD patients seen in the most recent 5 years were identified from a computerized billing database at the Center for Parkinson's Disease and Other Movement Disorders at the Institute. Each patient had

received a diagnosis of ET, PD, or ET-PD from their treating neurologist at the Institute. One of the authors (E.D.L.) reviewed the office records of identified patients; those with diagnoses of or physical signs consistent with other movement disorders were excluded. During the review, the most recent daily dose (mg) of levodopa was recorded for PD and ET-PD patients as well as the most recent Unified Parkinson's Disease Rating Scale (UPDRS) score [7].

The CUMC Institutional Review Board approved study procedures. Signed informed consent was obtained upon enrollment. Analysis of data was also approved by the Internal Review Board at Yale Medical School.

2.2. Study Evaluation

During the single in-person assessment, a trained research assistant administered a series of structured questionnaires, which elicited data on:

1. demographic variables (e.g., age, gender, education, race) and family history of tremor,
2. disease duration and medication use,
3. overall health, including the Cumulative Illness Rating Scale score (range = 0–42 [maximum co-morbidity])[8], total number of prescription medications, self-rating of overall health from the Quality of Life in Essential Tremor (QUEST) questionnaire (0 [very poor] – 100 [excellent/perfect health])[9],
4. tremor severity/disability (including but not limited to: number of hours spent per day shaking, tremor-related disability questionnaire score (0 [no disability] – 100 [maximum disability])[10],
5. cognition and mood, including the Folstein Mini-Mental state test score [11], and the Center for Epidemiological Studies Depression Scale (CESD-10) (0 – 30 [greater depressive symptoms]) [12],
6. sleep, including the Epworth Sleepiness Scale (ESS, 0–24 [maximum daytime sleepiness]) [13] and the Pittsburgh Sleep Quality Index (PSQI, 0–21 [worst sleep quality])[14],
7. balance and mobility using the Berg Balance Test (0 [most impaired] - 56)[15], which is a performance-based test during which patients are rated on their ability to maintain balance while performing 14 functional tasks; the Activities-specific Balance Confidence Scale (ABC -6, range = 0 [most impaired]– 100%), which asks the patient to self-assess confidence during 6 activities [16]; and the Timed Up and Go test (time taken in seconds to rise from a seated position, walk three meters, turn, walk back and sit then down again at a self-determined comfortable speed, with two trials and an average score)[17].

The QUEST was administered [9]. In this questionnaire, 30 items are rated on a five-point scale (0 – 4), corresponding to the frequency (never, rarely, sometimes, frequently, always) with which tremor is perceived to currently impact a function or to be associated with various feelings or attitudes [9]. There are 6 additional items in which tremor is rated in the

head, voice and each limb (for each, score 0 – 4), corresponding to the severity of tremor (none, mild, moderate, marked, severe). Four items from the work/finance domain did not apply to the vast majority of our patients, who were elderly, so that in our analyses of the psychometric attributes of QUEST, we used a 26 item version of QUEST that included only the two relevant work/finance items (tremor resulted in early retirement, tremor lead to financial problems/concerns). The psychometric attributes of QUEST in ET patients have been assessed and most are satisfactory [9]. The psychometric attributes of QUEST have also been assessed in PD and are satisfactory [18].

Validation of ET diagnosis is a critical feature of all clinical and epidemiological research on ET, as self-reports and prior diagnoses of ET may not be invalid. Therefore, during the in-person assessment of the patients with ET (and ET-PD), a videotaped neurological examination was performed for the purposes of the validation of the ET diagnosis. The same set of issues was not present for patients with pure PD. This included one test for postural tremor and five for kinetic tremor (e.g., pouring, drinking) performed with each arm (12 tests total). A neurologist specializing in movement disorders (E.D.L.) used a valid [19] and reliable [20] clinical rating scale, the Washington Heights-Inwood Genetic Study of ET (WHIGET) tremor rating scale, to rate postural and kinetic tremor during each test: (0 – 3). These ratings resulted in a total tremor score (range = 0 – 36).

