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Rapid eye movement sleep behavior disorder in adults younger than 50 years of age

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ABSTRACT

Rapid eye movement (REM) sleep behavior disorder (RBD) occurring prior to age 50 is termed early-onset RBD. Early-onset RBD comprises a substantial minority of cases, and demonstrates the differences in demographics, comorbidities, and clinical considerations from previously described typical RBD with onset >50 years. The world literature on RBD is reviewed with specific focus on features that distinguish early-onset RBD, including more gender parity, increased proportion of idiopathic cases, increased proportion of cases associated with narcolepsy, parasomnia overlap disorder, antidepressants, and possibly autoimmune disorders, and clinical presentation.

1. Introduction

Rapid eye movement sleep behavior disorder (RBD) has previously been described as a disorder predominantly of older men, with men comprising 80–89% of cases [1–6]. Several groups have convincingly demonstrated a strong association between RBD and neurodegenerative disease in the α-synucleinopathy group, and that even in its idiopathic form, in middle-aged and older adults RBD appears to indicate a preclinical stage of neurodegenerative disease [3,5,7]. Subsequently, intense clinical interest and research has focused on RBD. In recent studies, early-onset RBD, as defined as RBD beginning prior to 50 years of age, has been distinguished from "late-onset" or typical RBD, and comprises a sizable (~40%) proportion of reported cases (Table 1) [8–10]. While early-onset RBD is not a separate nosologic entity, demographic and clinical characteristics of RBD in younger adults differ in some important ways from previous descriptions of RBD. This review summarizes demographic characteristics, associated comorbidities, and clinical features of early-onset RBD, with particular attention to differences from late-onset RBD.

2. Gender parity

Early-onset RBD is characterized by relative gender parity compared to what had previously been reported for typical RBD. Table 1 summarizes the gender data in published series. In contrast to a marked male predominance of 80–89% in six prior large case series [1–6], the three most recent studies drawn from sleep center populations reported 55–59% of early-onset RBD cases were in men [8–10]. In this series, even when including all cases regardless of age, the proportion of men was 65–75%. In an additional series, which did not analyze early-onset cases separately, reported a similarly modest male predominance of 64% [11]. The authors attributed this to the different ethnicity of the background population; however, this figure is in line with other recent studies. Furthermore, in a study which recruited from a young (mean 42.4 years) outpatient psychiatry clinic population, 56.7% of patients having a RBD-like disorder by clinical criteria (but not confirmed by video polysomnogram (vPSG)) were female [12]. The female predominance in this study partially reflects the underlying study population, which was 68.1% female; however, this is nevertheless quite remarkable compared to the high male predominance that would be expected for typical RBD. Furthermore, some of the increased proportion of women in early-onset RBD may be due to higher rates of antidepressant usage in women (see section below). Overall, despite variation in recruitment populations, there is a clear trend toward an increasing proportion of RBD being recognized in women, particularly in early-onset RBD, in which there is near gender parity (women 41–44%).

3. Increased proportion of idiopathic RBD

A notable feature of early-onset RBD is the relatively high proportion of cases which are idiopathic, meaning they are not secondary to neurodegenerative disease, narcolepsy, or any other identifiable cause. In earlier reports, idiopathic RBD comprised 13–41% of cases [1,2,13]. The majority of RBD cases were associated with neurodegenerative disease, either occurring at the same time as, or developing after, RBD symptoms. Thus far, the proportion of early-onset RBD cases associated with neurodegenerative disease is minimal: 2.6% and 8.9% in the two case series, which

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Table 1
Summary of case series of RBD.

Author/year	*N*	Age (SD)[a]	% <50 years[a]	% Male	% With neurodegenerative disease	% With narcolepsy	% With antidepressant medication	% Idiopathic
Schenck 1993 [1]	96	52.4 (16.9)	N/A	87.5	22.9	13.5	1.0	41.7
Sforza 1997 [13]	52	Idiopathic 66.2 (2.1)[a] secondary 59.9 (1.2)[a]	N/A	N/A	73.1[b]	N/A	N/A	13
Olson 2000 [2]	93	60.9 (36–84)	N/A	87	56.6[b,c]	4.8[c]	15.1	36.1[c]
Iranzo 2006 [3]	44	62.6 (7.3)	N/A	89	All idiopathic by study inclusion criteria. 45.5% developed neurodegenerative disease; all had late-onset RBD.			
Okura 2007 [4]	67	61.4 (8.8)	N/A	85.1	17.9[d]	N/A	N/A	N/A[d]
Wing 2008 [6]	82	62.1 (12.9)	N/A	82	19.5	1	33[e]	
Lam 2008 [12]	30[f]	40.2 (9.7)	N/A	43.3[f]	0[f]	N/A	86.7[f]	N/A
Postuma 2009 [5]	93	65.4 (9.3)[a]	N/A	80.6	All idiopathic by study inclusion criteria. 28.0% developed neurodegenerative disease.			
Bonakis 2009 [8]	91	52.2 (19)[a]	42.9[a]	68	17.6	17.6	4.4	58.2
Early-onset	39			59.0	2.6	38.5	7.7	51.3
Late-onset	52			75	28.8	1.9	1.9	63.5
Teman 2009 [9]	48		41.7	75	All idiopathic by study inclusion criteria.			
Early-onset	20	34.1 (11.5)[a]		55.0			80.0	
Late-onset	28	69.9 (5.7)[a]		89.3			46.4	
Lin 2009 [11]	70	60 (N/A)	N/A	64.3	54.2	4.2	5.7[g]	65.7
Ju 2011 [10]	115	53.7 (16.4)[a]	39.1[a]	65.2				
Early-onset	45			55.6	8.9[b]	11.1	57.8	75.6, 40[h]
Late-onset	70			71.4	38.6[b]	8.6	38.6	50, 31.4[h]

