Incidence and Progression of Rapid Eye Movement Behavior Disorder in Early Parkinson’s Disease

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Abstract: Background: Rapid eye movement (REM) sleep behavior disorder (RBD) is associated with neurodegenerative diseases; however, few longitudinal studies assess the individual evolution of RBD and REM sleep without atonia (RWA) in Parkinson’s disease (PD).

Objectives: We aimed to evaluate RBD and RWA changes over time as well as potentially influential factors.

Methods: RBD and RWA were analyzed using video-supported polysomnography (vPSG) in initially de novo PD patients at baseline and every 2 years for a total of 6 years. The influence of time, age, sex, levodopa equivalent daily dose (LEDD), unified Parkinson’s disease rating scale (UPDRS) sum scores, benzodiazepine intake, Mini-Mental State Examination (MMSE) total scores, and dyskinesia on RWA were investigated using mixed-effect models to account for intra-individual correlations.

Results: After 6 years, vPSG data were available from 98 of the initial 159 de novo PD patients. RBD prevalence increased from 25% at baseline to 52%. Of the 31 PD patients with RBD and valid vPSGs at all time-points, RWA increased from an average of 19% at baseline to 41% at 6-year follow-up modeled to grow by 29.7% every 2 years (P < 0.001). Time was an independent factor (P < 0.001) for RWA increase. Age was an independent factor influencing RWA increase (P = 0.04). Sex, LEDD, UPDRS sum scores, benzodiazepines, MMSE total scores, and dyskinesia did not have any significant influence.

Conclusions: RBD and RWA increased significantly over time in PD; time and age were independent factors in a prospective cohort. RBD and RWA can be considered PD progression markers.

Rapid eye movement (REM) sleep behavior disorder (RBD), a parasomnia characterized by dream-enacting motor behaviors and/or vocalizations,1,2 is a precursor to neurodegenerative diseases associated with the misprocessing of α-synuclein.3,4 A recent meta-analysis calculated an annual conversion rate of 6.3% of patients with isolated RBD (iRBD) into any neurodegenerative disease.5 Data from functional imaging studies6 highlighted the role of RBD as a premotor manifestation of Parkinson’s disease (PD) and as a diagnostic marker for α-synuclein aggregation disorders. A recent study using the REM sleep behavior screening questionnaire tried to identify “probable RBD” and an association was found between motor and cognitive decline in probable RBD patients.7

In manifest PD, a recent meta-analysis (n = 2462) calculated an overall mean prevalence of RBD of 23.6% in newly diagnosed PD, with a wide range (4.3%–69.4%) most likely because of the lack of polysomnographic validation in all but 1 of the 8 studies.8 This 1 study comprised the baseline report of our de novo Parkinson (DeNoPa) sleep cohort and identified polysomnographically validated RBD in 25% of newly diagnosed, drug-naïve PD patients.9 RBD prevalence increased to 43% at 2-year follow-up.10 In a large cohort of PD patients at various...
disease stages, RBD prevalence was 46%. Analysis of associated factors supports the hypothesis that RBD signals the entrance into a more advanced stage of neurodegeneration. Previous results from the DeNoPa cohort indicate a worsening of symptoms in PD patients over 4 years. Therefore we hypothesize that RBD is a clinical progression marker in PD and is clinically manifest in many PD patients, even years after they are diagnosed with PD according to United Kingdom (UK) Brain Bank (UKBBC) or International Parkinson and Movement Disorder Society (MDS) diagnostic criteria.

Methods

In this study, we sought to investigate the individual development of RBD and REM sleep without atonia (RWA) with video-supported polysomnography (vPSG) in the DeNoPa cohort of PD patients who were initially drug-naïve, from baseline to 6-year follow-up.

The data for this study are part of a prospective longitudinal single-center observational cohort study of 139 initially de novo PD patients and 110 healthy controls for the assessment of biomarkers from baseline with ongoing biannual follow-up investigations ("DeNoPa cohort"), including vPSG. Details of the recruitment process, inclusion, and exclusion criteria have been described previously. Participants had to be between 40 and 85 years old, have PD with 2 of the following (1) resting tremor, (2) bradykinesia, and (3) rigidity according to UKBCC, and be drug-naïve for PD medications. Healthy controls were required to have no known central nervous system condition and no family history of idiopathic PD.

