Comorbidity and medication in REM sleep behavior disorder

A multicenter case-control study

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ABSTRACT

Objective: This controlled study investigated associations between comorbidity and medication in patients with polysomnographically confirmed idiopathic REM sleep behavior disorder (iRBD), using a large multicenter clinic-based cohort.

Methods: Data of a self-administered questionnaire on comorbidity and medication use of 318 patients with iRBD and 318 matched controls were analyzed. Comparisons between cases and controls were made using logistic regression analysis.

Results: Patients with iRBD were more likely to report depression (odds ratio [OR] 2.0, 95% confidence interval [CI] 1.3–2.9) and concomitant antidepressant use (OR 2.2, 95% CI 1.4–3.6). Subanalysis of antidepressant agents revealed that the increased use of antidepressants in iRBD was due to selective serotoninergic reuptake inhibitors (OR 3.6, 95% CI 1.8–7.0) and not due to other antidepressant classes. Patients with iRBD reported more lifetime antidepressant use than comorbid depression (antidepressant use: OR 1.9, 95% CI 1.1–3.3; depression: OR 1.6, 95% CI 1.0–2.5). Patients with iRBD reported more ischemic heart disease (OR 1.9, 95% CI 1.1–3.1). This association did not change substantially when adjusting for cardiovascular risk factors (OR 2.3, 95% CI 1.3–3.9). The use of inhaled glucocorticoids was higher in patients with iRBD compared to controls (OR 5.3, 95% CI 1.8–15.8), likely reflecting the higher smoking rate in iRBD (smoking: OR 15.3, 95% CI 2.0–118.8; nonsmoking: OR 2.4, 95% CI 0.4–13.2) and consequent pulmonary disease.

Conclusions: This large study confirms the association between comorbid depression and antidepressant use in iRBD. In addition, there was an unexpected association of iRBD with ischemic heart disease that was not explained by cardiovascular risk factors. *Neurology*® 2014;82:1076–1079

GLOSSARY

CI = confidence interval; **iRBD** = idiopathic REM sleep behavior disorder; **IRBDSG** = International RBD Study Group; **OR** = odds ratio; **RBD** = REM sleep behavior disorder; **SA** = sleep apnea.

Idiopathic REM sleep behavior disorder (iRBD) has attracted notice particularly because it is often the first nonmotor symptom of synucleinopathies.[1] Although REM sleep behavior disorder (RBD) has been linked to neurodegeneration and narcolepsy, systematic studies on comorbidity and medication in iRBD are lacking. Some evidence exists for an association between iRBD and antidepressant use or comorbid depression.[2–6] However, all published studies are single-center studies with limited numbers of patients with iRBD.[2–6] To overcome these sample

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size limitations, the International RBD Study Group (IRBDSG) was founded to enable multicenter synergetic collaborative efforts.

In the current study, the IRBDSG investigated the association between comorbid medical conditions and medication in patients with iRBD compared to controls, using a large clinic-based cohort.

METHODS

Participants. Data for the current analysis were retrieved from the largest clinic-based cohort of patients with iRBD, which was collected for a broad risk factor assessment of iRBD as previously described.[7] Diagnosis of iRBD was made according to criteria of the International Classification of Sleep Disorders, 2nd revision. No patient had known neurodegenerative disease or antidepressant-induced RBD, defined as presence of a temporal relationship between RBD onset and introduction of antidepressants. Cases were compared to sex-, age-, and center-matched controls (sleep laboratory patients, healthy volunteers).

Standard protocol approvals, registrations, and patient consents. Ethical committee approval was obtained by each center. All patients granted written informed consent according to the Declaration of Helsinki.

Self-administered questionnaire. All participants filled out a self-administered questionnaire designed for the assessment of environmental risk factors for RBD. As part of this questionnaire, a subset of questions addressed physician-diagnosed comorbidities and concomitant medication use (appendix e-1 on the *Neurology*® Web site at Neurology.org). Specific questions addressed ischemic heart disease, other heart disease, cerebrovascular disease, migraine, epilepsy, cancer, diabetes mellitus, hypertension, hypercholesterolemia, arthritis, depression or other psychiatric illnesses, as well as present or past use of neuroleptics and antidepressants. Questions were answered with "yes" (1), "no" (0), or "don't know" (0). We assessed all other medical conditions and medications in an open-ended format and grouped them in categories as best applicable. Due to the exploratory nature, we decided to assess main medication categories, which were only further subclassified in case of a significant finding.

