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Prevalence of REM sleep behavior disorder in multiple system atrophy: a multicenter study and meta-analysis

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Abstract

Objectivey—Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia frequently affecting patients with synucleinopathies but its exact prevalence in multiple system atrophy (MSA) is unclear. Whether questionnaires alone are sufficient to diagnose RBD is also unknown.

Methods—Cross-sectional study of patients with probable MSA from six academic centers in the US and Europe. RBD was ascertained clinically and with polysomnography; and meta-analysis according to PRISMA guidelines for studies published before September 2014 that reported the prevalence of RBD in MSA. A random-effects model was constructed using weighted prevalence proportions. Only articles in English were included. Studies were classified into those that ascertained the presence of RBD in MSA clinically and with polysomnography. Case reports or case series (≤5 patients) were not included.

Results—Forty-two patients completed questionnaires and underwent polysomnography. Of those, 32 (76.1%) had clinically-suspected RBD and 34 (81%) had polysomnography-confirmed RBD. Two patients reported no symptoms of RBD but had polysomnography-confirmed RBD.

The primary search strategy yielded 374 articles of which 12 met the inclusion criteria The summary prevalence of clinically suspected RBD was 73% (95% CI, 62%-84%) in a combined sample of 324 MSA patients. The summary prevalence of polysomnography-confirmed RBD was 88% (95% CI, 79%-94%) in a combined sample of 217 MSA patients.

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Interpretation—Polysomnography-confirmed RBD is present in up to 88% of patients with MSA. RBD was present in some patients that reported no symptoms. More than half of MSA patients report symptoms of RBD before the onset of motor deficits.

Keywords

α-synuclein; sleep disorders; parasomnias; polysomnography; parkinsonism

Introduction

Normal sleep is divided into periods with and without rapid eye movements (i.e., REM and non-REM sleep). During REM sleep, normally about 20% of total sleep time, skeletal muscle tone is lost (i.e., atonia) and subjects are immobile except for their eyes. Dreams usually occur during REM sleep.

The inhibition of muscle tone during REM sleep requires the activity of pontomedullary brainstem nuclei [9, 24]. Lesions affecting these neurons result in a peculiar parasomnia named REM sleep behavior disorder (RBD). RBD was first described in 1986 [31] in patients who were acting out their dreams. The behavior included moving their limbs, sleep talking, shouting, or screams. In extreme cases, patients hurt themselves and their spouses. Interestingly, if patients are waken-up by their bed partner they frequently describe a dream that explains their behavior.

RBD is often associated with synucleinopathies including Parkinson disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA); and in patients with these disorders frequently predates motor and cognitive deficits [23]. In postmortem studies of patients with RBD neurodegeneartion with abnormal deposition of α-synuclein affecting pontomedullary brainstem nuclei is the most frequent finding [3, 7].

Several studies have reported that RBD is frequent in patients with MSA [8, 10, 16, 22, 26, 27, 32, 33, 36, 37, 40, 41] but its exact prevalence and whether RBD affects all patients with MSA is not known. Moreover, whether questionnaires are sufficient to diagnose RBD or polisomnography showing abnormal muscle activation (i.e., lack of atonia) and vocalizations/motor behavior during REM is required for the diagnosis is unclear.

To answer these questions we investigated the prevalence of RBD in patients with MSA prospectively enrolled in a multicenter study of academic medical centers in the US and Europe. We also performed a systematic review and meta-analysis of published studies on the prevalence of RBD in MSA.

Methods

Prevalence study

Cross-sectional study including patients with probable MSA[18] evaluated at the New York University School of Medicine (New York, NY), Mayo Clinic (Rochester, MN), Vanderbilt Medical Center (Nashville, TN), University of Michigan (Ann Arbor, MI), Stanford University School of Medicine (Stanford, CA) and the University Clinic of Navarra

(Pamplona, Spain). Patients with both phenotypes (MSA-P and MSA-C) were included [18]. All patients underwent clinical and neurological evaluations by a board-certified neurologist. Institutional review boards at each participating site approved this study and written informed consent was obtained from all participants at enrolment.