The study presented here is based on vPSG data collected during the DeNoPa study from baseline to third follow-up (FU3), 6 years after enrolment. We identified PD patients with RBD at baseline, after 2 years (FU1), 4 years (FU2), and 6 years (FU3) and assessed RWA. Individual RBD and RWA values were mapped over time. The influence of RWA on time, age, sex, levodopa equivalent daily dose (LEDD), unified Parkinson’s disease rating scale (UPDRS) sum scores, Mini-Mental State Examination (MMSE) total scores, dyskinesia, and the intake of substances potentially suppressing RBD such as benzodiazepines and melatonin, were analyzed.

Sleep Data

At baseline, patients were investigated in the sleep laboratory for 2 nights. The second night was used for analysis. If the patient refused to undergo the second recording or 1 of the 2 polysomnographies (Xitec: Excel Tech, Oakville, Canada) was invalid because of technical artifacts, the valid recording was used. For follow-up investigations, only 1 vPSG night was performed, using the same recording and evaluation techniques as the baseline assessment. The presence or absence of RBD was identified according to the criteria of the International Classification of Sleep Disorders 2nd edition (ICSD-2) that was in effect at the start of the study, the only exception was that dream-enacting behaviors and/or vocalizations during REM sleep had to be present on the time-synchronized vPSG. Comfort moves, neck myoclonus, arousal-related events, and respiratory noises were omitted. Patients with untreated or insufficiently treated sleep-disordered breathing, with severe insomnia (sleep efficiency <30% time in bed (TIB)) as well as patients with a total REM sleep time under 10 minutes were excluded from the study. RWA was measured in the mentalis muscle according to the method used by Frauscher et al. whereby each REM sleep 30-s epoch was divided into ten 3-s mini epochs. Mini epochs showing any chin muscle activity on electromyography (EMG) exceeding 0.1 s with an amplitude higher than twice the background EMG activity were counted as positive for RWA. Muscle activity associated with snoring, apnea, and arousals as a result of respiratory events were excluded. The number of mini epochs positive for RWA was calculated as a percentage of all REM sleep mini epochs. The cut-off value with 100% specificity for RBD was set at a mentalis EMG activity rate of 18.2%, which is consistent with criteria established by Frauscher et al. We followed the recommended method and validated cut-offs by considering “any” muscle activity as mentioned above. This technique does not differentiate between tonic and phasic muscle activity. Following the scoring rules defined by Frauscher et al, measurements were additionally assessed by a second scorer blinded to the results of the first scoring.

In accordance with our earlier observations, we classified REM-associated minor motor behaviors and/or vocalizations with RWA measured below the above mentioned cut-off value as REM behavioral events (RBE).

Clinical Data

Data on the age at the time of vPSG, sex, comorbidity, and LEDD were collected. LEDD was calculated according to Tomlinson. Overall impairment, as a measure of disease severity, was assessed with the UPDRS. Dyskinesia was assessed with UPDRS-IV. Because clonazepam can be used for the treatment of RBD, we also registered the intake of benzodiazepines.

Statistical Analysis

Measured variables were summarized by mean (±SD and minimum, maximum) or by absolute and relative frequencies as appropriate. Because we include data from only 31 PD patients, we refrain from fitting a model using all potentially influential factors simultaneously. Instead, for each potentially influential factor, the influence of the potential factor on RWA was modeled separately using mixed-effect models (with auto-regressive correlation structure) to account for intra-individual correlations allowing for random intercepts and random slopes over time. To account for time progression effects, time was used as an additional fixed effect in every model. RWA share was modeled on a logarithmic scale. Age was included as a baseline variable. The interaction between baseline age and time proved non-significant and was therefore not included in the model. The influence of time on the risk of developing RBD was modeled using mixed-effect logistic regression. The significance level was set to $\alpha = 0.05$ for all statistical tests. All analyses were performed with the statistics software R (version 3.6.1; R Core Team 2018) and IBM SPSS Statistics 25.0.
Data Availability Statement

The clinical data of the DeNoPa trial are part of the Neuroshare initiative and can be accessed through The Michael J. Fox Foundation of Parkinson’s Research. Polysomnographic and other anonymized data not published within this article will be made available by request to the corresponding author from any qualified investigator.

