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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.

Keywords

REM sleep behavior disorder (RBD); Narcolepsy; Antidepressant; Parasomnia; Parasomnia overlap disorder (POD); Autoimmune

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

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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 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 RBD, in which behaviors tend to occur in the second half of the night, when REM sleep constitutes a greater percentage of sleep time. Therefore, in a young person presenting with abnormal behaviors during sleep, the timing of behaviors may not be a reliable clue as to whether they are occurring during REM or non-REM (NREM) sleep, making vPSG even more essential for an accurate diagnosis. Moreover, even in individuals with narcolepsy, but without clinical features of RBD, vPSG revealed increased phasic motor activity similar to narcoleptics with RBD [23]. Due to limited sampling in this study, it is unknown whether individuals with RBD associated with narcolepsy have a significant difference in the type or severity of movements. However, given the high prevalence of other nocturnal behaviors such as, sleep-related eating disorder (SRED) and other compulsive behaviors [24] in narcolepsy, vPSG is crucial during the evaluation of abnormal behaviors during sleep in young people.

The pathophysiological basis by which narcolepsy is closely linked to RBD has not been conclusively demonstrated. Part of the association is likely due to treatment of cataplexy with antidepressant medications (see section below). However, even in drugnaïve narcoleptic patients, RBD and RWA are common [18,23]. There are no known structural lesions in narcolepsy, which affect pontine regions that maintain REM sleep atonia. Rather, narcolepsy results from a low or absent level of orexin (hypocretin) [25,26]. A recent review proposes a model whereby in narcolepsy, there is reduced excitatory orexinergic input to the sublaterodorsal tegmental nucleus, which in turn, would usually send inhibitory input to spinal motoneurons; therefore, resulting in excessive phasic activity during REM sleep but with maintained REM sleep atonia [27]. Notably, orexin neurons are decreased in α-synucleinopathies [28,29]. However it is yet unknown whether there is a common pathophysiological mechanism underlying RBD associated with narcolepsy and RBD associated with α-synucleinopathy.

5. Parasomnia overlap disorder

Individuals with early-onset RBD also tend to have more complex parasomnias with both REM and NREM sleep parasomnias, or what is termed parasomnia overlap disorder (POD). In the first series of POD, Schenck and colleagues described 33 individuals with abnormal nocturnal behaviors and vPSG findings fulfilling criteria for both RBD and NREM sleep

parasomnia [30]. These comprised 21% of all RBD cases seen at this center during the recruitment period. The mean age was very young for RBD, 33.8 years. Moreover, those with idiopathic POD were even younger, with mean age 30.6 years. Age of onset of abnormal nocturnal behaviors is very young in POD, often in childhood. In this series, parasomnias began at age 14.6 years on average and age 8.8 years in the idiopathic cases. The authors noted three clusters of parasomnia onset age: childhood (~5 years), adolescence (~15 years), and middle-aged adults. A male preponderance in all age groups, 69.7% overall and 68.2% in the idiopathic cases, was consistent with injurious nocturnal behaviors in general [31].

Subsequent studies have confirmed the considerable prevalence of POD among RBD patients, particularly in early-onset RBD. In an early series of RBD, 11% had sleep walking or wandering, which is more typical for NREM sleep parasomnia, in addition to the behaviors typical for RBD (during which patients usually remain in the bed, or at most awaken when they fall out of bed) [2]. Of the subset of 74 specifically assessed for NREM sleep parasomnia, 7% reported past history of parasomnia; the overlap with the 11% who had current sleep walking or wandering is unknown. In a recent series of RBD, 15.7% had been wandering both inside and outside the bedroom; however, the proportion of cases that were early-onset was not reported [11]. A study that specifically analyzed early versus late onset RBD reported 33% of early-onset RBD patients had two types of events, consistent with POD. One was typical for RBD, during which patients could be easily awakened and had clear recall of dream enactment. The other was typical for NREM sleep parasomnia, during which patients had sleep-talking or sleepwalking, could not be easily aroused, and of which they had poor recollection [8]. Additional unusual case reports of POD, including a 37 year old man with RBD, sleepwalking, and sexsomnia [32], and two Parkinson disease-related RBD patients (age 28 and 37) with SRED [33], suggest some subtypes of POD may occur more frequently in early-onset RBD than others. Idiopathic POD and POD variants—including SRED, sexsomnia, rhythmic movement disorder, status dissociatus, or those symptomatic of central nervous system lesions, were recently reviewed, along with an additional discussion of cumulative literature on POD and RBD in younger adults [34]. Due to the limited number of reported cases thus far, further study is necessary to determine whether age affects the variant of POD that may manifest in an individual.

