

## Brief Reports

# Probable REM-Sleep Behavior Disorder and Dysautonomic Symptoms in Essential Tremor

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## Abstract

**Background:** Non-motor symptoms can be present in essential tremor (ET). We intend to assess the frequency of rapid eye movement (REM) sleep behavior disorder (RBD) and dysautonomic symptoms in ET patients and evaluate the differences between patients with ET and RBD (ET-RBD and ET without RBD [ET-nonRBD]).

**Methods:** All ET patients were contacted by telephone. Autonomic symptoms were assessed using the Scales for Outcomes in Parkinson's Disease-Autonomic (SCOPA-AUT) questionnaire, and RBD symptoms with the RBD screening questionnaire (RBDSQ) using  $\geq 5$  as a cut-off for probable RBD (pRBD).

**Results:** From 92 ET patients contacted, 53 (55% female) were included. The mean age at assessment was  $73.6 \pm 19$  years, and the average disease duration was  $19.9 \pm 17.3$  years. Fourteen patients (26.4%) had pRBD and 52 (98.1%) reported at least one autonomic symptom, the most prevalent being urinary symptoms (96%). The ET-RBD group had higher SCOPA-total and thermoregulatory scores than ET-nonRBD patients ( $13.9 \pm 9.6$  vs.  $7.7 \pm 5.1$ ,  $p=0.017$  and  $2.5 \pm 2.0$  vs.  $0.9 \pm 1.6$ ,  $p=0.001$ ). There were no other differences between groups.

**Discussion:** Our results suggest that pRBD is common in ET, and its presence is associated with dysautonomic symptoms. As these symptoms are known to be prodromal symptoms of Parkinson's disease (PD), we question if this patient subgroup has a higher risk of developing a synucleinopathy.

**Keywords:** Essential tremor, non-motor symptoms, REM-sleep behavior disorder, autonomic symptoms, synucleinopathies

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## Introduction

Essential tremor (ET) is the most common movement disorder.<sup>1</sup> Although classically described as a motor disease, several non-motor symptoms (NMS) have been consistently associated with ET,<sup>2</sup> supporting changing the paradigm from a monosymptomatic disorder to a disease affecting multiple motor and non-motor systems. Hearing impairment,<sup>3</sup> mild cognitive deficits, and neuropsychiatric disturbances such as depression and anxiety are all frequently observed in patients with ET.<sup>4,5</sup> However, evidence on the association of ET with rapid eye movement (REM) sleep behavior disorder (RBD)<sup>2</sup> or autonomic symptoms remains conflicting.<sup>2,9,10,11</sup>

Although previous studies have found that patients with ET have up to a fourfold higher risk of developing Parkinson's disease (PD), most

chronic ET patients do not develop additional motor symptoms typically associated with PD, such as bradykinesia, rigidity, or postural instability.<sup>12</sup>

As autonomic dysfunction and particularly RBD are known NMS associated with the development of synucleinopathies such as PD,<sup>13,14</sup> we studied the prevalence of these two NMS in ET patients. We also investigated whether there was any difference between ET patients with and without RBD regarding demographics, tremor characteristics, and prevalence of autonomic symptoms.

## Methods

We contacted by phone and reviewed the clinical files of all patients who attended the Egas Moniz Hospital movement disorders outpatients'

clinic in Portugal, with a diagnosis of ET during 2014. All patients had at least two visits 6 months apart.

Verbal informed consent was obtained from all patients. This study was approved by the research and ethics board of Centro Hospitalar de Lisboa Ocidental.

ET was diagnosed by the movement disorders neurologist responsible for the patients, according to the diagnostic criteria proposed by the Tremor Investigation Group (TRIG), which require bilateral, largely symmetric postural or kinetic tremor involving the upper limbs. Additional or isolated head tremor may occur in the absence of dystonic postures.<sup>15</sup> Patients who also fulfilled criteria for PD, Lewy body dementia, or atypical parkinsonism were not included.

A structured clinical form was constructed for data collection. We collected information regarding age at assessment, age of disease onset, and disease duration (defined as actual age minus age at symptom onset, as reported by the patient). We recorded locality of tremor onset and symmetry of tremor at onset (a symmetrical onset was considered if tremor started in both the upper or lower limbs, and an asymmetrical onset was defined when tremor started in one limb or one limb was clearly more affected than the other). Data about familial history of tremor and actual treatment (medication taken for tremor at the moment of the telephone interview) were also noted. We also collected information about hypertension, diabetes mellitus, and benign prostatic hyperplasia (BPH) diagnoses, as they can be associated with autonomic symptoms.

