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REM sleep behavior disorder and motor dysfunction in Parkinson's disease – A longitudinal study

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ABSTRACT

Objectives: Longitudinal assessment of a Parkinson's disease (PD) cohort, to investigate the evolution or REM sleep behavior symptoms (RBD) over time and to test the relation between RBD at onset and motor dysfunction progression.
Methods: An early stage PD cohort ($n = 61$) was assessed at two time points, separated by a two years interval. Diagnostic criteria for RBD were: violent behavior during sleep and body movements or vocalization indicative of dream enacting and at least six affirmative answers in the REM sleep behavior disorder screening questionnaire. Motor function assessment was performed with the Unified Parkinson's Disease Scale part II and III (total and partial scores for tremor, bradykinesia, rigidity, gait/postural instability and dysarthria).
Results: 25 Patients had RBD at baseline, vs. 35 at follow-up. Three RBD changed to non-RBD at follow-up, while 10 non-RBD patients developed RBD at follow-up (annual incidence of 12.5%). RBD and non-RBD patients did not differ significantly at baseline or follow-up. The presence of RBD at baseline was significantly related to an increase in UPDRS total and bradykinesia scores over time.
Discussion: RBD symptoms can vary over time and have a tendency to increase during the early stages of disease. The presence of RBD symptoms could be a risk factor for motor function deterioration and particularly for bradykinesia worsening.

1. Introduction

REM-sleep behavior disorder (RBD) is a REM sleep parasomnia characterized by violent behavior during sleep, related to loss of REM sleep muscular atonia and enactment of vivid dreams [1]. RBD can occur in isolation, but is most frequent in patients with neurodegenerative disorders, particularly those associated with Lewy body deposition, like Multiple System Atrophy, Lewy-body dementia and Parkinson's disease (PD) [2]. In a previous study, we have presented results from a cross-sectional analysis of a cohort of early stage PD patients, in which worse non-tremor motor symptoms were found to be associated with past or present RBD symptoms [3]. Several other cross-sectional studies have suggested that RBD could be associated with specific PD phenotypes, comprising a predominance of postural instability and gait difficulties [4–7]. However, there is a need for longitudinal studies, in which the significance of RBD as a risk factor can be determined more accurately.

We conducted a longitudinal assessment of the previously mentioned cohort, in order to assess the evolution of RBD over time and to evaluate the predictive value of RBD for motor dysfunction progression in PD.

2. Methods

Seventy-five early stage PD patients, diagnosed according to validated criteria [8], were consecutively recruited from Hospital Egas Moniz Neurology Department's outpatient clinic. All patients had clinically satisfactory response to dopaminergic treatment, and none presented with cerebellar dysfunction, signs of autonomic dysfunction, or other signs suggestive of multiple system atrophy or other atypical parkinsonism. Early stage PD was defined, at baseline, as disease duration (time in years from appearance of first motor symptoms to first assessment) up to 5 years and Hoehn and Yahr (HY) [9] stage from 1 to 2.5, included.

Patients were assessed twice, with a two year interval ($t0$ and $t1$), with the same instruments and by the same observer.

2.1. Motor assessment

Patients were assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) part II and III [10], after receiving their usual medication and while on *on* state. Separated scores were derived for tremor, rigidity, bradykinesia, speech and

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gait/postural stability symptoms, from items 20 and 21, 22, 23 to 27, 18, and 29 to 30, respectively. Patients were split into three motor groups, according to the classification system proposed by Jankovic and co-workers [11]: i. tremor predominant; ii. intermediate; iii. postural instability and gait difficulty (PIGD) predominant. Recent studies have shown that motor phenotype variation over time occurs usually in the tremor-PIGD direction and that this progression is predictive of worse prognosis [12]. For statistical purposes, motor status progression was defined as a change from the tremor dominant form to the intermediate or PIGD phenotype, versus maintenance of tremor subtype or a change from intermediate of PIGD subtype to tremor (patients who had PIGD subtype at baseline and maintained that status were excluded from this analysis). Dopaminergic treatment was calculated as L-Dopa equivalent doses (DED) [13].

2.2. RBD assessment

Clinical interview with the patients and bed partners was used to confirm the presence of minimal clinical criteria for RBD, according to the International Classification of Sleep Disorders (ICSD): violent behavior during sleep and body movements or vocalization indicative of dream enacting [14]. Assisted by their bed partners, the patients also answered the REM sleep behavior disorder screening questionnaire (RBDSQ), a recently proposed screening tool, which proved to have great sensitivity and reasonable specificity for RBD diagnosis as confirmed by polysomnography [15]. RBDSQ contains 13 questions, covering several aspects of RBD symptom spectrum. In the original study a score of at least five positive answers was proposed as the cut-off value for possible RBD. However, we chose to use 6 as the cut-off score, as proposed by a more recent investigation, that validated this scale for use in PD population [16]. Patients who fulfilled the ICSD minimal criteria and scored above cut-off on the RBDSQ were classified as possible RBD cases (RBDp). Patients which did not fulfill both criteria were classified has non-RBDp patients.

2.3. Statistical analysis

The annual incidence of RBDp was calculated as the number of new RBDp cases divided by the time elapsed (in years), divided by the total number of patients without RBDp at $t1$. We used the McNemar test to compare the proportion of RBDp and non-RBDp between baseline and follow-up. Two way independent sample t tests or Mann–Whitney tests (depending on the distribution of the variables) where used to compare continuous variables at baseline and follow-up, between RBDp and non-RBDp patients. Repeated measures ANOVA was used to test the relation between the presence of RBDp at baseline (between-patients factor) and the variation of motor scores over time (within-patients variables).