RBD was ascertained *clinically*, using validated questionnaires for RBD [13, 28] and with *polysomnography*. Polysomnography was performed using dedicated inputs for electroencephalogram (EEG, according to the 10-20 system: Fp1, Fp2, F3, F4, F7, F8, C3, C4, P3, P4, T3, T4, T5, T6, O1, O2, common reference), tibial and chin EMG, electrooculogram, oronasal flow, respiratory effort, oxymetry, heart rate, body position, recording of sounds with microphone, and video recording. Sleep stages classification was performed following the current criteria [1]. RBD was diagnosed according to the Classification of Sleep Disorders [2] which requires detection of REM sleep without atonia and episodes of vocalization and/or motor behavior during REM sleep during polysomnography.

Systematic review and meta-analysis

This meta-analysis was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[25]. Articles on RBD and MSA were identified by searches of PubMed and EMBASE through September 1, 2014. Only articles in English were included. The following search strategy was used: (“Shy-Drager” AND sleep) OR (“multiple system atrophy” AND sleep) OR (“striatonigral degeneration” AND sleep) OR (“olivopontocerebellar” AND sleep) OR (MSA AND sleep) OR (“autonomic failure” AND sleep).

In addition, a manual search of bibliographies of included trials and related reviews was carried out for additional references. No unpublished data or data from abstracts were encountered or used. Articles were evaluated independently by two reviewers (J.A.P. and C.F.C.) who extracted the following data from each study: first author, year of publication, and prevalence of RBD in patients with definite, probable, or possible MSA according to the available criteria [17, 18, 29]. Studies were classified into those that ascertained the presence of RBD clinically (by means of questionnaires or history) and those that reported the prevalence of polysomnography-confirmed RBD. Case reports or case series (≤5 patients) were not included.

Statistical analysis

The primary outcome measure was frequency of RBD in MSA as reported in prevalence (%). The pooled prevalence of RBD and 95% confidence intervals were obtained by using a DerSimonian-Laird random-effects model with double arcsine transformation [11]. We ran a random-effect model rather than a fixed-effects model because of the high likelihood of heterogeneity between study variance. The heterogeneity of effect size estimates across studies was described with the I^2 index (with values of 25%, 50%, and 75% considered low, moderate, and high, respectively) and Q statistic's p value [19]. Analyses were performed with Stata 13 (College Station, TX).

Sensitivity analysis was performed using the leave-one-out approach. Publication bias was ascertained by funnel plot, with an asymmetrical plot suggesting possible publication bias. Egger's test was used to assess funnel plot asymmetry. $P < 0.05$ was considered as statistically significant.

Results

Prevalence of symptoms suggesting RBD

Sixty-four patients with MSA (23 MSA-P [35%], 41 MSA-C [65%]; 36 men, 28 women; aged 61.1±8 years; disease duration: 3.4±2 years; disease onset at 57.7±8.3 years) completed sleep questionnaires. Of these, 53 (83%) reported symptoms suggesting RBD. Twenty-nine (53.7%) reported symptoms of RBD before the onset of motor deficits. Symptoms of RBD were present in 82% of MSA-P and 83% of MSA-C patients (p=0.99).

Prevalence of polysomnography-confirmed RBD

Forty-two patients with MSA (14 MSA-P [34 %], 28 MSA-C [66%]; 23 men, 19 women; aged 62.2±7.8 years; disease duration: 3.3±1.8 years; disease onset at 57.1±8.2 years) completed questionnaires and underwent polysomnography. Of those, 32 (76.1%) had symptoms suggesting RBD and 34 (81%) had signs of RBD during the polysomnography. Signs of RBD were present in 86% (13/15) of MSA-P and 78% (21/27) of MSA-C patients (p=0.48) (**Supplementary Video 1**).

Six (14%) patients had no signs of RBD in the polysomnography, of which 5 had MSA-C and 1 had MSA-P. These subjects were not taking benzodiazepines or any other medications known to disrupt REM sleep. Disease duration in these 6 patients was 6.7±4.1 years.