Autonomic symptoms were assessed using the Scales for Outcomes in Parkinson's Disease-Autonomic (SCOPA-AUT) questionnaire. It is divided into six domains: gastrointestinal, urinary, cardiovascular, thermoregulatory, pupillomotor, and sexual. Each domain includes seven, six, three, three, one, and two questions, respectively. Each autonomic domain was scored as the frequency of symptom occurrence with response options ranging from 0 ("never") to 3 ("often"). The urinary and sexual questions have an additional response option to indicate if a subject used a catheter or had not been sexually active, respectively. The total SCOPA score is the sum of values of gastrointestinal, urinary, cardiovascular, thermoregulatory, and pupillomotor domains. The sexual function domain was not included in further analysis since 27/53 (50.9%) of the patients answered "not sexually active" for one of the sexual questions.<sup>17</sup>

The RBD screening questionnaire (RBDSQ) was used to assess RBD symptoms. The cut-off for a probable RBD (pRBD) diagnosis is  $\geq 5$ , with a sensitivity of 96% and a specificity of 92%.<sup>16</sup> According to the RBDSQ results, we divided the patients into two groups of ET patients with pRBD (ET-RBD) and without pRBD (ET-nonRBD), knowing that RBD is a known marker of synucleinopathy.

### Statistical analysis

Continuous variables are expressed as mean  $\pm$  standard deviation and were compared using the Mann-Whitney U test. Categorical variables are expressed as percentages, and comparisons were performed using the chi-squared test (Fisher's exact test was used when chi-squared assumptions were not fulfilled).  $P < 0.05$  was considered

statistically significant. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) 20.0 version software package.

### Results

From 92 ET patients, 53 (55% female) consented to participate and completed the telephone interview. There were no significant differences in age or sex between participants and non-participants (55% vs. 46% female,  $p = 0.417$ ; age  $73.6 \pm 11.0$  vs.  $78.2 \pm 7.8$ ,  $p = 0.076$ ). The mean age at assessment was  $73.6 \pm 11.0$  years with a disease duration of  $19.9 \pm 17.3$  years. In most patients (58.5%), tremor started before age 65. Forty-one (77.4%) patients were receiving treatment, with primidone being the drug most prescribed (22 patients, 53.6%). There were no differences in prescriptions between the ET-RBD and ET-nonRBD groups. Almost all (98.1%, 95% confidence interval [CI]: 90.0–99.7%) patients reported at least one autonomic symptom (96% urinary symptoms, 70% gastrointestinal, 42% cardiovascular, 53% thermoregulatory, and 28% pupillomotor dysfunction), and 14/53 (26.4%, 95% CI: 16.4–39.6%) had a diagnosis of pRBD. Full group data can be found in Table 1.

RBD patients had higher SCOPA-total scores ( $13.9 \pm 9.6$  vs.  $7.7 \pm 5.1$ ,  $p = 0.017$ ) and higher thermoregulatory domain scores ( $2.5 \pm 2.0$  vs.  $0.9 \pm 1.6$ ,  $p = 0.001$ ) compared to ET-nonRBD. There were no other differences between groups regarding age, age at onset, family history, disease duration, or tremor characteristics (Table 1).

Regarding comorbidities, 20, 9, and 3 patients had hypertension, diabetes, and BPH, respectively. When comparing the ET-RBD and ET-nonRBD groups, there were no differences regarding the prevalence of comorbidities (Table 1). When comparing patients with and without comorbidities, there was no difference in SCOPA total score ( $8.7 \pm 8.1$  vs.  $9.9 \pm 5.9$ ,  $p = 0.164$ ) but patients with comorbidities had lower SCOPA-gastrointestinal ( $1.85 \pm 2.78$  vs.  $2.85 \pm 2.28$ ,  $p = 0.030$ ) and SCOPA-pupillomotor scores ( $0.230 \pm 0.651$  vs.  $0.406 \pm 1.219$ ,  $p = 0.028$ ).

### Discussion

The common view of ET as an exclusively motor and mono-symptomatic disorder has been changing since NMS were first described in ET patients. This suggests that the pathophysiology of the disease involves more than the motor domain.

