Increased Prevalence of Non-motor Symptoms in Essential Tremor

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Abstract

Background: Cases with essential tremor (ET) have been described with Lewy body inclusions, the hallmark of Parkinson disease (PD). Patients with PD may suffer from anosmia, depression, constipation, and rapid eye movement sleep behavior disorder (RBD), sometimes years before the appearance of their motor syndrome. The objective of this study was to evaluate the prevalence of these non-motor Parkinson’s associated symptoms in patients with ET.

Methods: Fifty ET subjects were contacted by phone and given questionnaires evaluating the presence or absence of anosmia, depression, constipation, and RBD. Frequencies of these symptoms were compared with their published prevalence in the general population.

Results: Of the patients with ET, 4.5% reported having anosmia or hyposmia and 21.7% reported being constipated, similar to what is observed in the general population. Using a screening questionnaire for RBD, 43.5% of ET patients are possibly suffering from RBD, whereas in the general population prevalence is estimated to be 0.5%. Finally, depression was detected in 21.7% of ET patients; in the general population, prevalence is 5%.

Discussion: Patients with ET seem to have more RBD and more depression than found in the general population. Prospective studies with normal control groups are needed to confirm these findings.

Keywords: Essential tremor, depression, constipation, rapid eye movement sleep behavior disorder, anosmia

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Introduction

Essential tremor (ET) is the most prevalent movement disorder, with a prevalence of 4–5.6% (age ≥40 years) that increases with age,1,2 yet some aspects of its clinical manifestations need clarification. ET is classically defined as a disease with exclusively motor features. The cornerstone characteristic of ET is an 8–12 Hz kinetic tremor of both upper limbs (90–95%), which can be asymmetrical, and may be accompanied by head (30%), legs (10–15%), and voice (20%) tremors.3 The population of ET patients is phenotypically heterogeneous; not every patient develops head tremor, and some patients even develop rest tremor,4–6 a feature highly characteristic of PD patients. In fact, ET is so heterogeneous that it is probably the most commonly misdiagnosed neurological disorder.7 Some studies have found that up to 30–50% of patients with an ET diagnosis actually do not have ET.8

Recently, several studies have uncovered non-motor features of ET,9 including decreased olfaction, depression, and rapid eye movement sleep behavior disorder (RBD). Amongst the studies that evaluated olfaction in ET patients, some have found a decrease,10,11 although others did not.12–14 The co-occurrence of ET and depression has been observed with a high frequency.15–18 Only one study has evaluated the prevalence of RBD in ET patients19 and found no evidence of an increased incidence of RBD. Finally, no study has evaluated the occurrence of constipation in ET patients.

Recent analysis of ET brains has unveiled two types of changes that possibly indicate two different mechanisms for the pathogenesis of ET.20 Including decreased olfaction, depression, and rapid eye movement sleep behavior disorder (RBD). Amongst the studies that evaluated olfaction in ET patients, some have found a decrease,10,11 although others did not.12–14 The co-occurrence of ET and depression has been observed with a high frequency.15–18 Only one study has evaluated the prevalence of RBD in ET patients19 and found no evidence of an increased incidence of RBD. Finally, no study has evaluated the occurrence of constipation in ET patients.

Recent analysis of ET brains has unveiled two types of changes that possibly indicate two different mechanisms for the pathogenesis of ET.20 Approximately 75% of the studied brains have cerebellar changes (torpedo cells), whereas other brains had Lewy bodies in the locus ceruleus, defining a “Lewy bodies ET” subtype. A link between PD and ET has been debated for years and the relationship between
the two disorders is still unclear. Pre-existing ET is a risk factor for the development of PD, the risk being slightly to highly increased depending on the study, with a fourfold increased risk being a figure commonly accepted. The two diseases may have a common genetic background: genome-wide association studies have found specific single nucleotide polymorphism in the leucine-rich repeat and Ig containing 1 gene (LINGO1) as a risk for both PD and ET, providing a genetic link between the two disorders, whereas others studies did not.

Obviously, even though ET is the most prevalent movement disorder, we have limited knowledge regarding its pathogenesis, its relationship to PD, and its non-motor features are just starting to be unveiled. We thus hypothesized that ET patients may have a higher prevalence of pre-clinical features that are associated with PD, namely depression, anosmia, constipation, and RBD.

**Methods**

**Study population**

Consecutive patients from a list of patients who had previously participated in a field survey about ET were contacted by phone and verbal informed consent was obtained. Diagnosis of ET had been previously made by a movement disorder specialist, based on specific criteria according to the Tremor Investigation Group (TRIG), which classify the degree of diagnosis certainty as confirmed, probable, or possible. Only participants who received a diagnosis of ET were contacted. Calls were carried out from June 30, 2011, to July 15, 2011. This study was approved by the research and ethics board of the University of Montreal Health Centre.