Polysomnographic data can distinguish between RBD and NREM sleep parasomnias, and also provide clues to the pathophysiology of POD. In the first series of POD, the investigators noted that NREM sleep parasomnias were associated with autonomic activation, whereas, RBD episodes were not [35]. In the study which specifically addressed early-onset RBD, EEG analysis demonstrated frequent arousals, as are seen in NREM sleep parasomnias, in 31% of early-onset RBD patients [8]. Another detailed EEG analysis was performed in a study of idiopathic RBD, specifically examining the cyclic alternating pattern (CAP). While CAP is not part of official sleep staging or scoring, it is a robust measure of arousal and sleep state instability. The A1 pattern in particular is associated with NREM sleep parasomnias, whereas the A2 and A3 patterns strongly correlate with EEG arousals [35]. In a study comparing 31 idiopathic RBD patients to controls, there was increased A2 and A3 pattern in RBD, again, demonstrating increased arousal frequency in RBD. A1 was decreased, however, it was noted that A1 was negatively correlated with age [36]. The study population for this study was mostly late-onset RBD, with mean age 60 years and an age range of 40–80 years. However, even with this limited range of ages, the negative correlation of A1 with age suggests that in younger individuals with early-onset RBD, there may be relatively increased A1, corresponding to the increased prevalence of NREM sleep parasomnias. Long term follow up studies of POD are lacking; therefore, it is unknown whether individuals with POD change over time in terms of the proportion of REM sleep or NREM sleep behaviors. Further investigation including detailed EEG analysis will be

required to ascertain the distinct pathophysiological mechanisms underlying RBD occurring as part of POD, and how age may interact with specific arousal patterns to produce distinct clinical phenotypes.

6. Depression and antidepressants

Antidepressants have a strong association with RBD, and this association appears more pronounced in early-onset cases. Even prior to RBD's initial description [37], investigators had noted that treatment of cataplexy in narcolepsy using antidepressants sometimes induced excessive motor activity during REM sleep [15,17]. An early report in 1992 described the case of a 31 year old man who developed RBD shortly following commencement of fluoxetine. Despite discontinuation of this medication, RBD was documented by vPSG 19 months afterward, and the patient still had disruptive and violent behaviors 27 months later [38]. Since then, antidepressants in the tricyclic antidepressant (TCA) and selective serotonin reuptake inhibitor (SSRI) classes have been implicated in medication-induced RBD, particularly in early-onset RBD. In two recent series which provided data separately for early-onset RBD, antidepressant usage was more prevalent in the early-onset compared to late-onset cases: 80% compared to 46% [9], and 57.8% compared to 38% [10]. Since a greater proportion of antidepressant-related cases were in women, some of the gender parity in early-onset RBD may be mediated by antidepressant usage. The majority of antidepressants were SSRI's in these two studies. In a large study of 1235 subjects recruited from an outpatient psychiatric population, sleep-related injury and RBD-like disorder (not all vPSG confirmed), were highly prevalent. Lifetime prevalence for RBD-like disorder was 5.8%, and the 1-year prevalence was 3.8% [12], which was substantially higher than reported rates of RBD symptoms in the local population [39]. Among individuals taking SSRI, RBD-like disorder was present in 5%, and further analysis demonstrated that usage of SSRI and antidepressants as a whole was significantly increased among patients with reported parasomnias. Other classes of neuropsychiatric medications such as benzodiazepines, non-benzodiazepine benzodiazepine receptor agonists, antipsychotics, and mood stabilizers were not associated with parasomnias [12]. Furthermore, RBD associated with antidepressants does not necessarily resolve the removal of the potentially causal medication. In a study following 15 individuals with antidepressant associated RBD (most were early-onset), about half of whom were changed to treatment with bupropion (which is not known to be associated with RBD or RWA), while subjective frequency and severity of nocturnal behaviors improved over a mean follow-up of 13 months, the degree of RWA as assessed by vPSG did not improve, and in fact, increased [40]. Overall, past or present antidepressant usage is strongly associated with RBD/RWA, and a key question to be addressed in future studies is whether there is a causal mechanism or simply an association.

