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Tremor and Other Hyperkinetic Movements

Brief Reports

Motor and Non-motor Features: Differences between Patients with Isolated Essential Tremor and Patients with Both Essential Tremor and Parkinson's Disease

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Abstract

Background: Patients with essential tremor (ET) who develop Parkinson's disease (PD) (i.e., ET→PD) may differ with respect to motor features (MFs) and non-motor features (NMFs) from patients with isolated ET. Few studies have assessed this issue.

Methods: In this retrospective chart review, we analyzed data on MFs and NMFs of 175 patients, including 54 ET→PD and 121 ET, actively followed in the Athens University 1st Neurology Department.

Results: Significantly more ET→PD than ET patients reported asymmetric tremor at ET onset (68.5% vs. 14.9%, $p<0.001$). Significantly more ET than ET→PD patients had head tremor (43.5% vs. 13.2%, $p<0.001$) and cerebellar signs (41.3% vs. 9.3%, $p<0.001$). More ET than ET→PD patients reported hearing impairment (65.3% vs. 28.3%, $p<0.001$) and restless legs syndrome (34.8% vs. 3.7%, $p<0.001$). Conversely, a larger proportion of ET→PD than ET patients reported rapid eye movement behavior disorder (51.9% vs. 10.0%, $p<0.001$), constipation (67.9% vs. 36.4%, $p<0.001$), and olfactory dysfunction (83.3% vs. 36.4%, $p<0.001$).

Discussion: The subset of ET→PD patients may have distinct MFs and NMFs that should be assessed further for the possible predictive value for the emergence of PD.

Keywords: Essential tremor, Parkinson's disease, tremor distribution, cerebellum, sleep, autonomic

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Introduction

A subset of patients with essential tremor (ET) will eventually develop Parkinson's disease (PD) (i.e., "ET→PD").[1] Only a small number of studies have examined the prevalence and evolution of clinical features seen in patients with this particular clinical combination.[2–4] Moreover, most studies have focused on motor features (MFs) of ET→PD patients.[2,3] Given the fact that ET is no longer considered a mono-symptomatic condition but, instead, a polysymptomatic disorder with both motor and non-motor elements,[5,6] we aimed to examine whether the ET→PD patients are distinct in terms of both MFs as well as non-motor features (NMFs). We also assessed the differences between ET and ET→PD in terms of signs at presentation. Characterization of these differences could provide clinical–prognostic indicators for subsequent PD development in ET patients and contribute to an improved understanding of the pathogenesis of these two disorders.

Methods

Patients

The clinical database of the Movement Disorders Outpatient Clinic of the 1st Neurology Department, Athens Medical School, was used for the current analyses, after approval was obtained from our

Institutional Review Board. The study was performed according to the Declaration of Helsinki. All patients provided informed consent. We searched the database for all patients who had visited the Outpatient Clinic during the past 3 years (September 2011 to August 2014) and who had the diagnosis of ET (assigned either prior to or during this time period). All patients were clinically evaluated by one of two neurologists specializing in movement disorders (A.G. or C.P.). The database search yielded 198 patients. Clinical records were retrospectively reviewed by A.G. Eight clinical records could not be located and 10 were incomplete. These 18 patients were excluded from the study, leaving 180 remaining patients.

The ET diagnosis was first assigned or confirmed by either A.G. or C.P. at the clinical assessment and then later confirmed during retrospective chart review by A.G. using criteria of definite ET according to the consensus statement of the Movement Disorder Society.[7] A diagnosis of ET was not assigned if bradykinesia, rigidity, or rest tremor appeared within 3 years of the onset of tremor attributed to ET. The diagnosis of PD was made by one of the two neurologists based on the presence during their neurological examination of at least two cardinal signs of PD in the absence of other possible etiologies. Based on the retrospective clinical record review, five patients either did not have ET or PD or had co-existing diagnoses (two psychogenic tremor, one dystonic tremor, one drug-induced parkinsonism, one vascular parkinsonism). After removing these five patients, 121 patients with ET and 54 patients with ET→PD remained (total = 175), in all of whom the ET preceded the diagnosis of PD by at least 3 years.