All case series of RBD are summarized, in order of year of publication. When available, data for early-onset and late-onset cases are separately listed below the aggregate data for the study. N/A = not available in publication. All numbers in brackets indicate reference numbers.

[a] Age of onset of symptoms is shown if reported, otherwise age at diagnosis was reported and is marked with superscript a in the table. Some studies report age of diagnosis rather than age of reported onset; since diagnosis lags behind symptom onset by 4–11 years [2,3,8], there may be some blurring between groups for individuals around age 50).

[b] Includes cases where RBD symptoms preceded neurodegenerative disease. For this table ALS was not counted as a neurodegenerative disease.

[c] Denominator is the 83 patients who underwent neurological exam.

[d] Neurological evaluation was not systematically performed in this series.

[e] This figure is for lifetime psychiatric disease, rather than antidepressant medication exposure.

[f] This series recruited from an outpatient psychiatric clinic where the majority of patients were female. RBD was not polysomnographically confirmed, therefore table displays reported data on those with "RBD-like disorder."

[g] RBD was reported to be medication-related, but did not specify whether they were antidepressant medications.

[h] First number considers individuals taking antidepressants as idiopathic RBD, and the second number excludes those taking antidepressants.

reported data separated by age [8,10]. Consequently, a higher proportion of early-onset RBD cases had idiopathic RBD in these studies, 51% and 76%. Inversely, in a study of idiopathic RBD, only 58 idiopathic RBD cases were identified out of 529 cases of RBD (~11%), and the idiopathic cases were fairly young, with 42% being early-onset cases [9]. Since neurodegenerative diseases increase in incidence with age, it is possible that some of the "idiopathic" RBD cases reported recently may develop a neurodegenerative disease in the future, especially since some RBD patients may not develop a neurodegenerative disease until decades later [14]. For the time being, however, it appears early-onset RBD is rarely associated with neurodegenerative disease at the time of diagnosis, and the majority of cases are idiopathic.

4. Narcolepsy

Narcolepsy is the most common cause of secondary RBD in early-onset RBD. Several early investigators described excessive phasic activity during REM sleep or REM sleep without atonia (RWA) in both untreated narcolepsy and in association with antidepressant treatment for narcolepsy with cataplexy [15–17]. The first systematic study of narcolepsy-associated RBD in 1992 examined 17 patients with narcolepsy and RWA, of whom 10 met the clinical criteria for RBD. This group of narcolepsy-RBD patients was very young compared to prior reports, with mean age at onset of RBD symptoms of 28.4 years; all but three were early-onset. Those with RWA, but without clinical features fulfilling RBD criteria, were also young, mean 33.8 years, and all but one being under 50 years of age [18]. Based on the age discrepancy compared to prior reports of RBD, and the coincidence of RBD and other narcolepsy symptom onset, the authors proposed that RBD is another manifestation of REM sleep dyscontrol in narcolepsy. This link between narcolepsy and RBD, particularly in the young, has been borne out in subsequent studies. A large survey of narcoleptic patients revealed a high rate of RBD, 38%, and in those with cataplexy, 60% [19]. Again, in this study, individuals with RBD and narcolepsy were younger than the typical RBD population, with mean age 41 years. Only l3 of 55 patients had vPSG, of whom five had definite RBD symptoms, yet notably, all 13 had REM sleep without atonia. While the survey format introduced volunteer and recall bias, and only a small proportion of RBD cases had vPSG confirmation, this study provides additional data to support an association between narcolepsy and early-onset RBD. Another study of 34 patients with narcolepsy with cataplexy found that 17 (50%) had RBD, with 13 of 17 being under age 50; however, age distribution was not different from those without RBD. Again in this study, patients with narcolepsy with cataplexy, regardless of nocturnal behaviors of RBD, had increased tone during REM sleep as assessed by systematic quantification [20]. In recent large series of RBD, when etiologies of RBD were examined separately for early-onset RBD, narcolepsy was present in 38.4% of early-onset RBD in one series [8], and 11.1% in another [10]. Narcolepsy associated with RBD does not necessarily have to be narcolepsy with cataplexy, in the former study, half of the individuals with narcolepsy and RBD did not have cataplexy. In fact, narcolepsy may present with abnormal nocturnal behaviors rather than hypersomnia or cataplexy, as reported in two cases of early-onset RBD [21].

Clinically, the nocturnal behaviors in RBD associated with narcolepsy may be different. In a study of 37 participants with narcolepsy and RBD, of whom the majority (62%) were early-onset RBD, there was no predilection for abnormal behaviors to occur in the first or second half of the night [22]. This is in contrast to typical