Two patients (4.7%) had no REM sleep during the study so it was not possible to ascertain the presence of RBD. All patients reporting symptoms of RBD (except the 2 patients with no REM sleep) did have signs of RBD during the sleep study.

Two patients did not report symptoms of RBD but actually had polysomnography-confirmed RBD.

Meta-analysis results

As shown in **Figure 1**, the primary search strategy yielded 374 articles of which 12 met the inclusion criteria. Ten of this articles included prevalence on clinically suspected RBD and nine articles included prevalence on polysomnography-confirmed RBD (**Table 1**). Including the results of the present study, the summary prevalence of symptoms suggesting RBD in MSA was 73% (95% CI, 62%-84%) in a pooled sample of 324 subjects (**Figure 2A**). Between-study heterogeneity was high (80%; p<0.001). The summary prevalence of polysomnography-confirmed RBD in MSA was 88% (95%, CI 79%-94%) in a pooled sample of 217 subjects (**Figure 2B**). Between-study heterogeneity was moderate (65%; p<0.001).

Sensitivity analysis showed unchanged results. There was no evidence of publication bias as the funnel plot was symmetrical and Egger's test was not significant (**Supplementary figure 1**).

Discussion

Our multicenter study confirms that RBD, as ascertained by polysomnography, is present in the vast majority of MSA patients (81%). The results of the meta-analysis, in which the prevalence of polysomnography-confirmed RBD in a sample of 225 subjects with MSA was 88%, is in keeping with the findings of our multicenter study.

The prevalence of clinically suspected RBD in MSA was lower (83% and 76.1% in the multicenter study and 73% in the meta-analysis) than the polysomnography-confirmed RBD. Conversely, patient-reported symptoms suggesting RBD accurately predicted the presence of RBD in polysomnography. Our results highlight that, although clinical recognition accurately diagnoses RBD in the majority of MSA patients, polysomnography is needed to diagnose RBD in some patients who do not report symptoms.

The pathways and nuclei involved in the pathophysiology of RBD are shown in **Figure 3**. Pontomedullary structures -including the magnocellular reticular formation (MCRF), sublaterodorsal (SLD), and pedunculopontine and laterodorsal (PPN/LDT) nuclei- are responsible for the atonia (i.e., lack of movement) during REM sleep [9]. The SLD has been identified in animals; the analog structure in humans is though to be the subcoeruleus (SC) nucleus. Lesions in SLD/SC and MCRF (even unilaterally) are thought to eliminate atonia during REM sleep, leading to dream enacting behavior [20, 24, 35, 42]. Whether depletion of locus coeruleus (LC) neurons contributes to RBD is uncertain [12].

Autopsy studies in MSA patients have shown depletion of cholinergic neurons in the PPN/LDN complex [6, 32]. The PPN may have, however, a modulatory role in REM-related phenomena rather than a primary role for the atonia during REM sleep [4, 24]. Also in MSA, neurons of the PAG [5] and the LC are depleted [6], although their specific role in RBD is unclear. In contrast to PD [15], depletion of SC neurons has not been investigated in MSA.

The absence of RBD in some patients with MSA is intriguing. Of note, the prevalence of polysomnography-confirmed RBD tended to be lower in MSA-C than in MSA-P (78% vs. 86%; p=0.49), and 4 of our 5 MSA patients with no RBD had MSA-C. However, the distribution of parkinsonian and cerebellar phenotypes in our sample was unusual as there were more MSA-C than P patients [30]. However, these patients also had longer disease duration, which suggests that RBD disappears as disease progresses, indicating degeneration of brainstem nuclei that control REM sleep as has been suggested previously[39]. Conversely, the absence of RBD in some MSA patients may be indicative of worsening rigidity [38]. Additional longitudinal studies are needed to answer this.

In our study, 54% of patients with MSA reported symptoms of RBD before the onset of motor deficits. This is in keeping with recent studies indicating that RBD represents a prodromal phase of PD, DLB and MSA [21, 23]. Further studies should determine whether

the presence or absence of autonomic dysfunction in patients with idiopathic RBD predicts the development of a specific neurodegenerative disease.

