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Familial Aggregation and Co-Aggregation of Essential Tremor and Parkinson's Disease

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Abstract

Background—Current data suggest that the two common tremor disorders, essential tremor (ET) and Parkinson's disease (PD), may be associated with one another. Familial aggregation studies allow one to further explore their relatedness.

Methods—Probands with ET (N = 110), PD (N = 130) or both ET and PD (N = 27) and control probands (N = 177) reported whether they had relatives with these diseases or with non-specific tremor.

Results—A greater proportion of ET probands than control probands reported relatives with ET (30.0% vs. 2.8%, $p < 0.001$), non-specific tremor (38.2% vs. 13.6%, $p < 0.001$), and both ET and PD

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Competing Interests

Dr. Louis has no competing interests.

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in different relatives (6.4% vs. 0.6%, $p = 0.004$). A greater proportion of PD probands than control probands reported relatives with PD (20.0% vs. 8.5%, $p = 0.003$), ET (11.5% vs. 2.8%, $p = 0.002$), and both ET and PD in different relatives (6.9% vs. 0.6%, $p = 0.002$).

Conclusions—This study provides evidence for the aggregation of ET in ET families and PD in PD families, and the familial co-aggregation of ET and PD.

Keywords

essential tremor; Parkinson's disease; genetic epidemiology; familial aggregation; neurodegeneration

Introduction

Essential tremor (ET) is among the most prevalent neurological diseases and is the most common cause of tremor in humans [1, 2]. Parkinson's disease (PD) is another neurological disorder characterized by tremor. Clinically, patients with ET and PD share a variety of motor and non-motor features [3–5]. This observation, in combination with a range of other data, suggests that these two tremor disorders may share some common mechanisms [6, 7]. In case-control studies, PD patients have an increased odds of having had ET [8], and a prospective, population-based study demonstrated that prevalent ET cases have an increased risk of developing incident PD [9]. Kindreds have been described in which some individuals have ET while others have both ET and PD (i.e., ETPD) [10]. Genetic studies have revealed shared variants for both diseases [11]. Brainstem Lewy bodies, well-described in PD, have also been reported to be more prevalent in ET cases than controls in some although not all studies [12–14].

Despite the many connections between ET and PD, their relatedness continues to be the subject of active debate [7, 15, 16]. Therefore, new studies on the links between these two tremor disorders are valuable. Three prior studies assessed whether PD families have a higher than expected prevalence of ET [17–19]. In the current study of more than 400 families of probands with ET, PD or both (ETPD), we assessed the proportion of probands who reported relatives with ET, PD, and non-specific tremor. Unlike previous studies that assessed the risk of ET in families ascertained through individuals with PD [17–19], we also assessed the risk of PD in families ascertained through individuals with ET. In addition, besides enrolling probands with ET or PD, we enrolled probands who were co-morbid for both diseases (i.e., ETPD). Beyond eliciting family history information on ET and PD, we also elicited information on non-specific tremor, which is highly prevalent and likely to be heterogeneous. Finally, we assessed the proportion of probands who reported having some relatives with ET and other relatives with PD (i.e., both conditions in the same family).

Methods

Participants

Patients with ET, PD, both disorders (ETPD), and controls were prospectively enrolled in a clinical-epidemiological study (2000 – 2014) [20, 21]. The ET, PD, and ETPD cases were identified from a computerized billing database at the Center for Parkinson's Disease and

Other Movement Disorders at the Neurological Institute, Columbia University Medical Center (CUMC), with a search conducted of all patients seen within the three years prior to enrollment. Each case had received a diagnosis of ET, PD or ETPD from their treating neurologist at the Neurological Institute and lived within two hours driving distance of CUMC. One of the authors (E.D.L.) reviewed the office records of all selected patients; patients with diagnoses or physical signs consistent with other movement disorders were excluded. At the time of the record review, the most recent Hoehn and Yahr score [22] was extracted for PD cases and, based on the most recent Unified Parkinson's Disease Rating Scale (UPDRS) score [23], the relative severity of tremor vs. non-tremor motor phenomenology was converted into a ratio and a designation of tremor-predominant PD vs. bradykinetic-rigid PD was assigned, as described [24].

Control subjects were recruited for the same study during this time period. Controls were identified using random digit telephone dialing within a defined set of telephone area codes that were represented by neurological cases within the New York Metropolitan area. They were screened for ET using a brief screening questionnaire. Controls were frequency-matched to ET cases based on current age (5 year intervals).

The CUMC Internal Review Board approved of all study procedures. Written informed consent was obtained upon enrollment.

