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# REM sleep behavior disorder and Prodromal Parkinson's Disease in patients with Essential Tremor

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ABSTRACT

Several studies suggested the presence of non-motor symptoms in Essential Tremor (ET), including REM sleep behavioral disorder (RBD). RBD is an essential criterion for Prodromal Parkinson's Disease (PPD), suggesting a link between ET and PD. Our objective was to assess the prevalence and features of ET patients with RBD and PDD.

RBD was diagnosed by questionnaire screening, followed by polysomnography. PPD risk factors and prodromic markers were assessed with a structured protocol. Patients were characterized regarding tremor features. ET patients with RBD (ET-RBD) and PPD (ET-PPD) were compared to patients without RBD (ET-nonRBD) and without PPD (ET-nonPPD), respectively. ET-RBD patients were also compared with a group of isolated RBD (iRBD) regarding PPD features.

We assessed a total of 64 ET patients. Five (8.3 %) and 4 (6.3 %) had criteria for RBD and PPD, respectively. ET-RBD patients did not differ from ET-nonRBD except for a higher prevalence of PPD. There were no significant differences between ET-RBD and iRBD (n = 12) groups. ET-PPD had a higher prevalence of positive DaT-Scans and RBD compared to ET-nonPPD. Three ET-RBD patients had PPD and 3 ET-PPD had RBD.

Both RBD and PPD are more frequent in ET patients than in general aged population but not related with specific tremor features. ET-RBD patients did not differ significantly from iRBD patients, a group prone to develop PD. These data suggest a link between ET and PD and are in accordance with studies showing an increase incidence of lewy-body pathology and PD in ET populations.

## 1. Introduction

Essential Tremor (ET) is defined by the presence of bilateral upper limb action tremor, with or without tremor in other body regions, in the absence of other significant neurological signs, including Parkinsonian signs. However, current criteria admit not only the co-existence of a rest tremor component, which is characteristic of Parkinson's Disease (PD), but also of soft motor (mild tandem gait defects, subtle dystonic posturing) and non-motor symptoms (memory impairment) that do not suffice to make an additional diagnosis but define a sub-population designated as ET-Plus [1]. An increased prevalence of cognitive dysfunction has been described in ET patients, as well as autonomic dysfunction, psychiatric disorders, and sleep symptoms [2]. Several studies have shown an increased prevalence of REM sleep behavior disorder [3–7], a parasomnia characterized by dream enactment behavior associated with loss of muscle atonia during REM sleep. Although its prevalence seems to be lower than in some neurodegenerative disorders, both questionnaire [3,4] as well as polysomnography based [5–7] studies have shown a prevalence of RBD in ET (26.3 %–43.5 % and 8.7 %–18.5 %, respectively) which is significantly higher than what is found in the general aged population (from 0.26 to 1.6 1 % [8–11]). Some studies have shown RBD in ET to be associated with autonomic dysfunction [3] symptoms, mild parkinsonian signs [6] and rest tremor [7], which has raised the suspicion that ET-RBD patients could constitute a sub-group of patients within the ET population sharing a common physiopathology with parkinsonian syndromes, given that RBD is exceedingly common in PD, Lewy Body Dementia (LBD) and Multiple System Atrophy [12].

RBD is not only common in established PD and LBD, but also a significant predictor of the emergence of these disorders in patients who do

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not yet present with overt cognitive or motor dysfunction [13]. Prodromic Parkinson's Disease (PDD) represents a state wherein the neuropathological process is already present but the disorder cannot yet be identified by the usual clinical criteria, and is defined by the presence of a variable group of symptoms, risk factors and ancillary examination results which constitute a high risk for developing PD or LBD [14]. Of these, the strongest predictor is RBD [14]. Given the heighten prevalence of this disorder in ET and the fact that its presence in this group of patients seem to be associated with other predictors of alpha-synucleinopathies, the hypothesis rises that some of these patients could in fact have PDD, a finding that would have implications for the understanding of both ET and PD physiopathology and their connection. However, as far as we know, there are no studies that have presented a systematic evaluation of PPD criteria in ET. In the present work, we aimed at systematically investigating a population of ET patients, with instruments validated for determining RBD and PPD, so as to assess the prevalence of these diagnosis in ET and the characteristics of patients that harbor it.