Results

After 6 years (FU 3), full vPSG REM sleep evaluations were available for 98 of the original 159 de novo PD patients from the DeNoPa cohort. Reasons for missing/invalid vPSG data were: exclusion because of technical artifacts (n = 1), the absence of REM sleep in the vPSG recording (n = 4), the absence of sleep in the sleep lab night (n = 5), patient refusal of vPSG (n = 10),

### TABLE 1 Demographic and clinical data, RWA values of 31 PD patients with 4 valid vPSGs over 6 years

| n | Baseline (BL) | 2-year follow-up (FU1) | 4-year follow-up (FU2) | 6-year follow-up (FU3) |
|---|---|---|---|---|
| Total patients with RBD diagnosisa n (%) | 31 | 31 | 31 | 31 |
| Age, years | 60 ± 9 (48–73) | 62 ± 9 (42–75) | 64 ± 9 (44–77) | 66 ± 9 (46–79) |
| Gender male, n (%) | 28 (85) | 28 (85) | 28 (85) | 28 (85) |
| UPDRS sum score | 25 ± 12 (9–61) | 30 ± 15 (3–73) | 37 ± 19 (9–73) | 38 ± 20 (9–90) |
| LEDD mg | n.a. | 322 ± 178 (60–700) | 508 ± 283 (8–1350) | 713 ± 276 (285–1325) |
| Benzodiazepines n (%) | 0 | 2 (3) | 4 (6) | 5 (7) |
| RWA % REM | 19 ± 19 (3–99) | 29 ± 14 (10–61) | 33 ± 19 (9–100) | 41 ± 24 (8–100) |
| Intake of SSRI/SNRI n (%) | 3 (10) | 4 (13) | 4 (16) | 5 (16) |
| Intake of beta-blockers n (%) | 6 (20) | 8 (26) | 8 (26) | 9 (29) |
| AHI | 2 ± 3 (0–15) | 1 ± 3 (0–16) | 2 ± 3 (0–11) | 2 ± 3 (0–16) |
| PLMs | 27 ± 37 (0–185) | 27 ± 48 (8–214) | 35 ± 8 (179) | 36 ± 57 (8–294) |
| MMSE | 29 ± 1 (25–30) | 29 ± 1 (26–30) | 28 ± 2 (24–30) | 28 ± 1 (25–30) |
| Dyskinesia n (%) | 0 | 1 (3) | 5 (16) | 11 (36) |

*aTotal patients with RBD diagnosis at follow-up out of 31 patients with 4 visits.

UPDRS, unified Parkinson’s disease rating scale; LEDD, levodopa equivalent daily dose calculated according to Sixel-Doring et al; RWA, REM sleep without atonia in chin measured by criteria from Frauscher et al; n.a., not applicable; AHI, apnea-hypopnea-index; PLMs, periodic limb movements during sleep index; MMSE, Mini-Mental State Examination total score.
patient drop out (n = 22), and patient death (n = 19). Details have been described previously.9 When considering all sleep lab investigations performed within the first 6 years of the DeNoPa study, a total of 78 patients were diagnosed with RBD at some point (Fig. 1). Of these 78 patients, 31 PD patients were identified with RBD at 1 time and also had valid vPSG data at every investigation. Demographic and clinical data as well as RBD occurrence and RWA measurements at every investigational time point for those 31 PD patients are summarized in Table 1. RWA increased significantly in all 31 patients over time (P < 0.001) (Table 2). Their RWA development across the observational period of 6 years is mapped in Figure 2.

Thirty-one PD patients had a mean age of 60 + 9 years at baseline and 66 + 9 years at 6-year follow-up. A total of 20 of 31 patients were men (65%). UPDRS sum scores increased from an average of 25 + 12 at baseline to 38 + 20 after 6 years. LEDD was not applicable at baseline but increased from 322 + 178 mg at FU1, to 508 + 283 mg at FU2 and 713 + 276 mg after 6 years at FU3. RWA increased in all 31 PD patients from an average of 19% + 19% at baseline to 29% + 14% at FU1, to 33% + 19% at FU2 and an average of 41% + 24% after 6 years. RWA was modeled to grow by 29.7% every 2 years (P < 0.001) in this cohort of 31 PD patients. The development of logarithmized RWA share is mapped in Figure 3 with age being presented as an influential factor (P = 0.04).