Study Evaluation

A trained research assistant conducted an in-person evaluation, administering demographic and medical history questionnaires. One of the questions asked the participant whether anyone in his or her family had shaking or tremor, with potential responses coded as “ET”, “PD”, “both”, or “non-specific tremor”. This included all relatives; however, the large majority of probands focused their responses on first- and second-degree relatives. Additional information about these conditions was provided if the participant required clarification. If the answer was “yes”, then further data were collected, using a semi-structured questionnaire, on the diagnosis and the relationship of the affected relative to the proband.

Validation of self-reported ET diagnosis is an important feature of all clinical and epidemiological research on ET, as these reports may not be correct. Therefore, during the in-person assessment of the probands with ET or ETPD, a videotaped neurological examination was also performed. This included one test for postural tremor and five for kinetic tremor (12 tests total) as well as assessments of parkinsonian features. A neurologist specializing in movement disorders (E.D.L.) used a reliable and valid 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 (none), 1 (mild), 2 (moderate), 3 (severe) [25]. Controls underwent the same videotaped neurological examination and tremor rating.

Diagnoses

Diagnoses of ET were re-confirmed by 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 including thyroid dysfunction or medication) [25]. The diagnosis of PD was confirmed using published diagnostic criteria [26]. Subjects with ETPD had to fulfill diagnostic criteria for both ET (except for the presence of co-existing PD) and PD; furthermore, we required that the ET diagnosis had been assigned by a movement disorder neurologist a minimum of three years prior to the PD diagnosis [27] and that no red flags were present during those first three years to suggest that the initial “ET” diagnosis was a *forme fruste* of emerging PD (e.g., unilateral tremor, postural tremor in the absence of kinetic tremor). Controls did not meet diagnostic criteria for ET, PD or another movement disorder.

Validation Sub-study

We performed a sub-study to assess the validity of the family history information reported by probands. We were particularly concerned about the possibility that probands might confuse PD with ET. Therefore, we re-contacted probands who reported some relatives with ET and others with PD. During the telephone call with these probands, a research assistant administered a separate 23-item questionnaire for each reportedly affected relative. The questions elicited information on the specific symptoms of ET or PD, whether a formal diagnosis was made by a physician, whether that diagnosis was made by a neurologist, and the medications taken for that condition. The proband was asked to contact the reportedly affected relative if he or she was unsure of the answer to any question, and the research called back to obtain this information. The family history was considered valid when the proband reported (1) a formal diagnosis was made by a physician and either (2) that physician was a neurologist or the relative was taking the appropriate medication for that condition (i.e., carbidopa-levodopa for PD and primidone or propranolol for ET).

Analyses

Analyses were performed in SPSS (Version 21.0). We compared demographic and clinical features of disease groups using chi-square tests and Kruskal-Wallis tests. We compared the proportion of disease probands (e.g., probands with ET, PD or ETPD) who reported PD, ET, or tremor in their relatives to the proportion of control probands (reference group) who reported PD, ET, or tremor in their relatives; we used chi-square tests for these analyses.

Results

There were 444 participants (probands): 110 with ET, 130 with PD, 27 with ETPD and 177 controls (Table 1). As expected, ETPD cases were older than the other groups, reflecting a longer disease duration, both the PD and ETPD cases had a preponderance of males, and the ET and ETPD cases had a younger age of onset than the PD cases. The median number of living first-degree and second-degree relatives was similar across groups (ET = 10, PD = 9, ET+PD = 10, controls = 9, Kruskal-Wallis test = 2.81, $p = 0.42$).

In our validation sub-study, we were able to reach 8 of 17 targeted probands (4 ET, 3 PD, 1 control). The remainder had either moved or died. There were no refusals. Combined, these 8 probands had 23 relatives with reported ET ($n = 11$) or PD ($n = 12$). We were able to validate the diagnosis in 22 of 23 relatives. The one remaining relative, a second-degree

relative of an ET proband, was reported to have PD but the proband lacked additional information.

Overall, the categories of proband differed with respect to their reported family history (chi-square = 117.99, $p < 0.001$, Table 2a). A greater proportion of ET probands than control probands had a family history of ET alone (30.0% vs. 2.8%, $p < 0.001$, Table 2b), non-specific tremor (38.2% vs. 13.6%, $p < 0.001$, Table 2a) and both ET and PD in different relatives (6.4% vs. 0.6%, $p = 0.004$, Table 2a). However, proportion with a family history of PD did not differ between ET probands and control probands (10.9% vs. 8.5%, $p = 0.49$, Table 2b).

A greater proportion of PD probands than control probands had a family history of PD alone (20.0% vs. 8.5%, $p = 0.003$, Table 2b), ET alone (11.5% vs. 2.8%, $p = 0.002$, Table 2b), and both ET and PD in different relatives (6.9% vs. 0.6%, $p = 0.002$, Table 2a).