## 2. Methods

### 2.1. Population

We assessed all consecutive patients attending the Movement Disorders Outpatients Clinic of Egas Moniz Hospital Neurology department during a one year period who presented with criteria for ET (including ET-Plus), according to 2017 Movement Disorders Society (MDS) Consensus Statement [1]. We excluded patients who concomitantly had criteria for PD (according to MDS criteria [15]) or LBD (according to the Fourth consensus report of the DLB Consortium [16]), or other neurological disorder. Patients with subtle ataxia, mild dystonia, rest tremor or cognitive dysfunction that did not constitute criteria for another neurologic disorder were not excluded.

### 2.2. Demographic, cognitive and tremor characterization data

All patients were observed in the outpatient clinic by a movement disorders specialist, that collected information according to a structured protocol, which included: demographic and disease related data (age, gender, tremor duration and age of onset, familial history, improvement with alcohol consumption, current medication for ET, other medication with CNS effects) tremor classification according to activation conditions (postural vs kinetic vs kinetic and postural), symmetry (symmetric versus asymmetric), body region (hands only versus hands and other regions), rest component (present versus absent), presence of symptoms defining ET-Plus (dystonic posturing, mild cognitive dysfunction, disequilibrium). All ET patients were evaluated with the Essential Tremor Rating Assessment Scale (TETRAS), to rate tremor severity and the Montreal Cognitive Assessment Scale to assess cognitive function.

### 2.3. Determination of ET-RBD cases

All ET patients were screened with the REM Sleep Behavior Disorder Screening Questionnaire [17], which has proven high sensitivity, although low specificity when compared to gold standard video-polysomnography (PSG) [18]. Patients with scores $<5$ were considered as non-RBD. Patients with score $>4$ were proposed video-polysomnography, for confirmation. They were considered as ET-RBD if PSG confirmed RBD, according to the International Classification of Sleep Disorders III (ICSDIII) criteria [19]: 1) repeated episodes of behavior or vocalization that are either documented by PSG to arise from REM or are presumed to arise from REM based on reports of dream enactment 2); evidence of REM sleep without atonia (RSWA) on PSG. If they did not have ICSD III criteria for RBD they were considered ET-nonRBD. If it was not possible to determine these criteria in PSG, because patients lacked REM sleep or refused PSG, the result was classified as indeterminate. Patients with indeterminate PSG results were removed from ET-RBD vs ET-nonRBD analysis.

### 2.4. Assessment of prodromal Parkinson's disease

The patients were assessed with a protocol designed to assess the risk factors and prodromic markers used to define PPD, according to the method proposed by Berg and col [14]. Risk factors were the following: male sex; exposure to pesticides; exposure to solvents; low caffeine consumption ($<3$ cups of coffee weekly); smoking (past only, actual, never); sibling with PD before age 50; other first degree relative with PD. Prodromic markers were: presence of minimal parkinsonian signs (Unified Parkinson's Disease Rating Scale III $>3$, excluding postural tremor (item 21) punctuation); presence of constipation (score $>1$ on item 12. of the Unified Multiple System Atrophy Rating Scale - UMSARS); erectile dysfunction (score $>2$ on item 11. of the UMSARS); presence of orthostatic hypotension (drop of 20 mmHg or 10 if symptomatic); presence of excessive daytime somnolence (score $>9$ on the Epworth Sleepiness Scale); presence of Depression (Beck Depression Inventory score $>13$). MDS PDD criteria allow for RBD to be diagnosed either by questionnaire or by Video-PSG. However, the weight attributed to this marker is much lower in the first case. We used Video-PSG results whenever they were available. In patients that did not underwent PSG or when PSG result was considered indeterminate, the RBD according to questionnaire criterion was used. Our study did not include hyposmia assessment, as we did not have access to the currently accepted methods of evaluation. DaT-Scan was available only if clinically recommended, so information about this criterion was not avaliabe in all patients. Information thus collected was used to determine the presence of PPD (ET-PPD cases), according to the procedures described by Berg et al. [14].