Table 2 Coefficients from mixed effect models

| Term                  | Estimate | 95% CI        | P value |
|-----------------------|----------|---------------|---------|
| Model 1 (Intercept)   | 1.69     | [0.69;2.68]   | 0.001   |
| Model 2 (Intercept)   | 2.68     | [2.38;2.97]   | <0.001  |
| Model 3 (Intercept)   | 2.81     | [2.53;3.12]   | <0.001  |
| Model 4 (Intercept)   | 3.29     | [2.93;3.65]   | <0.001  |
| Model 5 (Intercept)   | 2.89     | [2.37;3.4]    | <0.001  |
| Model 6 (Intercept)   | 2.72     | [2.46;2.99]   | <0.001  |
| Model 7 (Intercept)   | 1.45     | [0.85;3.75]   | 0.215   |
| Time                  | 0.15     | [0.1;0.2]     | <0.001  |
| Sex                   | 0.09     | [0;0.17]      | 0.058   |
| Benzodiazepines       | 0.15     | [0;0.8]       | 0.189   |
| Time                  | 0.16     | [0.1;0.21]    | <0.001  |
| Dyskinesia            | −0.11    | [−0.4;0.18]   | 0.459   |
| Time                  | 0.15     | [0;0.2]       | <0.001  |
| MMSE                  | 0.04     | [−0.04;0.21]  | 0.271   |

To study the effect of potentially influential factors, for each factor a time adjusted mixed-effect model was fit to the data. The columns hold the coefficient with the 95% confidence interval and the P value.

UPDRS, unified Parkinson’s disease rating scale; LEDD, levodopa equivalent daily dose calculated according to Tomlinson.19

FIG. 2. RWA values of 31 PD patients with 4 valid vPSGs and RBD at any time point.

FIG. 3. RWA values of PD patients with 4 valid vPSGs and RBD at any time point.
Sex, UPDRS sum scores, LEDD, MMSE, dyskinesia, and the intake of benzodiazepines did not show any influence on RWA values (Table 2). Melatonin was not used by any patient.

Discussion

To the best of our knowledge, this is the largest and longest prospective study on the development of RBD and RWA in clinically manifest PD patients with sequential vPSGs. Across the observational period of 6 years from baseline to FU3, a total of 78 of 158 (49%) PD patients of the DeNoPa sleep cohort with biannual vPSG were identified with RBD at some time point. The relative quota of RBD rose from 25% at baseline to 52% after 6 years. Apart from the >100% increment of RBD occurrence across this timespan, we demonstrate that RBD did not abate in the individual PD patient after its first manifestation.

In this study, we also observed a significant increase of RWA from baseline to FU3 after 6 years in cohesion with previous results. The fact that time and age were identified as the only relevant influential factors for RWA increase, and UPDRS sum scores, sex, dopaminergic medication, MMSE, dyskinesia, and the intake of benzodiazepines did not influence the manifestation of RBD or the amount of RWA, supports the hypothesis that RWA, as well as RBD, are progression markers in PD.

In addition, we confirmed that RBE at baseline converts into full-blown RBD, which is consistent with previous results, because the 7 of 31 patients diagnosed with RBE at baseline all converted into full-blown RBD after 6 years. A recent micro-sleep analysis demonstrated a significant increase in micro–sleep instability in those RBE-positive PD patients who were about to convert to RBD.

These findings imply that RBE, RBD, and RWA appear as the result of an ongoing underlying pathological process with degeneration of nucleus subcoeruleus circuits projecting to the medullary reticular formation and spinal ventral interneurons. The malfunction of gamma-aminobutyric acid (GABA)/glutamatergic neurotransmission in the ventromedial medulla facilitates the occurrence of abnormal motor enactments. The impairment of the locus subcoeruleus leads to increased EMG activity, especially in the mentalis muscle. The mentalis muscle provides the highest EMG activity rate in RBD patients compared to any other muscle. Any activity in the mentalis muscle above the 16.4% cut-off was shown to be highly sensitive for synuclein aggregation disorders like PD. PD patients with RBD have higher RWA shares than patients with iRBD. iRBD patients with dream-enactment behaviors starting after the age of 55 were shown to have a faster rate of developing neurodegenerative diseases compared to those who developed dream–enactment behaviors before the age of 55. This implies that the aging brain may be more vulnerable to the spreading of α-synuclein than the younger brain even in diagnosed PD patients and may explain the age–dependency of RBD in this cohort with an age range of 40 to 73 years at baseline (Table 1). The origin of movements during RBD episodes is currently not fully understood.