A greater proportion of ETPD probands than control probands had a family history of ET alone (18.5% vs. 2.8% $p < 0.001$, Table 2b) and non-specific tremor (40.7% vs. 13.6%, $p < 0.001$, Table 2a).

We also performed four analyses in which we stratified probands by (1) median age, (2) gender, (3) median age of onset and (4) in PD, tremor-predominant PD vs. bradykinetic-rigid PD; these analyses revealed a similar pattern of familial aggregation as the primary analyses (data not shown).

For each type of proband, we also performed an analysis in which we determined whether the relatives who were reported to have ET, PD or tremor were first-degree or second-degree relatives. For each type of proband, the number of reportedly affected first-degree relatives was approximately double the number of reportedly affected second-degree relatives (for ET probands, the ratio was 2.0:1; for PD probands, the ratio was 2.1:1; for ETPD probands, the ratio was 2.8:1; for control probands, the ratio was 2.5:1).

Discussion

When compared with control probands, a greater proportion of ET probands reported relatives with ET and a greater proportion of PD probands reported relatives with PD. These data are consistent with published data on the familial aggregation of each disorder [28, 29], and are one of several indicators of the importance of genetic factors in the etiology of these diseases.

We also found that a greater proportion of PD probands than control probands reported relatives with ET, providing evidence for shared familial risk of PD and ET. In addition, a family history of both ET and PD was reported by significantly more probands with either PD or ET than controls, pointing to familial co-aggregation of the two disorders.

When compared with control probands, a greater proportion of ET probands reported relatives with non-specific tremor. Some of these relatives are presumed to have ET or early (evolving) ET [30, 31]. While some may have had other forms of tremor (e.g., medication-

induced tremor), there is no evidence that ET families are more susceptible than control families to the tremor-inducing effects of certain medications

ETPD probands were more likely than controls to report relatives with ET or nonspecific tremor, resembling ET probands more than PD probands. The similarity of their pattern of familial risk to that of ET probands may reflect greater genetic similarity to ET than PD in this group.

The results were somewhat asymmetric in the sense that a family history of ET was reported significantly more often by PD probands than controls, whereas a family history of PD was reported by 10.9% of ET probands vs. 8.5% of control probands, a difference that was not statistically significant (Table 2b). There are several possible explanations. The sample size, though large for the entire group, was small in some subgroups, lessening the precision of some comparisons. Biological differences could have accounted for this asymmetry as well. PD and ET may each be influenced by a mixture of genetic effects, some of which are specific to each disorder while others influence risk for both disorders. The distribution of these effects may differ between PD and ET, so that among probands with PD, a substantial fraction of the susceptibility variants influence risk for ET as well as PD whereas among probands with ET, most of the susceptibility variants do not influence risk for PD.

Three prior studies assessed whether PD families have a higher than expected prevalence of ET [17–19], and our results agree with those reports. In 2007, investigators in the Mayo Clinic Family Study of Parkinson's Disease compared 981 first-degree relatives of 162 PD patients with 838 first-degree relatives of 147 controls, and reported that relatives of PD patients had a modest and marginally significantly increased risk of ET compared with relatives of controls (hazards ratio, HR = 1.51, $p = 0.08$) [17]. In 2009, a familial aggregation study of 303 PD patients and 249 controls was conducted through the PD Epidemiology Program Project of Crete [18]. Twenty-six (8.6%) of the PD patients reported at least one first-degree relative with ET, compared to 8 (3.2%) controls (odds ratio, OR = 2.83, $p = 0.015$) [18]. In 2010, a population-based family study in rural California evaluated the occurrence of ET in the relatives of PD patients compared to controls. For the PD patients, 45 of 2,980 (1.5%) first-degree relatives had ET; for controls, 31 of 2,981 (1.0%) first-degree relatives had ET (HR = 1.44, $p = 0.13$) [19]. One additional study of 56 probands (including 40 with PD and 9 with ET), examined the concordance of movement disorders in family members (77 secondary movement disorder cases, including those with ET and PD), finding a high but not perfect concordance; however, as noted by those authors, the study did not assess the frequency of these disorders so it is not possible to discuss the issue of increased risk [32].