2.3. Diagnoses

Each ET patient had received a clinical diagnosis of ET from their treating movement disorders neurologist at the Institute, based on the presence, pattern and severity of action tremor. After enrollment, ET diagnoses were then carefully re-confirmed (E.D.L.) using the videotaped neurological examination and WHIGET diagnostic criteria (moderate or greater amplitude kinetic tremor [tremor rating ≥ 2] during three or more tests or a head tremor, in the absence of PD, dystonia or another cause) [21]. The WHIGET diagnostic criteria for ET were developed for a population-based genetic study and, based on data from approximately 2,000 non-diseased healthy controls, these criteria carefully indicate the specific examination maneuvers during which tremor should be present and the severity of tremor that should be evident during these maneuvers.

Similarly, each PD and ET-PD patient had received a diagnosis of PD or ET-PD from their treating movement disorders neurologist at the Institute. In addition, based on office record review, the diagnosis of PD was confirmed (E.D.L.) prior to enrollment using published diagnostic criteria, which required the presence of at least two cardinal signs [22]. The diagnosis of ET-PD was further reviewed prior to enrollment, and required that (1) the ET diagnosis was present for at least five years prior to the PD diagnosis (indeed, the median was 18.0 years), (2) the initial ET was characterized by moderate or greater amplitude kinetic tremor in the absence of any signs of PD (e.g., rest tremor, bradykinesia), and (3) the initial ET diagnosis occurred in absence of red flags for possible emerging PD (isolated postural tremor without kinetic tremor, unilateral kinetic tremor). In most cases the history was obtained from the patient as well as accompanying family members in order to obtain additional construct validity for the initial ET diagnosis.

2.4. Final Sample

The initial sample ($n = 265$) comprised 134 ET, 102 PD, and 29 ET+PD patients. After frequency-matching by age across all 3 groups, the final sample included 171 patients: 109 ET, 35 PD and 27 ET+PD patients. This matching was performed by selecting a group of individuals in each of the remaining diagnostic groups (ET and PD) whose age conformed to the distribution observed in the ET+PD cases. This matching was performed within each diagnostic category blinded to all data other than age.

2.5. Statistical Analyses

Data were analyzed in SPSS (Version 21). Demographic and clinical characteristics were compared across the three groups using analysis of variance (ANOVA) and chi-square tests. For variables that were not normally distributed, we used Kruskal Wallis tests. When differences were detected across all three groups in these initial comparisons, additional comparisons were performed (ET vs. PD, ET vs. ET-PD, PD vs. ET-PD) using parametric (student t test, chi-square test) or non-parametric (Mann-Whitney test) approaches. To test for a trend across the three groups, we used the Jonckheere-Terpstra test. We also performed sensitivity analyses, removing the 24 cases who had had brain surgery, and repeated the primary analyses.

3. Results

The three groups were carefully matched on age (Table 1) and were similar in race, and median years of education (16.0 for each group). There were fewer females in the two PD groups (i.e., PD and ET-PD) than the ET group, although the difference was not significant (Table 1). The duration of PD in the two PD groups (PD and ET-PD) was also similar (9.5 ± 4.3 vs. 10.8 ± 7.4 years, Table 1, Mann-Whitney test = 0.50, $p = 0.62$), as was the duration of the ET in the two ET groups (ET and ET-PD, 37.3 ± 19.5 vs. 33.3 ± 19.4 years, Table 1, Mann-Whitney test = 0.95, $p = 0.34$). The proportion who were taking medications with potential tremor-enhancing properties (e.g., prednisone, valproate) was similar across groups: 38 (34.9%) ET, 10 (28.5%) PD, and 7 (25.9%) ET-PD (chi-square test = 1.05, $p = 0.59$).

Family history of ET or tremor was present in 70.3% of ET patients and 62.5% in ET-PD patients yet only 32.4% of those with PD. Family history of PD was present in 23.6% of PD but only 9.6% of ET and 12.5% of ET-PD.

The number of hours per day shaking was lowest in PD (median = 3.0), intermediate in ET (median = 10.0) and highest in ET-PD (median = 14.0) (Jonckheere -Terpstra test for trend, $p < 0.001$) (Table 1). The tremor-related disability score was lowest in PD (35.7 ± 28.4), intermediate in ET (53.6 ± 25.3), and highest in ET-PD (66.3 ± 27.8) (Jonckheere -Terpstra test for trend, $p < 0.001$) (Table 1), and tremor-related quality of life (QUEST total score) was least impaired in PD (18.4 ± 20.5), intermediate in ET (24.0 ± 19.8), and most impaired in ET-PD (35.0 ± 23.7) (Jonckheere -Terpstra test for trend, $p = 0.001$) (Table 1).