The question is why only a minority of newly diagnosed PD patients have RBD. Based on Braak’s concept of the gradual ascension of Lewy bodies one would expect RBD to affect all PD patients at the time of diagnosis. The spreading of synuclein in PD may, however, differ in phenotypes of PD and the clinical manifestation of RBD may not be fully congruent with the neuropathological infiltration of synuclein pathology. Furthermore, recent evidence from imaging studies suggests 2 different primary spreading routes in the development of PD, 1 starting in the gut and ascending via the vagal nerve into the brain stem with the manifestation of RBD prodromal to PD, and the other entering the brain primarily via the olfactory bulb.

The absence of RBD in the majority of de novo PD patients, as well as the failure to detect any significant difference in macro-sleep structure based on conventional sleep staging, implies that sleep pathology in PD does not follow an “all-or-nothing” principle but rather represents a gradual transition process. Recent studies on the cyclic alternating pattern (CAP) have shown significant changes in CAP rates implying dysfunction of sleep regulatory mechanisms detectable in micro-sleep analysis before the macrostructure of sleep is altered, with a significant influence of disease duration on CAP rate in the course of the disease.

Two study limitations need to be mentioned. First, the relatively high loss of valid vPSGs during the study resulted in only 31 PD patients with RBD at some time point and valid vPSG data at every investigational time point. This was not only a result of patients’ discontinuation but also because of technical reasons preventing the accurate calculation of RWA when using the criteria established by Frauscher et al. In the case of a non-informative recording, we did not have the possibility of a second sleep lab night because patients were investigated only for 1 night, based on the observation that although there may be a considerable intra-individual night-to-night variability of motor behaviors in RBD, EMG activity scores were found to be stable on 2 consecutive nights, allowing for identification of RBD based on only 1 night of vPSG.

The second limitation is the restriction of EMG analysis to chin muscle activity; at the time of the baseline investigation, measurement of RWA in other muscles had not yet been validated for the detection of RBD, so that for comparative studies over time we had to rely on chin muscle EMG alone. This, however, seems especially prone to pick up snoring or other respiratory artifacts, facilitated by PD patients’ preference for lying in a supine position during the night. Following the scoring rules as defined by the method from Frauscher et al., measurements were additionally assessed by a second scorer blinded to the results of the first scoring. In case of discrepant results, mental EMG was re-evaluated and consensus established. We, therefore, aimed to weaken the subjectivity factor. Automated atonia indices are not available.

In conclusion, we have shown that the frequency of RBD, as well as the amount of RWA, increases significantly over 6 years in PD patients independently of factors such as sex, the motor and mental progression of the disease, dosage of dopaminergic treatments, or benzodiazepine intake. In view of the pathophysiological considerations mentioned above, we, therefore, assume...
RBD and RWA to be progression markers of PD. With time, we would expect every PD patient in the study to develop RBD. Further follow-up of the DeNoPa sleep cohort is pending. Finally, future research should focus on those who do not develop RBD in the course of PD to characterize their outcome, phenotype, and possible protective factors.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

L.Z.: 1A, 1B, 1C, 2B, 3A
M.-L.M.: 1A, 1C, 3B
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B.M.: 1A, 1B, 2B
C.T.: 1A, 1B, 2C, 3B
F.S.-D.: 1A, 1B, 2C, 3B

Disclosures

Ethical Compliance Statement: The DeNoPa study is registered with the German Register for Clinical Trials (DRKS00000540) in accordance with the World Health Organization Trial Registration Dataset. All participants gave consent for their data to be scientifically evaluated and signed additional consent for the scientific evaluation of their nighttime videos (Ärztekammer Hessen, Approval N. FF89/2008). We, the authors confirm that we have read the Journals position on issues financially evaluated and signed additional factors for REM sleep behavior disorder. We, the authors confirm that we have read the Journals position on issues financially evaluated and signed additional factors for REM sleep behavior disorder. The authors report no conflicts.

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