Ethics: Patients and controls signed informed consent forms. The ethics committee of the institution approved the investigation protocol. The investigation was performed according to the Declaration of Helsinki.

3. Results

Of the 75 patients assessed at $t0$, 61 patients were reassessed at $t1$. Two patients died, from causes unrelated to PD; 1 refused reassessment; diagnosis changed in 4, who at follow-up were found not to have PD; 7 patients could not be found at $t2$. Patients who could not be assessed at $t1$, showed a tendency for older age (75.4 ± 4.55 vs. 71.9 ± 7.53, $p = 0.099$), and older age of onset (72.7 ± 4.75 vs. 69.1 ± 7.76, $p = 0.098$). There were no significant differences in demographic or motor variables between these patients and those that were available for reassessment. RBDp prevalence was not significantly different: 4 (29%) vs. 28 (46%), $p = 0.370$.

The number of RBD cases increased from $t0$ to $t1$, although the difference did not reach significance (28–35, $p = 0.950$). Annual incidence of RBD was 12.5%. Variation from non-RBD to RBD was more frequent than in the opposite direction, but most patients maintained the baseline diagnosis (Fig. 1).

Forty-seven patients were on dopaminergic treatment at $t0$ (mean DED 390 ± 355.8), 18 exclusively on L-Dopa (mean DED 267.2 ± 287.9), 7 exclusively on dopamine agonists (mean DED 170 ± 164.4) and 22 on both (mean DED 674.1 ± 370.7). Four patients were additionally under treatment with MAO inhibitors (2 with selegiline, two with rasagiline), as a co-adjuvant treatment to L-Dopa. At $t1$, 59 patients were on dopaminergic treatment, 21 exclusively on L-Dopa (mean DED 498.4 ± 213.9), 8 exclusively on dopamine agonists (mean DED 185.0 ± 118.9) and 30 on both

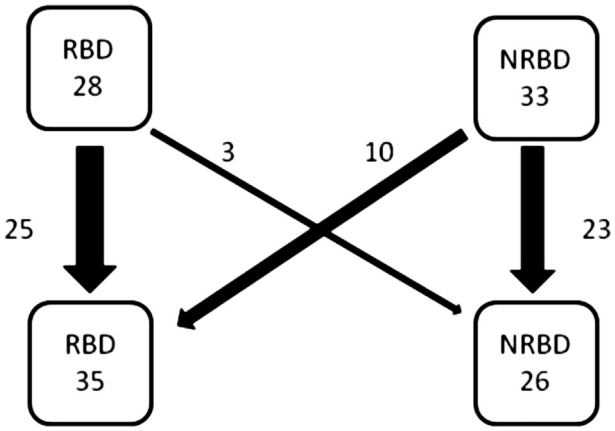

Fig. 1. Evolution of RBD symptoms between $t0$ and $t1$. Legend: values represent number of patients.

(mean DED 751 ± 370.8). To investigate the relation between dopaminergic doses increase (calculated as DED at $t1$ − DED at $t0$) and RBD diagnosis change from $t0$ to $t1$, we compared total, L-Dopa, and dopamine agonist doses increase between patients that changed from to RBDp to non-RBDp, maintained non-RBDp diagnosis, maintained RBDp diagnosis or changed from non-RBDp to RBDp (ANOVA followed by Bonferroni post-hoc analysis). We found no significant differences. Ten patients were on SSRI at $t0$ (7 had RBD symptoms) and 1 RBD patient was on clonazepam. There were no patients on rivastigmine. At $t1$, 15 patients were on SSRI (11 with RBD), 5 were on rivastigmine (3 with RBD) and 3 on clonazepam (all RBD patients). There was no significant relation between the use of these medications and the presence of RBD at $t0$ or $t1$. Two patients who were on SSRI at $t0$ suspended this medication at $t1$, while three who were not on SSRI at $t0$, had started this medication at $t1$. Change in SSRI was not significantly related with change in RBD diagnosis (Chi-square tests).

Fifteen patients presented with PIGD phenotype at $t0$, and maintained that status at $t1$, being excluded from motor status progression analysis. Of the other 46 patients, 16 showed motor status progression. Nine of these patients had RBDp at $t0$, a non significant relation ($p = 0.352$).

RBDp and non-RBDp groups did not differ significantly regarding motor scores, either at $t0$ or $t1$. The presence of RBDp at onset was significantly related to increase in UPDRS total scores and very significantly related to increase of bradykinesia scores (Table 1). Paired samples t test revealed a significant ($p = 0.032$) increase in bradykinesia in patients who presented RBDp at $t0$, and a non significant increase in the non-RBD group ($p = 0.336$).

4. Discussion

We found a high prevalence of RBDp in our early stage PD cohort. Although most patients retained their baseline RBD diagnosis at follow-up, there was a net increase in RBDp cases over time, with an annual incidence of 12.5%. Lavault and coworkers [17] found a decrease in RBD cases over a two year follow up and a lower annual incidence (9%), although they started with a higher prevalence of RBD at baseline. In Gjerstad's et al. study [18], which had a longer follow-up (8 years, three visits), there was a much larger fluctuation in RBD symptoms, with only 3 out of 89 patients maintaining an RBD diagnosis at all three assessments and total RBD percentages varying from 14.7% at first assessment, to 27.3% on the second visit and 14.6% at the last appointment. Divergences regarding previous studies could be caused by differences in PD

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