### 2.5. Data analysis

We first performed a descriptive analysis of demographical, disease related, tremor characterization, RBD assessment and PPD prodromal risk factors and markers of the ET group as an all, determining the prevalence of ET-RBD and ET-PPD. Categorical data were presented as frequency (percentage) and continuous data as mean (standard deviation). Demographical, disease related, tremor characterization, RBD assessment and PPD prodromal risk factors and markers were compared between ET-RBD/ET-nonRBD and ET-PPD/ET-nonPPD groups. We also compared ET-RBD patients with a group of iRBD patients, which were diagnosed according to ICSD III criteria [19] and underwent the same PPD assessment protocol, regarding demographic variables, the prevalence of PPD and the frequency of each of the PPD criteria. Chi-square (or Fisher tests, when appropriated) were used to compare categorical data. Mann-Whitney tests were used to test continuous data (given the small numbers, no variable had normal distribution, indicating the use of non-parametric tests).

### 2.6. Ethics

Patients signed informed consent forms. The ethics committee of the institution approved the investigation protocol.

## 3. Results

We assessed a total of 64 ET patients. Table 1 presents demographic, cognitive, tremor characterization and data regarding the presence of PPD risk factors and prodromal markers in the entire ET population.

### 3.1. ET-RBD vs ET-nonRBD

Of the 64 ET patients, 11 had RBD questionnaire scores above cut-off and were referenced for PSG. In 4 patients, PSG was inconclusive

**Table 1**
Demographic, cognitive, tremor characterization, PPD risk factors and prodromic markers data on ET patients.

| | ET patients (n = 64) |
|---|---|
| Age (yrs) | 73.19 (9.7) |
| Sex (m) | 34 (53.1) |
| MoCA | 20.73 (5.6) |
| Tremor characterization | |
| Age of tremor onset (yrs) | 57.69 (16.7) |
| Tremor duration (yrs) | 15.00 (12.8) |
| ET-Plus | 15 (12.0) |
| TETRAS ADL | 15.72 (7.1) |
| TETRAS Performance | 17.28 (8.2) |
| TETRAS total | 33.15 (12.3) |
| Activation conditions | |
| kinetic | 3 (4.7) |
| postural | 13 (20.3) |
| both | 48 (75.0) |
| Symmetry (assymmetric) | 21 (32.8) |
| Tremor in locations other than hands | 26 (40.6) |
| Rest tremor component | 21 (32.8) |
| Tremor treatment | |
| Propranolol | 25 (39.1) |
| Primidone | 28 (43.8) |
| Topiramate | 6 (9.4) |
| Gabapentin | 6 (9.4) |
| DBS (VIM) | 1 (1.6) |
| Other | 10 (15.6) |
| None | 17 (26.6) |
| Other CNS treatment | |
| SSRI | 18 (28.1) |
| Clonazepam | 3 (4.7) |
| Other | 4 (6.3) |
| Patients with criteria for ET-RBD | 5 (8.3)[a] |
| Risk factors for PPD | |
| Male gender | 34 (28.0) |
| Pesticide exposure | 5 (4.0) |
| Solvent exposure | 11 (8.8) |
| Low caffeine exposure | 16 (12.8) |
| Smocking | |
| Actual | 6 (9.4) |
| Never | 20 (31.3) |
| Past only | 27 (42.2) |
| Sibling with DP before 50 | 0 |
| Other first degree relative | 2 (3.1) |
| Prodromal markers for PPD | |
| RBD – PSG | 5 (7.8)[b)] |
| RBD – Questionnaire | 11 (17.2) |
| DaT-Scan | 5 (7.8)[c)] |
| UPDRS III >3 | 22 (34.4) |
| Constipation (UMSARS >1) | 12 (18.8) |
| Erectile dysfunction (UMSARS >2) | 13 (38.2)[d)] |
| Orthostatic hypotension | 3 (5.0) |
| Excessive daytime sleepiness (ESS >9) | 10 (15.6) |
| Depression (BDI>13) | 7 (10.9) |
| Patients with PPD | 4 (6.3) |

Values are frequency (percentage) or mean (standard deviation).
[a)] This percentage refers to an eligible population of 60 patients.
[b)] Only patients with positive questionnaire were eligible for PSG study. Percentage values refer to the entire ET population.
[c)] DaT-Scan was performed only if clinically indicated (12 cases). Percentage values refer to the entire ET population.
[d)] This percentage refers to a population of 34 male patients.