Definitions and terms

The following terms were used: *abnormal fine movements*, abnormal or slow finger tap-counting (i.e., tapping each finger to the thumb while counting backwards) or finger tapping (i.e., tapping the thumb to the pointing finger as rapidly as possible); *action tremor*, tremor that occurs during voluntary movement of the affected body part; *asymmetric tremor at onset of ET*, unilateral tremor or markedly asymmetric tremor; *bradykinesia*, slow movements during at least one of the following, finger tapping, toe tapping or other rapid alternating movements; *cerebellar signs*, dysdiadochokinesia assessed by rapid alternating movements, or dysmetria assessed by the finger-to-nose maneuver, or nystagmus assessed by the moving finger test, or ocular dysmetria defined as the constant under- or over-shooting of the eyes when attempting to fix gaze on an object; *gait swing*, decreased arm swing while walking; *gait tremor*, rest tremor in the arm(s) while walking; *rigidity*, resistance to passive movement of major joints; *head (i.e. neck) tremor*, rhythmic shaking of the head; *hypophonia*, soft voice; *hypomimia*, reduced facial expression; *intention tremor*, tremor that increases as finger reaches target in finger-to-nose maneuver, or as hand reaches mouth when drinking from a cup; *postural tremor*, tremor when holding arms horizontally extended in front of the body; *thumb tremor*, tremor of thumb at rest; *widespread tremor*, tremor not limited to hands or arms but also present in the head or legs.

Data collection and abstraction procedures

A data summary form included self-reported family history (first-degree relatives) of ET or/and PD, ages at onset (based on first motor symptom) of ET and, separately, of PD, type of first PD motor symptom. Data from each visit included data from the history (age, current ET and PD medications, predominant side of tremor at onset, response to ethanol, constipation, olfactory dysfunction, rapid eye movement behavior disorder [RBD], restless legs syndrome [RLS]), data from the neurological examination (cerebellar signs [intentional tremor, dysdiadochokinesia, dysmetria, nystagmus, or ocular dysmetria], arm swing, rest tremor, rigidity, bradykinesia, postural instability, cogwheel sign, blink reflex) and data based on both history and examination (hearing impairment, hypophonia, anatomic distribution of tremor [i.e., upper and lower limbs, head/neck, voice], description of tremor [i.e., action, postural, rest]). The NMFs were routinely assessed by a standard questionnaire (Table 1). In addition to history, hearing impairment was assessed during examination by asking the patient to repeat questions presented over a range of volumes. When the predominant clinical sign was tremor, we characterized PD as tremor-predominant. When the predominant clinical sign was rigidity or axial bradykinesia, we characterized PD as akinetic type. When both of the above were equally present, we characterized PD as mixed type.

Statistical analysis

Differences between ET→PD and ET patients were assessed using Pearson's chi-square tests or Fisher's exact tests (categorical variables) and Student's t-tests (continuous variables). All statistical analyses were performed using the STATA statistical package (INTERCOOLED STATA 12.0 Stata Corp, College Station, TX). Associations were considered significant when $p<0.05$.