In conclusion, RBD is present in up to 88% of patients with MSA, including some patients recalling no symptoms. The prevalence of RBD in MSA is significantly higher than the percentage reported in patients with PD (50-60%) [14, 34]. Our findings argue for the inclusion of RBD as a supportive feature for MSA in forthcoming consensus criteria.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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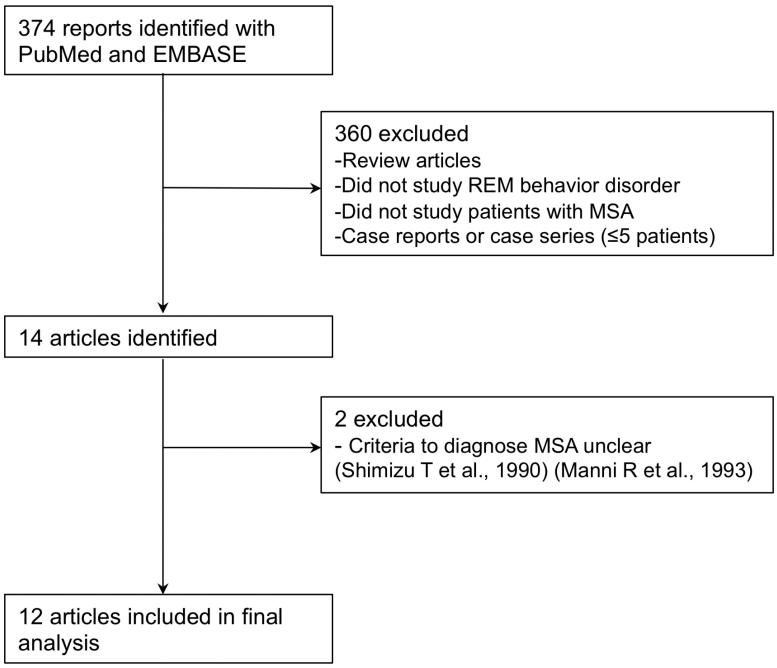

Figure 1.

Flow diagram of literature search to identify studies reporting the prevalence of REM sleep behavior disorder in MSA.

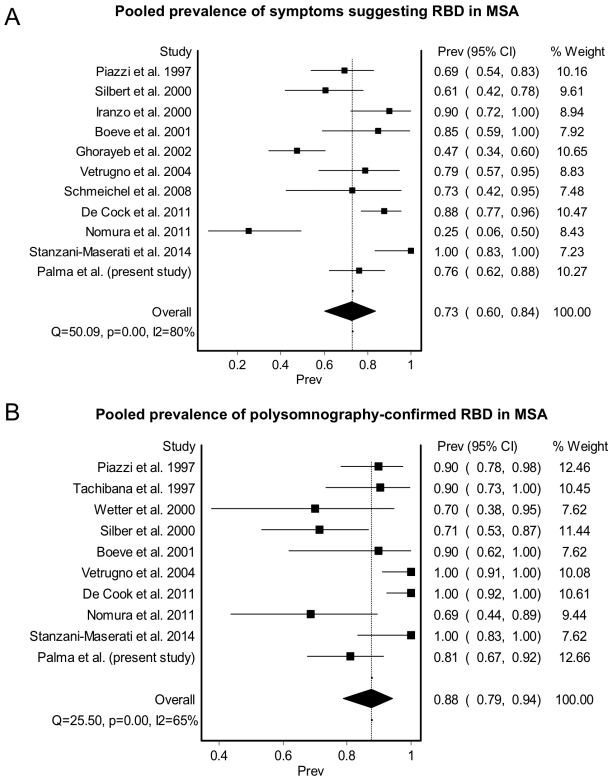

Figure 2.

Meta-analysis results on the pooled prevalence of REM sleep behavior disorders in MSA according to symptoms (A) and polysomnography (B).