Each of the measures of balance and mobility (Berg Balance test, Activities-specific Balance Confidence Scale, Timed Up and Go test) worsened across the three groups in a similar

stepwise manner from ET to PD to ET-PD (Table 1, all Jonckheere -Terpstra tests for trend, $p < 0.05$). The mini mental state test score worsened (Jonckheere -Terpstra test for trend, $p = 0.002$) and daytime sleepiness increased (Jonckheere -Terpstra test for trend, $p = 0.002$) from ET to PD to ET-PD (Table 1). Self-rated overall health declined from ET to PD to ET-PD (Jonckheere -Terpstra test for trend, $p = 0.014$, Table 1).

Twenty-four patients (8 [7.3%] ET, 3 [8.6%] PD and 13 [48.1%] ET-PD) had had brain surgery for their tremor (chi square test = 30.96, $p < 0.001$); 21 (87.5%) of 24 had had thalamic deep brain stimulation surgery (10 bilateral, 3 right, 8 left). After removing the 24 cases who had had surgery, we repeated our primary analyses, and results were reproducible (e.g., the number of hours per day shaking was lowest in PD, intermediate in ET and highest in ET-PD ($p = 0.005$) and the mini-mental state test scores worsened from ET to PD to ET-PD ($p = 0.016$)).

4. Discussion

In many respects, inclusive of but extending beyond tremor burden, ET-PD is a double whammy (i.e., a two-fold blow or two-fold set-back). We prospectively enrolled and studied patients with ET, PD and both diagnoses (ET-PD) who were carefully matched by age. The duration of PD in the two PD groups (PD and ET-PD) was also similar. Number of hours per day shaking, tremor-related disability, and tremor-related quality of life worsened in a stepwise manner across these three groups from PD to ET to ET-PD. Numerous measures of mobility and balance declined across the groups in a similar stepwise manner from ET to PD to ET-PD. Mini mental state test scores worsened and daytime sleepiness increased from ET to PD to ET-PD. Self-rated overall health declined from ET to PD to ET-PD.

The UPDRS motor score was similar in PD and ET-PD patients (Table 1); however, the UPDRS tremor score was higher in ET-PD than PD patients (Table 1), indicating that it may be tremor itself rather than other parkinsonian features that was the major contributor to the overall lower rating of health in ET-PD compared to PD.

Mobility and balance deficits have been described in ET [23, 24]. They are also well described in PD. To our knowledge, published data are not available on mobility and balance in the combined condition, ET-PD. We showed that ET-PD patients had greater difficulty than both groups alone. Indeed, the mean Timed Up and Go score for ET-PD patients was well above the cut off score used for fall predication in PD (< 11.5) [25] and the mean Berg Balance score of for ET-PD patients was well below the falls prediction cut off score (47) [26] for the elderly. Hence, these data suggest that the combination of ET with PD results in even more mobility impairment than PD alone, substantiating the notion that the mobility and balance issues in ET-PD patients represent a double hit. Indeed, the mobility/balance impairment in PD may be the result of basal ganglia dysfunction as opposed to cerebellar dysfunction in ET, suggesting the involvement of two systems in patients with ET-PD.

Cognitive dysfunction has been described in ET [27]. It is also a well-known feature of PD. The same is the case with daytime sleepiness [28]. The current data also show that ET-PD

patients seem to have the more cognitive and sleep problems than patients with either condition alone. That is, the combined condition is associated with broader (i.e., non-motor) effects and clinical features aside from the tremor appear to be additive. In a prior study of the same cohort [29], we showed that Folstein Mini-mental state scores were lower in ET-PD than PD; however, we did not explore sleep or motor features that differentiated the two groups, nor did we compare them to a group of ET cases.