Statistics. Statistical analysis was performed with the Statistical Package for the Social Sciences version 20.0 by B.F. Comparisons between cases and controls were made using logistic regression analysis adjusted for age and sex. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Additional covariates were entered as indicated in Results. A sensitivity analysis was performed to account for the potential influence of the type of control (healthy volunteer control, other sleep disorder control, all controls except sleep apnea [SA]). A p value < 0.05 was considered to be significant.

RESULTS

Participants. A total of 318 patients with iRBD (259 men, 49 women) were compared to 318 controls (244 men, 74 women, $p = 0.144$). Controls were slightly younger than cases (66.2 ± 9.8 years vs 67.3 ± 9.8, $p = 0.048$) and consisted of healthy volunteers (137, 43.1%) and patients with sleep diagnoses other than RBD (181, 56.9%). Ninety controls (28.3%) had SA.

Comorbidity and medication use. iRBD cases were more likely to report depression and concomitant use of antidepressants (tables 1–3). Subanalysis of antidepressant agents revealed that the increased use of antidepressants in iRBD was due to selective serotoninergic reuptake inhibitors (OR 3.6, 95% CI 1.8–7.0) and not due to serotonin noradrenalin reuptake inhibitors (OR 1.6, 95% CI 0.6–4.3), trazodone (OR 0.7, 95% CI 0.3–2.1), or tricyclic antidepressants (OR 1.4, 95% CI 0.5–4.1). Duration of antidepressant use did not differ between cases and controls (2 [0–20] vs 3.5 [0–20] years; $p = 0.845$). Patients with iRBD reported more lifetime antidepressant use than comorbid depression (antidepressant use: OR 1.9, 95% CI 1.1–3.3; depression: OR 1.6, 95% CI 1.0–2.5).

Patients with iRBD reported more ischemic heart disease. This association did not change substantially when adjusting for cardiovascular risk factors such as hypercholesterolemia, arterial hypertension, diabetes mellitus, obesity, and smoking (OR 2.3, 95% CI 1.3–3.9). None of these risk factors was more prevalent in cases than controls. In fact, the rate of reported hypertension was lower in cases than controls.

The use of inhaled glucocorticoids was higher in patients with iRBD compared to controls. This appeared to serve as a proxy marker for chronic obstructive pulmonary disease or asthma, likely related to the higher prevalence of smoking in patients with iRBD (inhaled glucocorticoid use in smoking subjects: OR 15.3, 95% CI 2.0–118.8; inhaled glucocorticoid use in nonsmoking subjects: OR 2.4, 95% CI 0.4–13.2).

Table 1 Association of iRBD and comorbidity

Comorbidity	iRBD (n = 318)	Controls (n = 318)	OR (95% CI)
Depression	87 (28.8)	53 (17.5)	2.0[a] (1.3–2.9)
Cardiovascular disease	65 (20.4)	42 (13.3)	1.6 (1.0–2.5)
Cerebrovascular disease	22 (7.3)	16 (5.3)	1.3 (0.7–2.6)
Ischemic heart disease	49 (15.4)	27 (8.5)	1.9[a] (1.1–3.1)
Regular smoking	194 (61.0)	154 (49.7)	1.4 (1.0–1.9)
Nonischemic heart disease	38 (13.0)	27 (9.3)	1.4 (0.8–2.4)
Migraine	64 (21.6)	54 (17.6)	1.4 (0.9–2.1)
Autoimmune disease	36 (11.3)	34 (10.7)	1.1 (0.7–1.8)
Diabetes mellitus	38 (12.6)	40 (13.2)	0.9 (0.6–1.5)
Obesity	57 (17.9)	66 (20.8)	0.8 (0.6–1.3)
Hypercholesterolemia	91 (29.9)	103 (33.8)	0.8 (0.6–1.2)
Arthritis	44 (14.5)	53 (17.7)	0.8 (0.5–1.2)
Arterial hypertension	110 (36.2)	139 (45.0)	0.7[a] (0.5–0.9)

Abbreviations: CI = confidence interval; iRBD = idiopathic REM sleep behavior disorder; OR = odds ratio.
Values are n (%).
[a] Significant OR.