regarding RBD, due to absence of REM sleep. These 4 patients were excluded from analysis. In 2, PSG was negative for RBD. Five had RBD confirmed by PSG (8.3 % of valid cases). These five patients were considered as ET-RBD cases. The other 55 patients were considered as ET-nonRBD. There were no significant differences between ET-RBD and ET-nonRBD regarding demographic and tremor characterization features. ET-RBD patients had a significantly higher proportion of patients with criteria for PPD than ET-nonRBD. This difference was driven by the presence of RBD, as the groups did not differ significantly regarding other PPD criteria (Table 2.). When compared with the iRBD group,

**Table 2**
Demographic, tremor characterization, risk factors and prodromic markers for PDD: comparison between ET-RBD, ET-nonRBD and iRBD patients.

| | ET-RBD (n = 5) | ET-nonRBD (n = 55) | ET-nonRBD vs ET-RBD *p* | iRBD (n = 12) | ET-RBD vs iRBD *p* |
|---|---|---|---|---|---|
| Age (yrs) | 74.60 (3.2) | 73.45 (1.2) | 0.846 | 73.50 (2.4) | 0.879 |
| Sex (m) | 3 (60.0) | 30 (56.6) | 1.000 | 11 (91.7) | 0.191 |
| MoCA | 17.20 (2.6) | 21.28 (0.8) | 0.142 | 21.08 (1.2) | 0.279 |
| Tremor characterization | | | | | |
| Age of tremor onset (yrs) | 62.00 (9.6) | 58.69 (2.2) | 0.711 | | |
| Tremor duration (yrs) | 12.00 (4.5) | 14.58 (1.7) | 0.909 | | |
| ET-Plus | 0 | 17 (30.9) | 1.000 | | |
| TETRAS ADL | 18.60 (1.5) | 15.09 (1.0) | 0.209 | | |
| TETRAS Performance | 18.40 (1.9) | 18.64 (1.0) | 0.209 | | |
| TETRAS total | 37.00 (2.1) | 33.82 (1.7) | 0.900 | | |
| Activation conditions | | | 0.109 | | |
| kinetic | 1(20.0) | 2(3.6) | | | |
| postural | 2(40.0) | 10(18.2) | | | |
| both | 2(20.0) | 43(78.2) | | | |
| Symmetry (assymmetric) | 3 (60.0) | 17 (30.9) | 0.322 | | |
| Tremor in locations other than hands | 2 (40.0) | 2 (40.0) | 0.677 | | |
| Rest tremor component | 1 (20.0) | 19 (34.5) | 0.656 | | |
| PPD Risk factors | | | | | |
| Male sex | 3 (60.0) | 30 (56.6.2) | 1.000 | 11 (91.7) | 0.191 |
| Pesticide exposure | 0 | 4 (7.3) | 1.000 | 3 (25.0) | 0.324 |
| Solvent exposure | 1 (20.0) | 10 (18.2) | 1.000 | 5 (41.7) | 0.600 |
| Low cafeíne exposure | 2 (40.0) | 13 (23.6) | 0.591 | 3 (25.0) | 0.516 |
| Smocking | | | | | |
| Actual | 0 | 5 (9.1) | 1.000 | 12 (100) | 1.000 |
| Never | 1 (20.0) | 17 (30.9) | 1.000 | 3 (25.0) | 1.000 |
| Past only | 0 | 24 (43.6) | 1.000 | 0 | |
| Sibling with DP before 50 | 0 | 0 | | 0 | |
| Other first degree relative | 0 | 2 (3.6) | 1.000 | 0 | |
| Prodromal markers | | | | | |
| RBD – PSG | 5 (100) | 0 | [a)] | 12 (100) | [a)] |
| RBD – Questionnaire | 5 (100) | 2 (3.6)[b)] | <0.001 | | |
| DaT-Scan | 3 in 5 (60.0)[c)] | 2 in 7 (28.6)[c)] | 0.558 | 3 in 3 (100) | 0.464 |
| UPDRS III >3 | 1 (20.0) | 19 (34.5) | 0.656 | 2 (16.7) | 0.676 |
| Constipation (UMSARS >1) | 2 (40.0) | 9 (16.4) | 0.224 | 4 (33.3) | 1.000 |
| Erectile dysfunction (UMSARS >2) | 1 in 3 (33.3)[d)] | 7 in 30 (22.6)[d)] | 1.000 | 3 in 10 (30.0 %)[d)] | 0.689 |
| Ortostatic hypotension | 1 (20.0) | 2 (3.6) | 0.233 | 1 (8.3) | 0.515 |
| Excessive daytime sleepiness (ESS >9) | 0 | 7 (12.7) | 1.000 | 2 (16.7) | 0.485 |