This study should be interpreted within the context of several limitations. The PD patients did not undergo a videotaped tremor examination; hence, the total tremor score could not be calculated for PD patients. Despite this, numerous other measures of tremor severity were obtained in these patients. Second, the sample size for ET-PD was modest; despite this, we were able to detect numerous differences between these patients and those in the other groups. Third, given the younger age of onset of PD compared to ET in general, a large number of our initial sample of PD patients ($n = 84$) were below the mean age of our ET patients. To achieve an age-balance between the two groups, therefore, we had to exclude a large number of PD cases. This led to a difference in sample size between the two groups. Fourth, the diagnosis of ET-PD stringently required that (1) the ET diagnosis was present for at least five years prior to the PD diagnosis (although the median was 18.0 years), (2) the initial ET was characterized by moderate or greater amplitude kinetic tremor in the absence of any signs of PD (e.g., rest tremor, bradykinesia), and (3) the initial ET diagnosis occurred in absence of red flags for possible emerging PD (isolated postural tremor without kinetic tremor, unilateral kinetic tremor). While it is impossible to completely rule out the possibility that some of the initial ET diagnoses were misapplied to isolated PD-related action tremor, these criteria lessen that possibility significantly. Furthermore, in most cases the history was obtained from the patient as well as accompanying family members in order to obtain additional construct validity for the initial ET diagnosis. While dopamine transporter imaging could aid in the diagnoses, it is not feasible for observational-epidemiological studies. The study had a number of strengths, including its prospective enrollment rather than retrospective nature, the standardized study evaluation, and the breadth of evaluations performed on study subjects.

Often when the diagnosis of ET-PD is made in patients with prior ET, the therapeutic focus shifts to the PD, and this may be at the expense of the initial diagnosis, ET. From the current data, the ET-PD patient seems to be more than just a PD patient with a little more kinetic tremor. Aside from a significantly greater tremor burden, ET-PD patients exhibited more cognitive and sleep problems and more mobility and balance problems than patients with isolated PD. Clinicians should be sensitive to the full spectrum of these impairments.

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highlights

- Surprisingly few data are available on patients with both ET and PD.
- We carefully quantified motor and non-motor features in ET-PD.
- Mobility and balance worsened in a stepwise manner from ET to PD to ET-PD.
- Cognition and daytime sleepiness worsened across groups from ET to PD to ET-PD.
- The ET-PD patient seems to be more than just a PD patient with more kinetic tremor.

Table 1

Demographic and Clinical Characteristics of 171 Participants

	ET	PD	ET-PD	Significance
n	109	35	27	
<i>Demographics</i>				
Age (years)	76.4 ± 7.3	76.3 ± 3.2	76.9 ± 7.0	p = 0.92 ^a
Female gender	56 (51.4)	15 (42.9)	9 (33.3)	p = 0.21 ^b
Education (years)	16.2 ± 2.6 [16.0]	16.8 ± 2.6 [16.0]	15.0 ± 5.0 [16.0]	p = 0.14 ^c
White race	108 (99.1)	34 (97.1)	27 (100)	p = 0.53 ^a
<i>Disease duration/severity</i>				
ET symptom duration (years)	37.3 ± 19.5 [34.0]	NA	33.3 ± 19.4 [25.0]	p = 0.34 ^{d-1}
PD symptom duration (years)	NA	9.5 ± 4.3 [8.0]	10.8 ± 7.4 [10.0]	p = 0.62 ^{d-1}
Daily carbidopa-levodopa dosage (mg)	NA	512.5 ± 368.9 [362.5]	343.1 ± 317.6 [300.0]	p = 0.17 ^{d-1}
Taking a dopamine agonist	NA	7 (20.0)	3 (11.1)	p = 0.56 ^{d-2}
Taking anticholinergic medication	NA	1 (2.9)	1 (3.7)	p = 1.00 ^{d-2}
UPDRS motor score	NA	21.0 ± 9.3	20.4 ± 8.1	p = 0.84 ^e
<i>Overall health</i>				
CIRS score	76.4 ± 7.3	76.3 ± 3.3	76.9 ± 7.0	p = 0.92 ^a
Total current number of prescription medications	5.2 ± 3.1 [5.0]	6.5 ± 3.2 [6.0]	6.0 ± 3.4 [6.0]	p = 0.07 ^a
Self-rating of overall health	76.3 ± 17.7 [80.0]	70.6 ± 19.4 [75.0]	65.2 ± 26.7 [75.0] ^{1a}	0.05 ^c 0.014 (JT) ^f
<i>Tremor severity/disability</i>				
Number of hours per day shaking	9.8 ± 7.7 [10.0]	5.6 ± 6.5 [3.0]	11.9 ± 7.1 [14.0] ^{2a}	0.001 ^c <0.001 (JT) ^f
Tremor-related disability score	53.6 ± 25.3	35.7 ± 28.4	66.3 ± 27.8 ^{1b, 2a}	p < 0.001 ^a <0.001 (JT) ^f
QUEST score	24.0 ± 19.8 [17.8]	18.4 ± 20.5 [7.7]	35.0 ± 23.7 [26.9] ^{1a, 2a}	0.006 ^c 0.001 (JT) ^f
Total tremor score on neurological examination	20.2 ± 5.9	NA	24.4 ± 5.6	p = 0.002 ^{d-1}
UPDRS tremor score	NA	2.5 ± 2.9	5.5 ± 3.3	p = 0.01 ^e
<i>Cognitive/mood</i>				
Folstein mini-mental state test score	28.7 ± 1.5 [29.0]	28.6 ± 1.8 [29.0]	26.6 ± 3.1 [28.0] ^{1a}	<0.001 ^c 0.002 (JT) ^g
CESD-10 score	8.3 ± 5.8 [7.0]	10.9 ± 6.3 [11.0]	10.6 ± 6.2 [11.0] ^{1b}	0.04 ^c
<i>Sleep</i>				
ESS score	6.5 ± 4.0 [6.0]	8.8 ± 4.9 [8.0]	9.7 ± 6.4 [9.0] ^{1a}	0.009 ^c 0.002 (JT) ^g
PSQI score	8.3 ± 5.0 [7.0]	11.0 ± 6.8 [9.5]	8.6 ± 4.5 [8.0] ^{1a}	0.085 ^c