**Evaluation of subjects**

The following information was updated and recorded for each contacted subject, either from patient records or direct questioning: brief medical history, current drugs, alcohol intake, and smoking status. In order to evaluate olfactory function, RBD, constipation, and depression, the following questionnaires were performed by telephone interview.

**Olfaction.** Since no questionnaire is available to evaluate olfaction, we evaluated olfaction by simply asking patients if they have noted a change in their ability to smell or taste.

**Rapid eye movement sleep behavior disorder.** We used the REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ). The RBDSQ is a 10-item instrument that assesses the subject’s sleep behavior with short questions that have to be answered by yes or no. This questionnaire addresses 1) the frequency and contents of dreams and their relationship to movements during sleep, 2) self-injuries and injuries to the bed partner, 3) motor behavior while asleep (talking, sudden movements), 4) awakening and disturbed sleep and finally, 5) the presence of any neurological disorder. The cut-off for a positive test result is ≥5 with a sensitivity of 96% and a specificity of 92%.

**Constipation.** The diagnosis of functional constipation was based on the Rome III diagnostic criteria. The diagnosis criteria must include two or more of the following items for at least 25% of defecations: 1) straining, 2) lumpy or hard stools, 3) sensation of incomplete evacuation, 4) sensation of anorectal obstruction/blockade, 5) manual maneuvers to facilitate defecations, 6) fewer than three defecations per week. Moreover, loose stools are merely present without laxative use. The symptoms above should be present for the last 3 months and have started at least 6 months prior to diagnosis. Participants who received a diagnosis of constipation and were treated with laxatives were also considered as having constipation.

**Depression.** We used the geriatric depression scale-15 (GDS-15) to screen for the presence of current depression in ET patients. This is a 15-item yes/no questionnaire that does not focus on somatic symptoms and has no question on suicide. A score between 5 and 9 was categorized as a minor depressive disorder and a score of 10 and above as a major depressive disorder.

**Statistical analysis**

Statistical analyses were performed in SPSS (Version 17.0), using Student’s t-tests and chi-square tests to compare female and male subjects.

**Study sample description**

We contacted 63 patients. One patient was not able to complete the telephone interview because of a hearing deficit. Another patient refused to participate and did not provide any reason. One patient was deceased, and, finally, 14 patients did not return our calls. Of these there were 10 males and four females. The mean age of these 14 patients was 50 ± 17 years. Forty-six participants completed the questionnaires. More females (33 [71.7%]) were interviewed than males (13 [28.3%]). The mean age of the participants was 57.17 ± 19.48 years, with a range of 13–86 years. Mean duration of ET of our subjects was 24.67 ± 19.80 years and mean age of onset of ET was 31.49 ± 22.57. There were no significant differences between female and male subgroups (Table 1) in terms of age at the time of the interview (p = 0.393), duration of ET (p = 0.102), age of onset of ET (p = 0.426), ET diagnosis (p = 0.559), dominance (p = 0.783), alcohol intake (p = 0.496), caffeine consumption (p = 0.523), and tobacco use (p = 0.351).

**Non-motor symptoms**

Table 2 summarizes the non-motor symptoms. In our sample of 46 patients, two participants reported olfaction change or loss (4.5%). A substantial number of subjects (20 patients or 43.5% of the sample) reach the positive cut-off of 5 at the RBDSQ, suggesting that they
might be affected by RBD. When looking at the sex of the RBD-positive subjects, 14 (70%) were females while 6 (30%) were males.

Regarding the occurrence of constipation in our sample, nine subjects met the ROME III criteria while one patient reported using laxatives (without a concomitant constipation history), for a total of 10 subjects (21.7%). More women (eight) suffered from constipation than men (two).

Nine participants (19.6%) scored between five and nine on the GDS-15 test, suggesting a minor depressive disorder, whereas one patient (2.2%) scored above 10, suggesting major depressive disorder. The male/female ratio in our sample was 3:7. In addition, 17 patients (37%) reported previous diagnosis of depression, 14 of them being female patients.