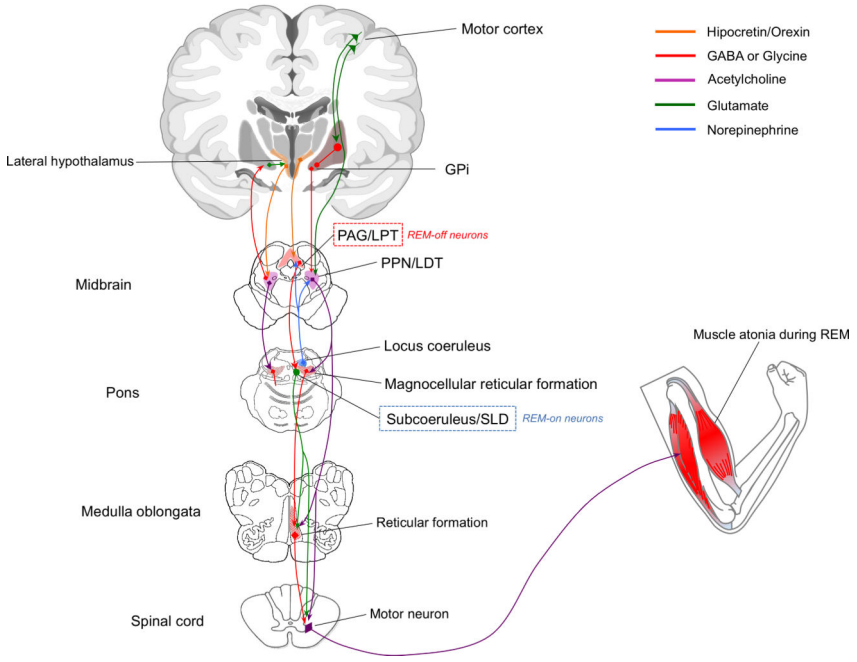

Figure 3.

Pathways and nuclei involved in the pathophysiology of REM sleep behavior disorder. The PAG/LPT contains *REM-off* neurons (i.e., suppressors of REM sleep). The LC activates *REM-off* neurons in the PAG/LPT, thus suppressing REM sleep. The SC/SLD contains *REM-on* neurons (i.e., promoters of REM sleep) The SLD (or SC in humans) projects to spinal chord and likely represents the final common pathway that causes inhibition of skeletal muscle activity during REM sleep. The indirect route, denoted by the line from SLD/SC to the reticular formation to the spinal chord, probably also contributes to atonia. In humans, it is not yet known whether lesions in structures projecting to and from the magnocellular reticular formation, and lesioning the MCRF itself, affect atonia during REM sleep. GPi = globus pallidus internus, LC = locus coeruleus, LDT = laterodorsal tegmental nucleus, LPT = lateral pontine tegmentum, MCRF = magnocellular reticular formation, PAG = periaqueductal grey matter, PPN = pedunculopontine nucleus, REM = rapid eye movement, SC=subcoeruleus nucleus, SLD = sublaterodorsal nucleus.

Table 1

Studies reporting the prevalence of REM sleep behavior disorder in patients with MSA.

			Clinically suspected RBD		Polysomnography-confirmed RBD	
Authors	**Year**	**Country**	**No of subjects studied**	**% with RBD**	**No of subjects studied**	**% with RBD**
Stanzani-Maserati et al.[36]	2014	Italy	10	100%	10	100%
Nomura et al.[26]	2011	Japan	16	25%	16	68.8%
De Cock et al.[10]	2011	France	49	91% (MSA-C) 84% (MSA-P)	22	100%
Schmeichel et al.[32]	2008	USA	11	72%	-	-
Vetrugno et al.[40]	2004	Italy	19	79%	19	100%
Ghorayeb et al.[16]	2002	France	57	47.5%	-	-
Boeve et al. [8]	2001	USA	13	84%	10	90%
Iranzo et al.[22]	2000	Spain	20	90%	-	-
Silber et al.[33]	2000	USA	28	60%	28	71%
Wetter et al.[41]	2000	Germany	-	-	10	70%
Tachibana et al. [37]	1997	Japan	-	-	21	90.5%
Piazzi et al.[27]	1997	Italy	39	69%	39	90%

RBD: REM sleep behavior disorder. MSA: Multiple system atrophy.