Results

Demographic and clinical characteristics

ET→PD patients were, on average, older than ET patients (72.63 [±9.25] vs. 66.90 [±12.35], p=0.003). There was no difference with regards to gender or age of onset of ET. Fewer ET→PD than ET patients reported a family history of ET (14/54 [25.9%] vs. 56/121 [46.3%], p=0.01). Conversely, more ET→PD than ET patients reported a family history of PD (7/54 [13.0%] vs. 1/121 [0.8%], p=0.001). The latency between ET and PD onset was 15.3 ± 12.0 (mean ± SD) years, and in the majority of ET→PD patients (36/54 [66.6%]), the latency was 10 years or more. The mean duration of ET was somewhat higher in the ET→PD group (18.39 ± 14.39 years in ET→PD vs. 13.69 ± 12.69 years in ET, p=0.03). More ET→PD than ET patients reported asymmetric tremor at ET onset (37/54 [68.5%] vs. 18/121 [14.9%], p<0.001). Among the 37 ET→PD patients with asymmetric tremor at ET onset, the side of greatest initial action tremor severity (ET) was the predominant side of PD signs in nearly all (35/37 [94.6%]). No difference was detected between the two groups in terms of the somatotopic spread of tremor, which was from the arms to the head in most of the cases (with the exception of

Table 1. **Assessment of Non-motor Features**

Assessment of hypophonia with three questions (+ clinical impression on the exam + reported by the caregiver)
1. Has your voice become weaker than it used to be?
2. Does your interlocutor often ask you to repeat what you said?
3. Do the above symptoms last more than three months?
(Yes to #3 AND to [#1 or 2] necessary for diagnosis)
Assessment of hearing impairment with four questions (+clinical impression at the exam)
1. Do you have a problem hearing voices over the telephone?
2. Are you frequently asking others to repeat the things they say?
3. Do you often think "my hearing is not as good as it used to be"?
4. Do the above symptoms last more than three months?
(Yes to #4 AND to [#1 or 2 or 3] necessary for diagnosis)
Assessment of olfactory dysfunction with four questions
1. Do you experience loss or change in your ability to taste or smell?
2. Can you enjoy the smell of your food?
3. Can you smell your perfume?
4. Do the above symptoms last more than three months?
(Yes to #4 AND to [#1 or 2 or 3] necessary for diagnosis)
Assessment of constipation with four questions
1. Do you have fewer than three defecations per week?
2. Are your stools lumpy or hard?
3. Do you need manual maneuvers or laxative drugs to facilitate defecations?
4. Do the above symptoms last more than three months?
(Yes to #1, #2 & #4 necessary for diagnosis)
Assessment of RLS with four questions
1. Do you sometimes experience unpleasant sensations (such as creeping, crawling, pulling, itching, tingling, burning, aching) in your legs and/or a strong urge to move your legs?
2. Do you feel relief from the symptoms after moving the legs?
3. Does this happen at night or while resting at other times as well?
4. Has any of your family experienced the same problem?
(Yes to #1, #2 & #3 necessary for diagnosis)
Assessment of RBD with four questions
1. Do you have frightening, intense, vivid dreams?
2. Have you ever hurt your bed partner or yourself during sleep?

Table 1. **Continued**

3. Has your bed partner complained of sudden movements, talking, laughing or any other motor behavior such as acting out a dream while you are asleep?
4. Has any of your family experienced the same problem?
(Yes to #1 & #3 necessary for diagnosis)

Abbreviations: RBD, Rapid Eye Movement Behavior Disorder; RLS, Restless Legs Syndrome.

one ET→PD and three ET patients who reported that they developed arm tremor several years after the onset of head tremor).

Motor features of ET→PD vs. ET, assessed at last visit

Significantly fewer ET→PD than ET patients had widespread tremor (24/54 [44.4%] vs. 77/121 [63.6%], p=0.03), head tremor (7/53 [13.2%] vs. 50/115 [43.5%], p<0.001), or cerebellar signs (5/54 [9.3%] vs. 50/121 [41.3%], p<0.001) (Table 2).