	ET	PD	ET-PD	Significance
n	109	35	27	
<i>Balance and Mobility</i>				
Berg Balance Test score	49.5 ± 10.0 [53.0]	47.5 ± 11.1 [51.0]	39.8 ± 17.4 [49.0] ^{1a, 2a}	p = 0.005 ^c 0.003 (JT) ^g
ABC-6 total score	60.9 ± 27.8	53.5 ± 31.4	45.1 ± 31.3 ^{1a}	p = 0.03 ^a 0.021 (JT) ^g
TUG time 1 score	10.9 ± 3.8 [10.2]	12.5 ± 4.4 [12.1]	16.4 ± 9.4 [12.1] ^{1a}	0.01 ^c 0.002 (JT) ^g
TUG2 time 2 score	10.9 ± 3.9 [10.1]	12.4 ± 4.3 [11.1]	17.0 ± 10.4 [13.3] ^{1a}	0.004 ^c 0.001 (JT) ^g
TUG3 average score	10.9 ± 3.8 [10.2]	12.4 ± 4.2 [11.5]	16.7 ± 9.8 [12.7] ^{1a}	0.006 ^c 0.001 (JT) ^g

Values are mean ± standard deviation [median] or number (percentage).

Significant values are in bold.

ABC = Activities of Balance Confidence, CESD = Center for Epidemiological Studies Depression Scale, CIRS = Cumulative Illness Rating Scale, ESS = Epworth Sleep Scale, JT = Jonckheere -Terpstra test, mg = milligrams, NA = not applicable, PSQI = Pittsburgh Sleep Quality Index, QUEST = Quality of Life in Essential Tremor Score, TUG = Timed up and go test, UPDRS = Unified Parkinson's Disease Rating Scale.

^a Analysis of variance comparing the 3 groups.

^b Chi-square test comparing the 3 groups.

^c Kruskal Wallis test comparing the 3 groups.

^{d-1} Mann-Whitney test comparing the 2 groups.

^{d-2} Fisher's test comparing two groups.

^e Student t test comparing the 2 groups.

^f Jonckheere -Terpstra test comparing 3 groups ordered as PD = 1, ET = 2, ETPD = 3.

^g Jonckheere -Terpstra test comparing 3 groups ordered as ET = 1, PD = 2, ETPD = 3.

^{1a} Significantly different from ET (p < 0.05).

^{1b} Marginally significantly different from ET (p < 0.10).

^{2a} Significantly different from PD (p < 0.05).

^{2b} Marginally significantly different from PD (p < 0.10).