We found autonomic symptoms in virtually all ET patients. While one study using the SCOPA-AUT only found a slight increase in sialorrhea in ET patients compared to controls,<sup>9</sup> another reported a significantly higher rate of autonomic dysfunction in ET,<sup>10</sup> with ET patients presenting higher SCOPA-total, SCOPA-genitourinary, and SCOPA-cardiovascular scores than controls. These findings reflect the ongoing debate regarding autonomic dysfunction in ET. The presence of autonomic dysfunction was studied using sympathetic skin response (SSR) tests, in a group of 27 ET patients (mean age of 47.06 years) and 26 controls (mean age of 43.34). The authors found a higher prevalence of abnormal SSR test results in ET patients than controls, indicating sympathetic dysfunction in these patients.<sup>11</sup>

Table 1. Clinical and Demographic Characteristics of ET Patients and RBD Subgroups

	All ET Patients (n=53)	ET-RBD (n=14)	ET-nonRBD (n=39)	p value (ET-RBD vs. ET-nonRBD)
Age, yrs	73.6 (±11.0)	70.1 (±15.5)	74.8 (±8.6)	0.558
Female sex	29 (54.7%)	8 (57.1%)	21 (53.8%)	0.832
Age at onset, yrs	53.7 (±20.3)	51.8 (±22.6)	54.4 (±19.8)	0.693
Onset before 65 yrs	31 (58.5%)	8 (57.1%)	23 (58.9%)	0.905
Disease duration, yrs	19.9 (±17.3)	18.3 (±15.8)	20.5 (±18.0)	0.746
Family history	30 (56.6%)	7 (50.0%)	23 (58.9%)	0.496
Onset of tremor				
Localization				
Upper limbs	48 (90.6%)	13 (93%)	35 (89.7%)	1.000 <sup>1</sup>
Other <sup>2</sup>	5 (9.4%)	1 (7.1%)	4 (10.2%)	
Symmetry <sup>3</sup>				
Symmetrical onset	36 (72%)	12 (92.3%)	24 (64.9%)	0.078 <sup>1</sup>
Asymmetrical onset	14 (28%)	1 (7.7%)	13 (35.1%)	
On treatment	41 (77.4%)	12 (85.7%)	29 (74.4%)	0.384
Propranolol	15 (36.5%)	6 (50.0%)	9 (31.0%)	
Primidone	22 (53.6%)	6 (50.0%)	16 (55.1%)	
Topiramate	6 (14.6%)	—	6 (20.7%)	
Others <sup>4</sup>	4 (9.7%)	—	—	
RBDSQ scores (mean ± SD)	3.7 (±2.9)	8.0 (±2.0)	2.2 (±1.2)	<0.001
SCOPA-AUT (mean ± SD)				
SCOPA-total	9.3 (±7.0)	13.9 (±9.6)	7.7 (±5.1)	0.017*
Gastrointestinal	2.4 (±2.5)	3.9 (±3.5)	1.8 (±1.8)	0.067
Urinary	3.9 (±3.4)	4.8 (±4.4)	3.6 (±2.9)	0.758
Cardiovascular	1.2 (±1.9)	1.8 (±2.5)	0.9 (±1.7)	0.157
Thermoregulatory	1.3 (±1.8)	2.5 (±2.0)	0.9 (±1.6)	0.001***
Pupillomotor	0.6 (±1.0)	0.0 (±1.3)	0.4 (±0.9)	0.137
Comorbidities	26	8	18	0.480
Hypertension	20	8	12	0.081
Diabetes	9	1	8	0.416 <sup>1</sup>
BPH	3	0	3	0.557 <sup>1</sup>

Abbreviations: BPH, Benign Prostatic Hyperplasia; ET, Essential Tremor; RBD, Rapid Eye Movement Sleep Behavior Disorder; RBDSQ, Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire; SCOPA-AUT, Scales for Outcomes in Parkinson's Disease-Autonomic; SD, Standard Deviation.

<sup>1</sup>Fisher's exact t test.

<sup>2</sup>Head (n=3), both lower limbs (n=2).

<sup>3</sup>For total ET patients n=50, for ET+RBD n=13, for ET no RBD n=37.

<sup>4</sup>Gabapentine (n=2), alprazolam (n=1), trihexyphenidyl (n=1).