The great majority of ET→PD patients (51/54 [94.4%]) were classified as tremor-predominant; the three remaining patients were classified as mixed type of PD. As expected, all extrapyramidal signs were more common in ET→PD than in ET patients. Rest tremor was the initial cardinal sign of PD in 100% of ET→PD patients, and was also found in a small proportion of ET patients at last visit (16/121 [13.2%], p<0.001). Certain extrapyramidal signs such as abnormal blink reflex, decreased arm swing during gait ("gait swing") and cogwheel sign were more common in ET→PD, but were also observed in some of the ET patients (abnormal blink reflex 51/54 [94.4%] vs. 24/107 [22.4%], decreased arm swing 42/52 [80.1%] vs. 11/118 [9.3%] and cogwheel sign 52/54 [96.3%] vs. 12/121 [10.0%], all three were significantly different, with p≤0.001). A larger proportion of the ET→PD than ET patients had thumb tremor at rest (6/54 [11.1%] vs. 2/121 [1.7%], p=0.01) and "gait tremor" (37/52 [71.1%] vs. 11/119 [9.2%], p<0.001).

Non-motor features ET→PD vs. ET, assessed at last visit

A larger proportion of ET→PD than ET patients exhibited the following NMFs: RBD (28/54 [51.9%] vs. 12/120 [10.0%], p<0.001), constipation (36/53 [67.9%] vs. 43/118 [36.4%], p<0.001), and olfactory dysfunction (45/54 [83.3%] vs. 66/121 [54.6%], p<0.001). Conversely, fewer ET→PD than their counterparts with ET reported hearing impairment (15/53 [28.3%] vs. 79/121 [65.3%], p<0.001) or RLS (2/54 [3.7%] vs. 41/118 [34.8%], p<0.001) (Table 2).

Discussion

A notable subset of ET patients will eventually develop PD,[1,8–10] raising the issue of whether there is a distinct clinical ET phenotype that is associated with the eventual co-occurrence of the two disorders. Few previous studies have explored the clinical features of this combination. These studies have indicated the possible presence of several differences in MFs[2–4,8,11] and NMFs[12,13] between patients with isolated ET and their ET→PD counterparts.

We performed a retrospective chart review of 54 ET→PD vs.121 ET patients. There were no significant differences between the two groups in age at ET onset, but age at last visit tended to be higher in the ET→PD group. There were no significant differences between the two groups in gender, in variance with a previous study where a male predominance in ET → PD was noted.[11]

ET is known to be highly familial[14–16] and a positive family history of ET is often reported in PD.[17] In our study, far fewer ET→PD than ET patients reported a first-degree relative with ET (25.9% vs. 46.3%, p=0.01). Conversely, a larger proportion of ET→PD than ET patients reported a first-degree relative with PD (13.0% vs. 0.8%, p=0.001). These findings suggest that among ET patients, the ET→PD subset either share common risk factors with PD, or that in certain families, ET and PD are genetically related, probably sharing a common hereditary predisposition.

We observed several clinical differences in tremor characteristics between ET and ET→PD groups. Most of our ET→PD patients (37/54 [68.5%]) reported that their action tremor was unilateral or markedly asymmetric at ET onset. This finding has been reported previously,[3] but not confirmed in a subsequent study.[11] The side of greatest initial ET action tremor severity was the side of predominant PD signs, in line with previous studies.[8,11] This finding supports the notion of one common process underlying both the ET prior to PD onset and the ET transition to PD. In terms of the anatomical distribution of tremor, significantly fewer ET→PD than ET patients had widespread tremor or head tremor, which is in line with previous results.[4] Overall, the above observations suggest possible distinct tremor features in ET patients who are prone to developing PD.

Fewer ET→PD than ET patients exhibited cerebellar signs at their last visit. This is in line with a previous study.[4] The interpretation is not clear, but could point to differences in involvement of the cerebellum in each patient subtype.