While there is an association between RBD and antidepressant usage, which is stronger in the early-onset group, this does not necessarily mean that younger individuals are more vulnerable to antidepressant-associated RBD. However, in the study described above which was recruited from a psychiatric population, the mean age of those with RBD-like disorders was young at 40 years. The background population was also young at 42.4 years [12]. Similarly, in a review of patients taking fluoxetine or TCA at a sleep center, RWA (but not frank RBD) was identified in six of 41 (14.6%) patients taking fluoxetine, and 2 of 52 (3.8%) of patients taking TCA, who had mean ages of 36.7 and 34.5 years, respectively. However, the mean age of all patients taking these medications was also quite young, 39.1 and 45.4 years, respectively [38]. The best available data are from a matched control study, which examined the relationship between antidepressants and RWA [41]. In this study, 15 individuals taking SSRI were compared with matched controls. Note that this study excluded anyone with report of any abnormal behavior during sleep, and therefore, this study examined RWA rather than RBD. The study population was relatively younger,

average 45.5 years for the SSRI group and 42.0 years for the control group, and 10 of 15 in each group were under 50 years old. Of the 10 individuals under age 50 in the SSRI group, 60% had RWA, while four of five (80%) of those above age 50 had RWA. Quantification of RWA through several different measures demonstrated that, within the SSRI group, there was a significant linear correlation between age and EMG tone, such that, there was increased RWA with increasing age. Therefore, it does not appear that younger individuals are particularly vulnerable to RWA (and therefore RBD) secondary to antidepressants, and in fact the opposite seems to be the case. The greater relative prevalence of antidepressant-associated RBD in early-onset RBD may be explained by several factors. One is the relative lack of neurodegenerative disease-related secondary RBD among young adults. Another is the young age at which affective and anxiety disorders tend to present, and therefore, the fairly young age of exposure to antidepressant medication. Lastly, since RWA and RBD related to antidepressants may persist after withdrawal of the causative medication, it is possible that some cases categorized as late-onset RBD (idiopathic or secondary) actually stem from a medication taken years earlier, but manifesting with disruptive behaviors later in life.

There is the possibility that depression or psychiatric disease itself may increase risk of RBD. Life-threatening, highly stressful situations have been reported to trigger RBD-type symptoms. In one study of 11 such individuals, four (two sea disaster survivors, one holocaust survivor, and one post-combat) had excessive motor activity during REM sleep [42]. A study at a Veteran's Administration hospital found that 56% of patients with RBD also had posttraumatic stress disorder [43]. There are no systematic studies assessing RBD prevalence in untreated depression. Teman et al. used multivariate logistic regression to determine odds ratio of RBD, using past psychiatric diagnosis, present psychiatric diagnosis, and antidepressant usage as predictor variables, adjusted for age. This showed that in early-onset RBD, prior psychiatric diagnosis, present psychiatric diagnosis, and antidepressants were each statistically significant predictors of RBD, while in late-onset RBD, only past psychiatric diagnosis was [9]. This suggests that psychiatric disease may confer a separate risk for RBD apart from that mediated by antidepressants. However, this post-hoc analysis was limited due to the small sample size (20 early-onset RBD cases) and lack of testing for interactions in the logistic regression model. Another study compared 31 individuals with psychiatric disorder-related RBD with matched psychiatric controls, as well as a group with idiopathic RBD [44]. This study found that patients with psychiatric disorder-related RBD had more nightmares and higher scores on depression and anxiety scales, suggesting that psychiatric symptoms confer additional risk for RBD, independent of antidepressant usage. The same investigators have proposed that altered dream content with heightened emotion that occur in psychiatric diseases may contribute to RBD behaviors [12,40]. Since most individuals with psychiatric disease are treated with antidepressant medications at least once, very large and likely multi-center studies will be required to tease apart the potential contributions of psychiatric disease and antidepressants to RBD risk.