Table 2 Association of iRBD with concomitant medication

Drug classes	iRBD (n = 318)	Controls (n = 318)	OR (95% CI)
Antidepressants			
Lifetime use	59 (18.6)	30 (9.4)	2.4[a] (1.5–3.8)
Present use	55 (17.3)	29 (9.1)	2.2[a] (1.4–3.6)
Past use	14 (4.4)	4 (1.3)	3.9[a] (1.3–12.2)
Corticosteroids	27 (8.5)	11 (3.5)	2.6[a] (1.3–5.4)
Inhaled preparation	20 (6.3)	4 (1.3)	5.3[a] (1.8–15.8)
Anticonvulsants	17 (5.4)	10 (3.1)	1.9 (0.8–4.3)
Respiratory drugs	25 (7.9)	19 (6.0)	1.4 (0.7–2.5)
Vitamins	54 (17.0)	47 (14.8)	1.2 (0.8–1.9)
Anticoagulants/antiplatelet drugs	102 (32.1)	85 (26.7)	1.2 (0.9–1.7)
Gastrointestinal drugs	74 (23.3)	70 (22.0)	1.1 (0.7–1.6)
Urinary system drugs	41 (12.9)	38 (11.9)	1.0 (0.6–1.6)
Thyroid medication	24 (7.5)	26 (8.2)	1.0 (0.6–1.8)
Dopaminergic drugs[b]	27 (8.5)	30 (9.4)	0.9 (0.5–1.6)
Lipid-lowering drugs	75 (23.6)	82 (25.8)	0.9 (0.6–1.2)
Antidiabetic medication	33 (10.4)	36 (11.3)	0.9 (0.5–1.4)
Analgesics	38 (11.9)	52 (16.4)	0.7 (0.5–1.2)
Antihypertensive drugs	125 (39.3)	142 (44.7)	0.7 (0.5–1.0)
Bone drugs	20 (6.3)	33 (10.4)	0.6 (0.3–1.1)
Medication for hyperuricemia	9 (2.8)	14 (4.4)	0.6 (0.2–1.4)
Hormones	7 (2.2)	16 (5.0)	0.5 (0.2–1.3)

Abbreviations: CI = confidence interval; iRBD = idiopathic REM sleep behavior disorder; OR = odds ratio.
Values are n (%). Only drug classes that were used by ≥20 subjects are listed.
[a] Significant OR.
[b] None of the patients was treated due to neurodegenerative disease.

We performed a sensitivity analysis to account for the potential influence of the type of control. Depression, cardiovascular disease, and antidepressant use had higher ORs comparing cases to healthy controls only (table 3), with less striking differences for other sleep center controls.

DISCUSSION This large multicenter study confirms findings from chart reviews done in single centers on a putative association between iRBD and depression and antidepressant use.[2–6] Although we found that iRBD was slightly stronger associated with antidepressant use than with depression, which may be an early sign of neurodegeneration, our study cannot determine whether antidepressants were a proxy marker for depression, or whether antidepressants themselves provoked RBD, since some centers excluded individuals with any prior antidepressant medication from the iRBD group, and all centers excluded individuals with a clear temporal relationship between antidepressant usage and iRBD symptom onset. In favor of the hypothesis that antidepressants themselves can provoke RBD would be a recent 4.5-year follow-up study that investigated patients with iRBD with concomitant antidepressant use at time of diagnosis. The authors found that, although patients with antidepressant-associated RBD had a lower risk of neurodegeneration than patients with purely idiopathic RBD, neurodegenerative markers were still present.[8]

We found that patients with iRBD reported a 2-fold increased rate of ischemic heart disease. It is possible that some of this relationship was due to healthy volunteer bias, as the results were attenuated when compared with sleep center controls. However, sleep apnea in the control group may also underlie this subgroup difference, as it is a well-established cardiovascular risk factor. One might presume that the cardiovascular disease association would be related to the underlying cardiovascular risk profile. However, surprisingly, cardiovascular risk factors were not increased in the iRBD group. One potential explanation is that prodromal synucleinopathy may have altered preexisting cardiovascular risk factors at the time of the questionnaire, but not during earlier critical periods for the development of