(*continued on next page*)

**Table 2** (*continued*)

| | ET-RBD (n = 5) | ET-nonRBD (n = 55) | ET-nonRBD vs ET-RBD *p* | iRBD (n = 12) | ET-RBD vs iRBD *p* |
|---|---|---|---|---|---|
| Depression (BDI>13) | 2 (40.0) | 5 (9.1) | 0.099 | 3 (25.0) | 0.600 |
| Patients with PPD | 3 (60.0) | 1 (1.8) | 0.001 | 8 (66.7) | 1.000 |

[a] Values not presented, as per definition, all ET-RBD and iRBD patients had PSG criteria for RBD and none of the ET-nonRBD had.
[b] Two patients had positive questionnaires but were confirmed as negative for RBD by PSG. The RBD-PSG criterion was used in these two cases.
[c] DaT-Scan was performed only if clinically indicated (12 cases).
[d] This percentage refers to a population of 35 male patients.

there were no significant differences regarding demographic features, PSG data, PPD prevalence and the frequency of each PPD criteria (Table 2).

### 3.2. ET-PPD vs ET-nonPPD

Four ET patients (6.3%) had criteria for PPD (ET-PPD) versus 60 (93.7) who did not have PPD (ET-nonPPD). There were no significant differences regarding demographic and tremor related features between ET-PPD and ET-nonPPD. Regarding the frequency of each PPD criteria, only a positive DaT-Scan and RBD were significantly more frequent in ET-PPD that in ET-nonPPD. (Table 3.).

### 3.3. Relation between ET-RBD and ET-PPD cases

Regarding the relation between ET, PPD and RBD, 3 out 5 ET-RBD patients had PPD and 3 out of 4 ET-PPD had RBD.

### 3.4. Comparison between DaT-Scan positive and negative patients

Given that no differences were found regarding tremor features between groups, contrary to studies that suggested ET-RBD patients to display some tremor characteristics similar to those of PD (rest tremor) [7] and because DaT-Scan has strong relation with dopaminergic denervation and thus with PD related features, we added an exploratory analysis comparing ET patients with positive DaT-Scans (n = 5) and negative DaT-Scans (n = 7), regarding tremor features, RBD and PPD criteria. There were no significant differences between the groups in terms of tremor characterization. In fact, rest tremor was more frequent in patients with negative DaT-scan (5 in 7), than those in with positive DaT-scan (1 in 5), although the difference was non-significant (p = 0.242). There was no significant relation between PSG confirmed RBD and DaT-Scan results, but only six patients had undergone both examinations. A trend level association was found between positive DaT-Scan and positive RBD questionnaire (4 out of 5, versus 1 out of 6, p = 0.072). PPD diagnosis was significantly more frequent in DaT-Scan positive patients (4 out of 5 versus 0 out of 7, p = 0.010), but there were no significant differences in particular PPD criteria.

## 4. Discussion

### 4.1. ET-RBD

Our results confirm a higher than expected prevalence of RBD in our ET population (8.3 %), when compared with data extracted from the general population in studies using similar questionnaire screening followed by PGS in positive cases [8,9] (although slightly lower than what the 11.6 % in our previous work).

Regarding tremor features, there were no significant differences between ET-RBD and ET-nonRBD patients. This disagrees with our previous study [7], which found a higher intensity of tremor as evaluated by TETRAS and a higher prevalence of rest tremor in ET-RBD. The difference seems to be associated with a reduced prevalence of rest tremor in the ET-RBD group in the present study, as rest tremor in the ET-nonRBD population was similar in both studies. Rest tremor has been described as variable feature in ET patients, with a tendency to regress in longitudinal studies [20]. In the present study, tremor duration is higher than in our previous one. As the present study includes some patients that participated in our previous one, we can suspect that the prevalence of this feature could decrease as disease progresses in ET-RBD patients (an alternative explanation would be that some of the ET-RBD patients with rest tremor developed PD and were not included in the present study). Tremor intensity has also been associated with rest tremor, which could also explain the difference [21]. In conclusion, as per this study results, ET-RBD patients do not to represent an isolated group in terms of tremor features. The hypothesis that rest tremor component in ET is not caused by the same pathophysiologic mechanisms as in PD (this is, dopaminergic denervation) is supported by the fact that we found no correlation between rest tremor and DaT-scan positivity in our sample.