A common and clinically relevant question, particularly in early-onset RBD, is whether antidepressant-associated RBD poses the same increased risk of future neurodegenerative disease as idiopathic RBD. This has not been studied in a well-controlled manner, primarily because insufficient time has passed for most reported cases of early-onset RBD to have reached an age when neurodegenerative diseases become symptomatic. Clearly, only a small proportion of individuals who take antidepressants have RBD; in the largest study, only 5% of patients taking SSRI had RBD-like disorder [40]. This suggests that this subset of individuals has a certain vulnerability, and possibly, that antidepressants unmask or hasten latent RWA or RBD. In a cohort of typical RBD (mean age 60.0 at symptom onset, with percent of early-onset cases not reported), a significantly higher proportion of the subset with psychiatric disease developed a neurodegenerative disease over mean 5.6 years, with an

adjusted hazard ratio of 7.0 compared to RBD patients without psychiatric disease [45]. Comparable data are unavailable for early-onset RBD, or for antidepressant exposure per se. Since the introduction of fluoxetine in 1988, SSRI and other antidepressants have become widely utilized medications: usage has increased four-fold, and 10.8% of Americans over age 12 are currently taking an antidepressant [46]. The parallel increase in antidepressant-associated RBD in the world literature (Table 1) is striking. Moreover, since the effects of antidepressants on REM sleep appear to last beyond the period of treatment, it is possible that some cases currently categorized as idiopathic or secondary to another cause are actually due to prior antidepressant exposure. A detailed history of lifetime psychotropic medication exposure should be elicited in the clinical evaluation of RBD. Careful longitudinal investigation in the next decade, when many early-onset RBD patients will enter middle age, will be able to answer whether antidepressant-associated RBD increases risk of neurodegenerative disease.

7. Inflammatory and autoimmune conditions

In addition to the more common conditions associated with RBD discussed above, isolated case reports and small studies suggest that inflammatory or autoimmune mechanisms may cause or be associated with RBD, particularly in younger adults. Some cases are due to an autoimmune or inflammatory structural lesion in the pons, presumably due to direct injury to regions mediating REM sleep atonia. The most frequent cause of such a lesion is multiple sclerosis, an autoimmune disorder that leads to central system demyelination. Two cases have been reported, a 51 year old woman [47] and a 25 year old woman [48]; in the latter case, RBD initially presented in “idiopathic” form, and clinical course and further evaluation determined multiple sclerosis as the underlying etiology. In a larger systematic study of sleep disorders occurring in multiple sclerosis, four out of 135 multiple sclerosis patients endorsed typical clinical symptoms of RBD. Three of the four who had PSG confirmation all had early-onset RBD [49]. Additional cases of inflammatory brainstem lesions causing RBD include a 40 year old woman with POD [50] and a 30 year old man with RBD and narcolepsy with normal orexin levels [51].

RBD can occur in the context of inflammatory or autoimmune syndromes in the central nervous system without a structural brainstem lesion. The most frequently reported cause is voltage-gated potassium channel (VGKC) antibody associated autoimmunity. VGKC antibody autoimmunity associated autoimmunity may manifest in a more central syndrome of limbic encephalitis, or as Morvan syndrome, a predominantly peripheral nervous system disorder which additionally variably demonstrates central nervous system symptoms. In one series of VGKC-antibody associated limbic encephalitis, five of six patients had RBD [52], and in another, 8 of 15 patients with Morvan syndrome had symptoms of RBD [53]. Due to severe insomnia and derangement of sleep architecture typical for VGKC antibody associated disorder, REM sleep could not be recorded in the majority, and therefore, RBD could not be confirmed. Dream enactment resolved in three of four patients treated with immunotherapy, although follow up vPSG data are not available to assess whether RWA also resolved. Additional cases of autoimmune or inflammatory encephalitis causing RBD include anti-Ma2 paraneoplastic syndrome [54] and one case of aseptic limbic encephalitis of unknown etiology [55]. All of these cases, except the last, were in individuals over age 50, reflecting the demographics of these specific types of usually paraneoplastic encephalites. An autoimmune disorder that occurs with more frequency in young adults is Guillain–Barre syndrome (GBS), a postinfectious autoimmune disorder affecting predominatly motor nerves, but also causing variable central nervous symptoms. Cochen et al. reported frequent REM sleep dyscontrol symptoms such as, REM-onset sleep, hypnogonic hallucinations, REM sleep without atonia, waking hallucinations described as “ nightmares,” and highly fragmented sleep in GBS. A case of a 42 year old woman who