Table 3 Sensitivity analysis of variables of interest according to control type

	iRBD (n = 318)	All controls (n = 318)	OR (95% CI)	Sleep disorder controls (n = 181)	OR (95% CI)	Healthy volunteers (n = 137)	OR (95% CI)	Controls except SA (n = 228)	OR (95% CI)
Depression	28.8%	17.5%	2.0[a] (1.3–2.9)	23.3%	1.4 (0.9–2.1)	9.9%	3.9[a] (2.1–7.4)	16.9%	2.1[a] (1.4–3.2)
Cardiovascular disease	20.4%	13.3%	1.6[a] (1.0–2.5)	16.0%	1.2 (0.7–2.0)	9.5%	2.4[a] (1.3–4.6)	11.0%	2.0[a] (1.2–3.3)
Arterial hypertension	36.2%	45.0%	0.7[a] (0.5–0.9)	43.8%	0.7[a] (0.5–1.0)	46.6%	0.7[a] (0.4–1.0)	45.2%	0.7[a] (0.5–0.9)
Antidepressants	17.3%	9.1%	2.2[a] (1.4–3.6)	10.5%	1.8[a] (1.0–3.2)	7.3%	3.0[a] (1.4–6.1)	9.2%	2.3[a] (1.3–3.9)
Corticosteroids	8.5%	3.5%	2.6[a] (1.3–5.4)	2.8%	3.2[a] (1.2–8.6)	4.4%	2.1 (0.8–5.2)	3.5%	2.6[a] (1.2–5.9)

Abbreviations: CI = confidence interval; iRBD = idiopathic REM sleep behavior disorder; OR = odds ratio; SA = sleep apnea.
[a] Significant OR.

atherosclerosis. Of note, the frequency of arterial hypertension was lower in patients with iRBD compared to controls, perhaps reflecting autonomic dysfunction, which is a common intrinsic feature of iRBD.[9] It is tempting to further speculate whether cardiac sympathetic denervation in iRBD[10] may have some additional influence on the occurrence of cardiovascular disease.

Usage of corticosteroids was more common in patients with iRBD than in controls. An association with autoimmune disease and iRBD as suggested by a prior case series[5] was not confirmed by the present data. Subanalysis of the type of preparation of corticosteroids revealed that this association was due to inhaled corticosteroids—a proxy marker for asthma or chronic obstructive pulmonary disease, likely reflecting the higher smoking rate in patients with iRBD.

This is the largest and only multicenter study of comorbidity and concomitant medication in iRBD. Potential limitations are the cross-sectional design, which does not allow for statements on causality, the fact that data were acquired from self-reported questionnaires, which may be subject to recall bias, and the exploratory nature of the study, as assessment of comorbidity and comedication were a subset of a broad risk factor analysis. Despite these limitations, due to the large sample size, we were able to confirm a close link between antidepressant use and depression with iRBD. In addition, we identified an unexpected association between iRBD and ischemic heart disease, which was not explained by typical cardiovascular risk factors.

AUTHOR CONTRIBUTIONS

B. Frauscher participated in the recruitment of subjects, analyzed and interpreted the data, and wrote the first draft of the manuscript. P. Jennum, Y.S. Ju, M. Terzaghi, B. Högl, G. Mayer, and R. Manni participated in the recruitment of subjects, analyzed and interpreted the data, and revised the manuscript. R.B. Postuma and J.Y. Montplaisir participated in the conception, design of the study, and recruitment of subjects, analyzed and interpreted the data, and revised the manuscript. I. Arnulf, V. Cochen De Cock, Y. Dauvilliers, M.L. Fantini, L. Ferini-Strambi, D. Gabelia, A. Iranzo, S. Leu-Semenescu, T. Mitterling, M. Miyamoto, T. Miyamoto, W. Oertel, A. Pelletier, P. Prunetti, M. Puligheddu, J. Santamaria, K. Sonka, M. Unger, C. Wolfson, and M. Zucconi participated in the recruitment of subjects for the study and revised the manuscript.

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DISCLOSURE

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