As expected, there was a significantly relation between ET-RBD and PPD, as 60 % of the patients with ET-RBD had PPD criteria, compared to 1.5 % in the ET-nonRBD. This is not unexpected, given the weight of RBD in PPD diagnosis. In fact, RBD appears as the singling factor

**Table 3**
Demographic, tremor characterization, risk factors and prodromic markers for PDD: comparison between ET-PPD and ET-nonPPD.

| | ET-PDD (n = 4) | ET-nonPDD (n = 60) | *p* |
|---|---|---|---|
| Age (yrs) | 75.75 (3.5) | 72.98 (1.2) | 0.640 |
| Sex (m) | 3 (75.0) | 31 (53.4) | 0.620 |
| MoCA | 18.25 (1.9) | 20.91 (0.8) | 0.187 |
| Tremor characterization | | | |
| Age of tremor onset (yrs) | 65.25 (3.0) | 57.67 (2.2) | 0.526 |
| Tremor duration (yrs) | 10.50 (2.5) | 15.12 (1.7) | 0.663 |
| ET-Plus | 1 (25.0) | 18 (30.0) | 1.000 |
| TETRAS ADL | 18.75 (2.0) | 15.52 (0.9) | 0.249 |
| TETRAS Performance | 19.13 (2.2) | 18.61 (0.9) | 0.879 |
| TETRAS total score | 37.88 (2.4) | 34.22 (1.6) | 0.381 |
| Activation conditions | | | 0.884 |
| kinetic | 0 | 3(5.0) | |
| postural | 1 (25.0) | 12(20) | |
| both | 3 (75.0) | 45 (75.0) | |
| Symmetry (assymmetric) | 1 (25.0) | 42 (70.0) | 0.099 |
| Tremor in locations other than hands | 2 (50.0) | 36 (60.0) | 0.539 |
| Rest tremor component | 1 (25.0) | 20 (33.3) | 0.602 |
| PPD Risk factors | | | |
| Male gender | 3 (75.0) | 32 (53.3) | 0.620 |
| Pesticide exposure | 0 | 5 (8.3) | 0.716 |
| Solvent exposure | 1 (25.0) | 10 (16.7) | 0.539 |
| Low caffeine exposure | 1 (25.0) | 15 (25.5) | 1.000 |
| Smocking | | | |
| Actual | 0 | 6 (10.0) | 0.668 |
| Never | 1 (25.0) | 19 (31.7) | 0.631 |
| Past only | 2 (50.0) | 25 (41.7) | 0.566 |
| Sibling with DP before 50 | 0 | 0 | |
| Other first degree relative | 0 | 2 (3.3) | 0.878 |
| Prodromal markers | | | |
| RBD – PSG | 3 in 3[a] | 2 in 9[a] | 0.045 |
| RBD – Questionnaire | 3 (75.0) | 8 (13.3) | 0.014 |
| DaT-Scan | 4 (100.0)[b] | 1 in 7 (12.5)[b] | 0.010 |
| UPDRS III >3 | 2 (50.0) | 20 (33.3) | 0.426 |
| Constipation (UMSARS >1) | 2 (50.0) | 10 (16.7) | 0.157 |
| Erectile dysfunction (UMSARS >2) | 2 in 3 (66.7)[c] | 6 in 32 (18.8)[c] | 0.124 |
| Orthostatic hypotension | 0 | 3 (5.0) | 0.821 |
| Excessive daytime sleepiness (ESS >9) | 0 | 10 (16.7) | 0.498 |
| Depression (BDI>13) | 1 (25.0) | 6 (10.0) | 0.378 |

[a] Only patients with positive questionnaire were eligible for PSG study.
[b] DaT-Scan was performed only if clinically indicated.
[c] These percentages refer to a total population of 35 male patients.

regarding PPD, as this was the only PPD criteria which prevalence differed significantly between ET-RBD and ET-nonRBD patients.

