Family history of idiopathic REM behavior disorder

A multicenter case-control study

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ABSTRACT

Objective: To compare the frequency of proxy-reported REM sleep behavior disorder (RBD) among relatives of patients with polysomnogram-diagnosed idiopathic RBD (iRBD) in comparison to controls using a large multicenter clinic-based cohort.

Methods: A total of 316 patients with polysomnography-confirmed iRBD were recruited from 12 RBD study group centers, along with 316 controls matched on sex and age group. All subjects completed a self-administered questionnaire that collected proxy-reported information on family history of tremor, gait trouble, balance trouble, Parkinson disease, memory loss, and Alzheimer disease. The questionnaire also included a single question that asked about possible symptoms of RBD among first-degree relatives (siblings, parents, and children).

Results: A positive family history of dream enactment was reported in 13.8% of iRBD cases compared to 4.8% of controls (odds ratio [OR] = 3.9, 95% confidence interval [CI] 2.0–7.7). ORs were increased for both siblings (OR = 6.1, 95% CI 2.1–18.1) and parents (OR = 3.2, 95% CI 1.4–7.8). We found no significant difference in sex, current age (65.3 ± 10.2 vs 66.9 ± 10.2 years), or age at self-reported RBD onset (55.2 ± 11.7 vs 56.6 ± 15.1 years) in possible familial vs sporadic iRBD. No differences were found in family history of tremor, walking and balance troubles, Parkinson disease, memory loss, or Alzheimer disease.

Conclusion: We found increased odds of proxy-reported family history of presumed RBD among individuals with confirmed iRBD. This suggests the possibility of a genetic contribution to RBD. *Neurology*® 2013;80:2233–2235

GLOSSARY

CI = confidence interval; iRBD = idiopathic REM sleep behavior disorder; OR = odds ratio; PD = Parkinson disease; PSG = polysomnography; RBD = REM sleep behavior disorder; RLS = restless legs syndrome.

REM sleep behavior disorder (RBD) is characterized by abnormal behaviors associated with dream mentation and loss of REM sleep atonia.¹ Most patients with idiopathic RBD (iRBD) eventually develop a neurodegenerative disorder such as Parkinson disease (PD), Lewy body dementia, and multiple system atrophy.² Although RBD has been reported in familial neurodegenerative conditions such as parkinsonism related to *parkin* and *DJ-1* mutations, spinocerebellar ataxia type III, and amyotrophic lateral sclerosis due to *SOD1* mutations,³ iRBD is generally considered to be a sporadic condition. One isolated genetic study performed on 25 patients with RBD reported an association with human leukocyte antigen DQw1.⁴ However, no studies have systematically assessed possible heritability. Therefore, we compared the frequency of proxy-reported RBD among relatives of patients with iRBD and controls, using a large multicenter clinic-based cohort.

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METHODS A total of 316 patients with polysomnography (PSG)-confirmed iRBD were recruited from 12 international RBD study group centers in a multicenter risk factor study.⁵ All cases met International Classification of Sleep Disorders–2 criteria for RBD (i.e., enhanced REM muscle tone on PSG with a history of dream-enactment or complex behaviors during REM sleep). All cases had neurologic examination confirming the absence of dementia and parkinsonism. A total of 316 age- and sex-matched controls were also recruited, including both normal controls (n = 110) and RBD-free controls with other sleep conditions (e.g., sleep apnea, restless legs syndrome [RLS], insomnia, hypersomnia; n = 206). All sleep center controls and 48 of the normal controls had PSG confirming the absence of RBD. No participants had narcolepsy. All participants provided written informed consent, and each sleep center obtained approval from its local institutional review board.

A structured self-administered questionnaire assessing demographic information, medical history, and lifestyle risk factors was completed.⁵ As part of this questionnaire we included an adapted version of the RBD single-question screen⁶ to query possible family history of RBD: “Do (or did) any of your family members ‘act out’ their dreams at night? (e.g., punching, kicking, or flailing during sleep while dreaming).” Participants were also asked about family history of parkinsonism or dementia, specifically querying tremor (head and hands), walking trouble, balance trouble, PD, memory loss, and Alzheimer disease. We limited our analysis to first-degree relatives only.

Statistical analysis. For each question, participants responded “Yes” (scored 1), “No” (scored 0), or “Don’t know.” For each positive response, participants reported who was affected (father, mother, brother, sister, children). Only first-degree relatives were scored as “Yes.” For “Don’t know” responses, the response was scored as 0, unless a specific relative was indicated as possibly affected, in which case the response was scored as 0.5. Sensitivity analyses were also conducted coding all “Don’t know” responses as missing values and as 0. Comparisons between cases and controls were made using univariate logistic regression analysis adjusting for age, sex, and center. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. We also conducted a sensitivity analysis separately analyzing cases relative to normal controls and to controls with another sleep diagnosis. Analysis was performed by R.B.P. (PASW Statistics 18, Quarry Bay, Hong Kong).

RESULTS A total of 312 cases and 315 controls completed the family history questionnaire (5 were adopted). A positive family history of dream enactment was reported by 13.8% of cases (i.e., 37 RBD families) and 4.8% of controls (OR 3.9, 95% CI 2.0–7.7) (table). Considering siblings and parents separately, siblings were reported as possibly affected in 7.2% of cases and 1.9% of controls (OR 6.1, 95% CI 2.1–18.1), with similar results for parents (7.2% vs 3.0%, OR 3.2, 95% CI 1.35–7.8). Only one child in each group was reported as having possible RBD symptoms.