The results of this study should be interpreted within the context of several limitations. First, while previous studies have shown that probands can provide reasonably accurate family history data for several neurological diseases (e.g., PD, seizures, migraine), they tend to under-report these diseases in their relatives [33–35]. Although we performed a careful validation sub-study, which provided reassuring evidence of the validity of reported ET and PD diagnoses among probands with ET or PD, we did not directly interview or examine the reportedly affected relatives, and this is clearly a study limitation. Furthermore, the various

non-study physicians assigning ET diagnoses likely used a range of different criteria, some of which may have been more and others less rigorous, and, in general, ET is often over-diagnosed [36]. We also provided an option, “non-specific tremor”, so that probands who were unsure of their relatives’ diagnosis could use this category, reserving the categories “ET” and “PD” for relatives about whose diagnoses they were more certain; this likely served to lessen the number of false reports of PD and ET. Second, one must also consider the possibility that probands with ET, already familiar with ET, may have been more likely to overreport ET in their relatives, and that the same may have held true for PD probands, whereas control probands, who were less familiar with ET and PD, might under-report such conditions in their relatives (i.e. family information bias). While this may have explained some of the aggregation we found (i.e., ET in ET families or PD in PD families), it would not necessarily have explained the evidence of co-aggregation that we found. Third, we did not report on the presence of both ET and PD in the same relative because we have found that most probands are generally not medically sophisticated enough to make this determination (i.e., that they may have a relative with a dual diagnosis of ET and PD). Hence, the value of reporting such data is limited. Furthermore, we did not include a proband category “non-specific” tremor because there was no need. The probands were all phenotyped in detail and so there was no lack of clarity as to their diagnoses.

In summary, the current study supports previous evidence of the familial aggregation of ET and PD separately. In addition, the study provides evidence of the co-aggregation of ET and PD. These findings have implications in terms of the debate about the links between ET and PD, suggesting that for some patients there are shared etiologies, shared genetic susceptibilities, and possibly, shared disease pathophysiologies.

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Table 1

Demographic and clinical features of 444 study participants (probands)

	Probands with ET n = 110	Probands with PD n = 130	Probands with ETPD N = 27	Control Probands N = 177	Significance
Age (years)	72.0 ± 12.2	69.1 ± 8.1	77.9 ± 7.2	74.8 ± 9.5	p < 0.001 ^a
Female gender [*]	61 (56.0)	57 (44.2)	10 (37.0)	111 (63.1)	p = 0.003 ^b
White race	103 (93.6)	122 (93.8)	23 (85.2)	159 (89.8)	p = 0.30 ^b
Education (years)	16.0 ± 2.5	16.4 ± 2.8	15.2 ± 4.5	15.8 ± 3.1	p = 0.10 ^a
Age of onset of symptoms (years)	41.0 ± 19.7	60.8 ± 11.3	45.1 ± 22.2	NA	p < 0.001 ^a

Values are numbers ± standard deviation or numbers (percentages).

^{*} Data missing on <1% of subjects.

ET = essential tremor, PD = Parkinson's disease, ETPD = essential tremor and Parkinson's disease, NA = not applicable.

^a Kruskal-Wallis test comparing all groups.

^b Chi-square test comparing all groups.

Table 2

a: Family history data in 444 probands				
Proband reported ...	Probands with ET n = 110	Probands with PD n = 130	Probands with ETPD N = 27	Control Probands N = 177
No tremor in any relatives	30 (27.3)	82 (63.1)	8 (29.6)	134 (75.7)
One or more relative with <i>non-specific tremor</i>	42 (38.2)^b	16 (12.3)	11 (40.7)^b	24 (13.6)
One or more relative with <i>ET</i>	26 (23.6)^b	6 (4.6)	5 (18.5)^b	4 (2.3)
One or more relative with <i>PD</i>	5 (4.5)	17 (13.1)	3 (11.1)	14 (7.9)
One or more relative with <i>ET</i> and one or more relative with <i>PD</i>	7 (6.4)^a	9 (6.9)^a	0 (0.0)	1 (0.6)

b: Family history of ET or PD in 444 probands				
Proband reported ...	Probands with ET n = 110	Probands with PD n = 130	Probands with ETPD N = 27	Control Probands N = 177
One or more relative with ET [*] No relatives with ET	33 (30.0)^b 77 (70.0)	15 (11.5)^a 115 (88.5)	5 (18.5)^b 22 (81.5)	5 (2.8) 172 (97.2)
One or more relative with PD ^{**} No relatives with PD	12 (10.9) 98 (89.1)	26 (20.0)^a 104 (80.0)	3 (11.1) 24 (88.9)	15 (8.5) 162 (91.5)

Chi-square (entire table) = 117.99, $p < 0.001$.

Values are numbers (percentages).

ET = essential tremor, PD = Parkinson's disease, ETPD = essential tremor and Parkinson's disease.

When compared with control probands, ^a $p < 0.01$, ^b $p < 0.001$ (chi-square test).

Significant values are in bold font.

^{*} including probands who reported one or more relative with ET and probands who reported one or more relative with ET and one or more relative with PD (see Table 2a).

^{**} including probands who reported one or more relatives with PD and probands who reported one or more relative with ET and one or more relative with PD (see Table 2a).