### 4.2. ET-PPD

The prevalence of PPD (6.2 %) was also higher than the values found in studies performed in the general, aged population (2.2 %) [22]. RBD-PPD patients did not differ significantly from the RBD-nonPPD except for the presence of the two strongest criteria for PPD: RBD diagnosis and a positive DaT-Scan. In fact, the only ET-PPD patient who did not have RBD had a positive DaT-Scan and a mixture of other criteria (minimal motor signs, as shown by the UPDRS III score, and sexual dysfunction). This suggests that there is a subset of patients with criteria for ET, thus presenting postural bilateral hand tremor, that are prone to develop PD in the long run. This is in accordance with longitudinal studies showing an increased incidence of PD in ET populations [23], and to neuropathological studies showing and excess of lewy-body pathology in ET patients [24] (although cerebellar Purkinje cell alterations, found in other cerebellar neurodegenerative disorders, seem to be the main neuropathological finding in ET [25]).

### 4.3. Conclusions

Taken together, our data shows that both RBD and PPD criteria are more frequent in ET patient than in general aged population and that the first is the main determinant of the second. ET-RBD and ET-PPD diagnoses were significantly related, but not interchangeable, as we found some ET patients to have RBD but not PPD and vice-versa. We should take in consideration that our cross-sectional method allows only to assess a specific point in time, while both RBD and PPD stem from a progressive condition, in which symptoms present sequentially. It is not improbable that more ET-RBD could develop sufficient criteria for PPD in time, and that PPD patients could present with RBD in the long run. ET-RBD patients did not differ significantly in terms of PPD prevalence or criteria frequency from iRBD patients, a group which we know, given the results of other studies, almost inexorably develop PPD features and later one of the alpha-synucleinopathy diagnosis [26]. In fact, the prevalence of PPD in our ET-RBD and iRBD groups (60.0 % and 67.7 %) was similar to the 63.3 % value found in a previous iRBD based study (a longitudinal analysis of this iRBD cohort found that 88.1 % had developed PPD after a 12-year follow-up period, and 39.7 had develop criteria for alpha-synucleinopathy) [26].

It doesn't seem possible to differentiate ET-RBD/ET-nonRBD or ET-PPD/ET-nonPPD patients by tremor characterization alone, as no single tremor feature seem to differentiate the groups (although this assertion should be taken with care, given the small number of patients in each group). One could thus suppose ET-RBD and ET-PPD patients to be manifesting ET-type tremor as an atypical, early form of parkinsonian tremor. Given the cross-sectional nature of this study, we have no way to determine if this postural tremor represents the first stage of typical rest tremor, possibly including a postural component, frequent in PD patients, or if there is coexistence of two tremor mechanisms in the same patient caused by the same neuropathological mechanism, or even the fortuitous coexistence of two common disorders (ET and PD), each with their different neuropathological mechanisms and clinical evolution.

Our study represents the first attempt to systematically assess PPD criteria in ET patients. However, our results should be taken with care, and considered as preliminary, given the studies limitations. These were mainly the size of the sample, yielding a small absolute number of RBD and PPD cases, which limits the significance of comparisons with non-RBD and non-PPD cases. Also, PPD screening lacked olfaction tests, which is an important criteria. Generalization of DaT-Scan and video-PSG testing to the entire sample (and not just to when clinical justified or after positive questionnaire screening, respectively) would also be of benefit and could have uncovered extra cases of PPD and RBD. Our methods could thus represent a conservative approach, which on the other hand underlines the significance of such high prevalence of RBD and PPD, suggesting that in fact they could represent an underestimation of the true numbers. This calls for further evaluation of our hypothesis, using larger cohorts and more complete methods of RBD and PPD screening, as well as more precise instruments to evaluate tremor features.

## CRediT authorship contribution statement

**Paulo Bugalho:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Bruna Meira:** Writing – review & editing, Investigation. **André Pinho:** Writing – review & editing, Investigation. **Rita Ventura:** Writing – review & editing, Investigation. **Marta Magriço:** Writing – review & editing, Investigation. **Miguel Serôdio:** Writing – review & editing, Investigation. **Danna Krupka:** Writing – review & editing, Investigation. **Vítor Mendes Ferreira:** Writing – review & editing, Investigation.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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