ET→PD patients more frequently exhibited certain NMFs than the ET group. We found that olfactory dysfunction (self-reported anosmia/hyposmia) was more likely to occur in ET→PD than ET. Several though not all prior studies demonstrated mild olfactory dysfunction in ET, attributed to a potential cerebellar dysfunction,[18] whereas PD olfactory dysfunction, which is more marked than that seen in ET, is associated with cellular damage in the olfactory bulb.[19]

Table 2. **Comparison of Demographic Data, Data from History, Motor Features and Non-motor Features of ET→PD Patients (N=54) vs. ET Patients (N=121) at Last Visit**

	ET→PD (n=54)	ET (n=121)	Significance (p)
Demographic data			
Gender (males: n; %)	24/54; 44.4%	52/121; 42.9%	0.86[1]
Age at last visit (mean ± SD years)	72.63 (±9.25)	66.90 (±12.35)	0.003[3]
Data from history			
Age at onset of ET (mean ± SD years)	54.24 (±15.24)	53.21 (±15.84)	0.69[3]
Age at onset of PD (mean ± SD years)	69.61(±8.95)		
Duration of ET (mean ± SD years)	18.39 (±14.39)	13.69 (±12.69)	0.03[3]
Duration of PD (mean ± SD years)	3.02 (±3.50)		
Family history of ET (n; %)	14/54; 25.9 %	56/121; 46.3%	0.01[1]
Family history of PD (n; %)	7/54; 13.0%	1/121; 0.8%	0.001[2]
Asymmetric tremor at ET onset (n; %)	37/54; 68.5%	18/121; 14.9%	<0.001[1]
Ethanol response (n; %)	17/22[4]; 77.2%	95/99[4]; 96.0%	0.003[1]
Extrapyramidal signs			
Bradykinesia (n; %)	40/52[4]; 77.0%	28/121; 23.1%	<0.001[1]
Rigidity (n; %)	50/50[4]; 100%	16/120[4]; 13.3%	<0.001[1]
Cogwheel sign (n; %)	52/54; 96.3%	12/121; 10.0%	<0.001[1]
Abnormal fine movements (n; %)	28/54; 51.9%	29/121; 24.0%	<0.001[1]
Postural instability (n; %)	13/54; 24.1%	10/102[4]; 9.8%	0.03[2]
Gait swing (n; %)	42/52[4]; 80.1%	11/118[4]; 9.3%	<0.001[2]
Camptocormia (n; %)	26/52[4]; 50.0%	9/119[4]; 7.6%	<0.001[2]
Hypophonia (n; %)	21/52[4]; 40.4%	33/120[4]; 27.5%	0.09[1]
Hypomimia (n; %)	31/52[4]; 59.6%	24/120[4]; 20.0%	<0.001[1]
Abnormal blink reflex (n; %)	51/54; 94.4%	24/107[4]; 22.4%	<0.001[1]
Tremor characteristics			
Head (neck) tremor (n; %)	7/53[4]; 13.2%	50/115[4]; 43.5%	<0.001[1]
Voice tremor (n; %)	14/51[4]; 27.5%	19/114[4]; 16.7%	0.11[1]
Jaw tremor (n; %)	3/54; 5.6%	10/121; 8.3%	0.76[2]
Hand tremor (n; %)	54/54; 100%	121/121; 100%	
Thumb (at rest) (n; %)	6/54; 11.1%	2/121; 1.7%	0.01[2]
Lower limb tremor (n; %)	5/54; 9.3%	15/121; 12.4%	0.62[2]
Widespread tremor (n; %)	24/54; 44.4%	77/121; 63.6%	0.03[1]

Table 2. **Continued**

	ET→PD (n=54)	ET (n=121)	Significance (p)
Gait tremor (n; %)	37/52[4]; 71.1%.	11/119[4]; 9.2%	<0.001[1]
Rest tremor (n; %)	51/51[4]; 100%	16/121; 13.2%	<0.001[2]
Postural tremor (n; %)	43/51[4]; 8.3%	97/121; 80.2%	0.52[1]
Action tremor (n; %)	51/54; 94.4%	119/121; 98.4%	0.17[2]
Intention tremor (n; %)	5/54; 9.3%	108/121; 89.3%	<0.001[2]
Cerebellar signs (n; %)	5/54; 9.3%	50/121; 41.3%	<0.001[2]
Non-motor features			
Hearing impairment (n; %)	15/53[4]; 28.3%	79/121; 65.3%	<0.001[1]
Olfactory dysfunction (n; %)	45/54; 83.3%	66/121; 54.6%	<0.001[1]
Constipation (n; %)	36/53[4]; 67.9%.	43/118[4]; 36.4%	<0.001[1]
RLS (n; %)	2/54; 3.7%	41/118[4]; 34.8%	<0.001[2]
RBD (n; %)	28/54; 51.9%	12/120[4]; 10.0%	<0.001[2]