\*p<0.05;

\*\*\*p<0.005

We are aware that the higher prevalence of autonomic symptoms in our cohort may be influenced by other comorbidities that are common in this age group. However, no association was found between higher SCOPA-total and subdomain scores and the presence of comorbidities (diabetes, hypertension, and BPH as a group). We also did not find any association between the presence of RBD and comorbidities (Table 1).

pRBD was present in 26% of our ET patients. Mahlknecht and collaborators<sup>18</sup> also used the RBDSQ to assess the prevalence of pRBD in the general population. In a cohort of 476 subjects (mean age of  $72.8 \pm 8.5$  years, similar to our sample), they found 5.5% had pRBD. This prevalence is lower than even the lower limit of our 95% CI. Our results are similar to those of the only other study that used the RBDSQ to assess patients with ET,<sup>2</sup> which also found an increased prevalence (43.5%) of this parasomnia. Although remaining below the prevalence of RBD in well-known synucleinopathies, the rate of pRBD in our ET patients seems to be closer to these patients than to the general population.

Pathologic studies of ET brains have revealed at least two different patterns of pathology: patients with degenerative changes in the cerebellum (including Purkinje cell loss) and patients presenting with brainstem Lewy bodies without cerebellar degeneration.<sup>19</sup> Lewy bodies are the pathological hallmark of synucleinopathies, which are known to be related to RBD and autonomic symptoms. In fact, our data hint at a relationship between RBD and dysautonomia in ET patients, a well-documented phenomenon in non-ET subjects.<sup>20</sup> These neuropathological findings support the growing evidence of an association between ET and PD, with some previous studies showing that ET patients have a fourfold higher risk of developing PD than the general population.<sup>12</sup>

Some studies have also compared the clinical characteristics of ET patients who later developed PD (ET→PD) with those who did not. Ghika and collaborator found that NMS like hyposmia, obstipation, and RBD are more common in ET→PD patients than their counterparts.<sup>8</sup>

RBD is a known prodromal marker of PD.<sup>13</sup> We question if its presence, which is associated with a higher rate of autonomic symptoms, could be a clinical marker of a higher risk of developing PD. A recent study found NMS to be exceedingly frequent in ET and unrelated to tremor severity and duration. The authors hypothesized that NMS could be both primary symptoms of the disease process, reflecting degeneration of various motor and non-motor neural systems, and also analogous to neurodegenerative conditions like PD and part of the premotor phase of ET.<sup>21</sup>

Our study has some limitations. The most significant is the lack of a control group. We acknowledge this could add clinically relevant information. Also, the patients were recruited from our outpatient clinic (where more severe ET is encountered). Although it is not likely that tremor severity is related with autonomic dysfunction or RBD,<sup>6</sup> we cannot exclude the possibility of selection bias. We used a structured interview to minimize possible bias due to different people performing the telephone interviews. In addition, the refusal of some subjects to participate could have affected the lack of demographic

differences. We are also aware that other comorbidities could influence autonomic symptoms and that inclusion of a control group could allow us to make better comparisons. Regardless, the observed association between RBD and autonomic symptoms severity is independent of this comparison.

Despite these limitations, we found pRBD in ET patients, and these individuals also had more autonomic symptoms. Our results back up previous reports of an association between ET and neurodegenerative disease (particularly PD).<sup>2,12</sup> RBD and obstipation have previously been associated with the ET→PD phenotype.<sup>8</sup> We believe our data indicate that the association of NMS in some ET patients is not by chance but could represent a subgroup at higher risk for PD progression.

There is a need for more and collaborative studies in this area, with larger numbers of patients and healthy control group subjects. It is also important to test the hypothesis that ET can evolve non-uniformly across patients. Long-term follow-up and neuropathological studies would clarify the possible link between which NMS and clinical characteristics of ET patients may predict conversion to PD.