**Discussion**

In our sample of 46 patients with ET, we found a higher prevalence of RBD, and depression but not of anosmia or constipation. A positive score for RBD was obtained in 43.5% of the subjects. Of note, two of our patients reported suffering from sleep apnea; the effect

| Table 1. Demographic Data |
|---------------------------|
| Variables                  | Female (71.7%) (n=33) | Male (28.3%) (n=13) | Total (n=46) |
| Age in years, m ± s (range) | 58.73 ± 19.55 (13–86) | 53.23 ± 19.48 (20–75) | 57.17 ± 19.48 (13–86) |
| Duration of ET, m ± s (range) | 27.84 ± 19.32 (3–66) | 17.54 ± 17.23 (3–59) | 24.87 ± 19.14 (3–66) |
| Age of onset, m ± s (range) | 29.78 ± 22.97 (1–75) | 35.69 ± 21.84 (10–69) | 31.49 ± 22.57 (1–75) |
| ET diagnosis, n (%)          |                       |                     |               |
| • Confirmed                 | 14 (42.42)            | 5 (38.46)           | 19 (41.3)     |
| • Probable                  | 6 (18.18)             | 5 (38.46)           | 11 (23.9)     |
| • Possible                  | 10 (30.30)            | 3 (23.07)           | 13 (28.3)     |
| • Others                    | 3 (9.09)              | 0 (0)               | 3 (6.5)       |
| Dominance, n (%)            |                       |                     |               |
| • Right                     | 26 (78.8)             | 11 (84.6)           | 37 (80.4)     |
| • Left                      | 5 (15.2)              | 1 (7.7)             | 6 (13)        |
| • Ambidextrous              | 2 (6.1)               | 1 (7.7)             | 3 (6.5)       |
| Alcohol consumers, n (%)    | 22 (66.7)             | 10 (76.9)           | 32 (69.6)     |
| Caffeine consumers, n (%)   | 28 (84.8)             | 10 (76.9)           | 38 (82.6)     |
| Smokers, n (%)              | 6 (18.2)              | 4 (30.8)            | 10 (21.7)     |

ET, Essential Tremor; m, Mean, s, Standard Deviation.

Table 2. Non-Motor Symptoms in Participants with Essential Tremor

| Non-Motor Symptoms                  | Total (n=46) | General Population (% only) |
|-------------------------------------|--------------|-----------------------------|
| Olfaction change/loss, n (%)        | 2 (4.5)      | 1.6%<sup>33</sup>           |
| RBD, n (%)                          | 20 (43.5)    | 0.5%<sup>34</sup>           |
| Constipation, n (%)                 | 10 (21.7)    | 19.4%<sup>29</sup>          |
| Depression, n (%)                   | 10 (21.7)    | 5%<sup>35</sup>             |
| Previous depression, n (%)          | 17 (37)      | 17%<sup>35</sup>            |

RBD, Rapid Eye Movement Sleep Behavior Disorder.
of this concomitant condition on the specificity of the RBDSQ is currently unknown.28

Interestingly, this number is very high compared to the prevalence in the general population which is estimated at 0.5%.34 So far, only one other group has evaluated the prevalence of RBD in ET patients, using a different questionnaire, and found no evidence of an increased frequency of RBD.19 In this study, probable RBD diagnosis was assigned to subjects on the basis of a unique question assessing dream acting only. As the questionnaire used in our study evaluates most aspects of RBD, its sensitivity and specificity are high, as determined by Stiasny-Kolster.29

The prevalence of RBD is of course also much higher in patients with α-synucleinopathies: Parkinson’s disease (between 14.6% and 33%36,37), and multiple system atrophy (69%38). This is comparable with the prevalence that we obtained in our survey and could support involvement of the same brainstem structures that are responsible for this sleep disorder, or perhaps similar synuclein pathology.

In our subjects, 21.7% were depressed and 37% had a depression history, which is higher than the 5% and 17% lifetime prevalence in the general population.35 Most patients with a history of depression developed ET at a young age (before 41). A twofold greater depression prevalence in females than in males was observed in our sample, which is also commonly reported in the general population.25 A previous study had found that 34% of ET patients were at least mildly depressed, according to the Beck Depression Inventory (BDI).15 In the same study, 48% of PD patients were found to be depressed. In our cohort, the prevalence of depression is thus in between that of the general population and the PD population.

In our study, two patients out of 46 (4.5%) reported anosmia/hyposmia whereas in the general population, self-reported prevalence of anosmia/hyposmia is 1.6%.35 Most studies have not found hyposmia in ET patients,12,13,39 whereas other studies have shown a small diminution of olfaction,10,11,40,41 albeit to a lesser degree than in PD patients. The number that we found may be an underestimate since decreased olfactory function is likely often subclinical.10,11,14,41

We also did not find different rates of constipation in our patients compared to the general population: 21.7% of our subjects presented constipation, whereas constipation occurs in up to 27% of people depending on demographic factors, and the constipation definition used to perform the study.29

It remains unclear why both depression and RBD are so common in ET patients. Are these markers more specific to ET than constipation and olfactory deficit? Are they specific to brainstem structures involved in ET by Lewy bodies?2

This study has a number of important limitations but we feel it provides some preliminary data that would be interesting to pursue with prospective studies using a larger number of patients, including a matched control group for age and sex, among other things. Also, using a validated questionnaire against more definitive measures such as polysomnography to confirm RBD and smell tests for anosmia would increase the reliability.42

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