Abbreviations: ET, Essential Tremor; PD, Parkinson's Disease; RBD, Rapid Eye Movement Behavior Disorder; RLS, Restless Legs Syndrome; SD, Standard Deviation.
[1]Pearson's chi-square test.
[2]Fisher's exact test.
[3]Student's t-test two-group mean comparison.
[4]Data not available for all subjects.

We showed that ET→PD patients were comparatively less likely to report hearing impairment (self-reported deficit/examination) at their last visit than their ET counterparts. To our knowledge, no prior studies have assessed hearing in ET→PD patients vs. ET patients. Previous studies suggested that abnormalities in the ventral thalamus could result in both tremor and hearing loss in ET patients,[20–22] and that ET patients have a higher probability of reporting a hearing problem than PD patients.[20]

In our study, a significantly higher proportion of ET→PD than ET patients reported constipation at their last visit. Constipation is a common NMF in PD, attributed to peripheral autonomic neuronal degeneration;[23] by contrast, no difference in the prevalence of constipation has been reported between ET patients and the general population.[24]

Several studies indicate that ET is associated with sleep disorders.[24–26] We found that more ET→PD than ET patients reported RBD at their last visit. RBD is common in PD, whereas significant associations between ET and RBD have been previously observed in some studies[24] but not in others.[27]

As expected, all extrapyramidal signs were far more common in ET→PD than in ET patients. Certain cardinal extrapyramidal signs such as rest tremor, abnormal blink reflex, decreased arm swing during gait and cogwheel sign were also observed in some of the ET patients, in agreement with previous series.[28–30] Rest tremor, which was the initial cardinal sign of PD in 100% of ET→PD patients, was also present in a small proportion of ET patients with prolonged disease duration (≥15 years).

The main limitation of the study was the retrospective chart design. A prospective design is preferred, but is not feasible for many reasons, including costs and the extremely long follow-up period required. There is a paucity of data in this area, and the current study, even with these methodological limitations, adds to our knowledge. Another limitation was the lack of extended follow-up into very old ages, raising the possibility that some of the patients classified as "ET only" might later also develop PD. A third issue is that standardized PD rating scale scores were not available for all patients; hence, these data were not presented in the present paper. Fourth, a large number of comparisons were made, which increases the risk of Type I errors. One approach would have been to correct for multiple comparisons (e.g., Bonferroni correction), although this approach would have been far too conservative and run the risk of Type II errors. Given the paucity of data in the field, it is preferable to treat these analyses as exploratory analyses that yield putative associations for further confirmatory testing. Additionally, ET→PD patients were not all examined in a

standardized manner with respect to levodopa dosing (e.g., all in the On or Off state) and this could have influenced our results. Finally, another limitation of our study is that we are not able to estimate the number of our ET patients who are likely to develop incident PD in the future, as the study does not provide an estimate of the incidence rate of PD among ET cases.

In conclusion, we found that the subset of ET patients who subsequently develop PD probably has distinct MFs and NMFs from their ET counterparts who do not develop PD. The significance of the study is threefold. First, it underscores that ET is not a monosymptomatic movement disorder but is a more complex entity with motor as well as non-motor manifestations, which do not manifest uniformly across all patients. Second, while most of the findings are essentially in line with previous observations, the association of certain clinical features with ET→PD co-occurrence has been relatively unexplored and its further study may offer insights into both ET and PD pathologies. Third, it provides data around which to structure further prospective studies on potential predictive factors of the conversion from ET to PD.

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