## References

1. Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. *Mov Disord* 2010;25:534–541. doi: 10.1002/mds.22838
2. Lacerte A, Chouinard S, Jodoin N, Bernard G, Rouleau GA, Panisset M, et al. Increased prevalence of non-motor symptoms in essential tremor. *Tremor Other Hyperkinet Mov* 2014;4. doi: 10.7916/D82V2D91
3. Ondo WG, Sutton L, Dat Vuong K, Lai D, Jankovic J. Hearing impairment in essential tremor. *Neurology* 2003;61:1093–1097. doi: 10.1212/01.WNL.0000086376.40750.AF
4. Bermejo-Pareja F. Essential tremor – a neurodegenerative disorder associated with cognitive defects? *Nat Rev Neurol* 2011;7:273–282. doi: 10.1038/nrneurol.2011.44
5. Benito-León J, Louis ED, Bermejo-Pareja F; Neurological Disorders in Central Spain (NEDICES) Study Group. Population based case-control study of cognitive function in essential tremor. *Neurology* 2006;66:69–74. doi: 10.1212/01.wnl.0000192393.05850.ec
6. Musacchio T, Purrer V, Papagianni A, Fleischer A, Mackenrodt D, Malsch C, et al. Non-motor symptoms of essential tremor are independent of tremor severity and have impact on quality of life. *Tremor Other Hyperkinetic Mov* 2016;6. doi: 10.7916/D8542NCH
7. Adles CH, Hentz JG, Shill HA, Sabbagh MN, Driver-Dunckley E, Evidente VGH, et al. Probable RBD is increased in Parkinson's disease but not in essential tremor or restless legs syndrome. *Parkinsonism Relat Disord* 2011;17:456–458. doi: 10.1016/j.parkreldis.2011.03.007
8. Ghika A, Kyrozis A, Potagas C, Louis ED. Motor and non-motor features: differences between patients with isolated essential tremor and patients with both essential tremor and Parkinson's disease. *Tremor Other Hyperkinet Mov* 2015;5. doi: 10.7916/D83777WK
9. Damian A, Adlerb CH, Hentz JG, Shill HA, Caviness JN, Sabbagh MN, et al. Autonomic function, as self-reported on the SCOPA-autonomic questionnaire, is normal in essential tremor but not in Parkinson's disease. *Parkinsonism Relat Disord* 2012;18:1089–1093. doi: 10.1016/j.parkreldis.2012.06.008

10. Lee SM, Kim M, Lee HM, Kwon KY, Koh SB. Nonmotor symptoms in essential tremor: comparison with Parkinson's disease and normal control. *J Neurol Sci* 2015;349:168–173. doi: 10.1016/j.jns.2015.01.012
11. Habipoglu Y, Alpua M, Bilkay C, Turkel Y, Dag E. Autonomic dysfunction in patients with essential tremor. *Neurol Sci* 2017;38:265. doi: 10.1007/s10072-016-2754-z
12. Benito-León J, Louis ED, Bernejo-Parja F. Risk of incident Parkinson's disease and parkinsonism in essential tremor: a population based study. *J Neurol Neurosurg Psychiatry* 2009;80:423–425. doi: 10.1136/jnnp.2008.147223
13. Postuma R. Prodromal Parkinson's disease – using REM sleep behavior disorder as a window. *Parkinsonism Relat Disord* 2014;20 Suppl 1:S1–S4. doi: 10.1016/S1353-8020(13)00400-8
14. Dahms C, Gunthert A, Schwab M, Schultze T, Nowack S, Hoyer D, et al. Dysautonomia in prodromal  $\alpha$ -synucleinopathy: peripheral versus central autonomic degeneration. *Eur J Neurol* 2016;23:878–890. doi: 10.1111/ene.12957
15. Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorders Society on tremor. *Mov Disord* 1998;13:2–23. doi: 10.1002/mds.870131303
16. Stiasny-Kolster K, Mayer G, Schäfer S, Möller JC, Heinzel-Gutenbrunner M, Oertel WH. The REM sleep behavior disorder screening questionnaire – a new diagnostic instrument. *Mov Disord* 2007;22:2386–2393. doi: 10.1002/mds.21740
17. Visser M, Marinus J, Stiggelbout AM, Van Hilten JJ. Assessment of autonomic dysfunction in Parkinson's disease: the SCOPA-AUT. *Mov Disord* 2004;19:1306–1312. doi: 10.1002/mds.20153
18. Mahlknecht P, Seppi K, Frauscher B, Kiechl S, Willeit J, Stockner H, et al. Probable RBD and association with neurodegenerative disease markers: a population-based study. *Mov Disord* 2015;30:1417–1421. doi: 10.1002/mds.26350
19. Louis ED, Faust PL, Vonsattel JP, Honig LS, Rajput A, Robinson CA, et al. Neuropathological changes in essential tremor: 33 cases compared with 21 controls. *Brain* 2007;130:3297–3307. doi: 10.1093/brain/awm266
20. Strombi-Ferini L, Orrtel W, Dauviliers Y, Postuma RB, Marelli S, Iranzo A, et al. Autonomic symptoms in idiopathic REM behavior disorder: a multicentric case-control study. *J Neurol* 2014;261:112–118. doi: 10.1007/s00415-014-7609-z
21. Lenka A, Benito-León J, Louis ED. Is there a premotor phase of essential tremor? *Tremor Other Hyperkinet Mov* 2017;7. doi: 10.7916/D80SOIVK