Similar results were obtained when the analysis was performed scoring the “Don’t know” answer as 0 (OR 3.0, 95% CI 1.5–5.7) or as a missing value (OR 3.2, 95% CI 1.7–6.3). The more conservative approach (score = 0 for unclear responses) revealed 33 possible first-degree RBD families, including 4 multiplex families with at least 3 members possibly affected. We found no difference in results whether using normal volunteer controls (4.7% with affected family members) or sleep center controls (4.9%). Elimination of patients with iRBD and controls who reported antidepressant use did not modify the results (14.4% vs 3.9%, OR 4.5, 95% CI 2.1–9.7).

Comparing patients with and without reported family history, we detected no significant difference in sex (72% male vs 71% male), age (65.3 ± 10.2 vs 66.9 ± 10.2 years), or age at self-reported RBD onset (55.2 ± 11.7 vs 56.6 ± 15.1 years). A total of 72% of possibly affected relatives were male (72% among RBD patients, 71% among controls).

No significant center or ethnicity effect was found on the reported RBD family history. Between cases and controls there was no difference in reported family history of hand tremor, head tremor, walking trouble, balance trouble, PD, memory loss, or Alzheimer disease (table).

Table Family medical history characteristics of patients with idiopathic RBD and controls^a

	iRBD (n = 312), %	Controls (n = 315), %	OR (95% CI)	p Value
Family history of dream enactment	13.8	4.8	3.9 (2.0–7.7)	<0.001
In siblings	7.2	1.9	6.1 (2.1–18.1)	<0.001
In parents	7.2	3.0	3.2 (1.35–7.8)	<0.009
Family history of tremor, hands	11.2	8.1	1.51 (0.87–2.6)	0.14
Family history of tremor, head	4.2	3.3	1.38 (0.60–3.18)	0.46
Family history of walking trouble	12.1	11.2	1.11 (0.67–1.82)	0.69
Family history of balance trouble	14.1	13.0	0.95 (0.60–1.52)	0.84
Family history of Parkinson disease	7.3	6.3	1.14 (0.60–2.13)	0.70
Family history of memory loss	21.4	19.5	1.13 (0.76–1.67)	0.55
Family history of Alzheimer disease	11.5	7.7	1.57 (0.70–2.97)	0.11

Abbreviations: CI = confidence interval; iRBD = idiopathic REM sleep behavior disorder; OR = odds ratio; RBD = REM sleep behavior disorder.

^aOdds ratios are adjusted for age, sex, and center.

DISCUSSION This study reports a possible familial component of iRBD, with a significantly higher frequency of a positive family history of presumed RBD among PSG-confirmed patients with iRBD (13.8%) compared to controls (4.8%).

Some limitations should be noted. Since identification of a family history of RBD was determined through proxy report, there is potential for misclassification bias. The question used to screen family members was an adaptation of the RBD1Q, a screening question with 94% sensitivity and 87% specificity among probands⁶; however, proxy report has not been tested. It is likely that some family members were incorrectly classified as having or not having RBD (this limitation also would presumably apply to controls). Proxy reports could be subject to recall bias, in which the cases are more likely to be aware of a similar condition in a family member. The fact that family history of presumed RBD was equal in normal controls vs sleep center controls (who may also have an increased awareness of sleep disorders) may suggest that recall bias was not so large, at least not sufficient to negate an OR of 4. It is also possible that some family members had non-REM parasomnia with dream enactment⁷ and were incorrectly identified as having RBD. However, only one child per group was reported as affected; given that non-REM parasomnias are more common in childhood, the proportion of misidentified non-REM parasomnia may be relatively low. Similarly, we cannot ensure that some apparent RBD in family members was not obstructive sleep apnea, periodic leg movements of sleep, or RLS.⁸ However, if this was common, we might have seen a higher prevalence in sleep center controls (given that RLS is a familial condition).

As iRBD is an important risk factor for neurodegenerative diseases, especially α -synucleinopathies, the absence of an increased frequency of parkinsonism or dementia in relatives of iRBD patients is intriguing. Certainly, family history of PD is relatively uncommon, so it is possible that this study was underpowered to detect differences.

Considering the methodologic limitations inherent in proxy reports, this study has nonetheless found an increase of dream-enactment symptoms and therefore presumed RBD in family members of patients with PSG-confirmed iRBD, raising the possibility of a genetic contribution to RBD. Further studies are required to fully validate these findings using face-to-face clinical interview and video-PSG to test candidate genes and to perform linkage analysis or whole

exome sequencing in the high segregated iRBD families.

AUTHOR CONTRIBUTIONS

Y. Dauvilliers participated in the conception, design of the study, and recruitment of subjects, analyzed and interpreted the data, and wrote the first draft of the manuscript. Ron Postuma and Jacques Montplaisir participated in the conception, design of the study, and recruitment of subjects, analyzed and interpreted the data, and revised the manuscript. Ferini-Strambi Luigi, Arnulf Isabelle, Hogl Birgit, Manni Rafaele, Miyamoto Tomoyuki, Oertel Wolfgang, Fantini Maria Livia, Puligheddu M, Jennum Poul, Sonka Karel, Zucconi Marco, Leu-Semenescu Esmeranda, Frauscher Birgit, Terzaghi Michele, Miyamoto Tomoyuki, Unger Marcus, Desautels Alex, Wolfson Christina, and Pelletier Amélie participated in the recruitment of subjects for the study and revised the manuscript.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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