had frank RBD as part of GBS was reported as part of this study [56]. The accumulation of these cases and small series of RBD associated with autoimmune causes suggests that there may be more cases that have not been diagnosed due to RBD not being a well-described manifestation of such disorders.

Additional data suggest a potential autoimmune mechanism in at least a subset of RBD cases. In a recent series, 35% of women with early-onset RBD had an autoimmune disorder [10]. Since the presence of one autoimmune disorder often signifies another, this suggests that RBD may be due to an autoimmune mechanism. In a study of 25 RBD patients, human leukocyte antigen (HLA) class II antigen typing showed an association with the DQw1 (DQB1*05 and DQB1*06) allele, significantly higher than in community matched controls [57]. This finding was not replicated in a study of patients with RBD secondary to Parkinson's disease [58], possibly indicating that an autoimmune or inflammatory etiology may be more contributory in " idiopathic" RBD. Another study examining serum antibodies against the locus coeruleus and did not identify these in RBD or controls [59]. Of course, there is considerable evidence to support narcolepsy is an autoimmune disorder, including post infectious disease presentation and associations with specific T-cell receptor polymorphisms and HLA type DQB1*0602 [60]. As described above, RBD is frequently comorbid with narcolepsy, especially early-onset RBD, further suggesting that some cases of RBD may be due to autoimmune mechanisms disrupting REM sleep atonia directly or indirectly through decreased orexin levels. In summary, several lines of evidence suggest that autoimmune and inflammatory pathological mechanisms may produce RBD, however, no pathogenic antibody or definitive causal mechanism has been identified.

8. Clinical features of early-onset RBD

Early-onset RBD may present and respond to medications differently from typical late-onset RBD; disparities may be due to differential causes of secondary RBD and relative gender parity. In the Bonakis et al. series which focused on early-onset RBD, all patients had abnormal behavior with vivid and violent content, which worsened with alcohol intake and stress. However, of the 15 early-onset individuals with RBD secondary to narcolepsy, only two presented with abnormal behaviors, and 12 presented initially with hypersomnia [8]. In the Ju et al. series, which had a high percentage of early-onset cases, only a minority (40%) were initially referred for violent behaviors during sleep [10]. The case may be that in general, RBD does not present with textbook symptoms: in a review of 703 consecutive patients at a sleep center to identify patients with RBD, only six of 34 were referred for suspected RBD [61]. Additionally, since there is more gender parity in early-onset RBD and women tend to have less violent RBD behaviors [62], early-onset RBD, may therefore, present less frequently with dramatic nocturnal behaviors. Also, as discussed above, the timing of nocturnal behaviors may not be a reliable marker of REM sleep versus NREM sleep parasomnias, due to the preponderance of narcolepsy in early-onset RBD. Furthermore, at least in one report, there was nocturnal wandering in 15.7% of RBD cases, without prior history of sleepwalking, suggesting that some individuals with RBD may get out of bed during RBD episodes and therefore, the type of behavior may not be a reliable marker of RBD either [11].

Polysomnography may also show differences in early-onset cases. Bonakis et al. quantified RWA as the percentage of REM sleep epochs with loss of REM sleep atonia. Among individuals with idiopathic RBD, the amount of RWA was equal (34%) in early-onset and late-onset cases. Secondary cases had a higher RWA, with narcoleptic patients having 42–44% RWA among early-onset RBD and 46% in late onset RBD and for RBD associated with neurodegenerative diseases, RWA was present in 32–68% of REM sleep. In contrast, RBD associated with antidepressants had the lowest proportion of RWA, with 30% RWA in

early-onset RBD and 23–24% RWA in late-onset RBD [8]. Consequently, since a relatively higher proportion of early-onset cases are idiopathic or associated with antidepressants, one can infer that the amount of RWA would be lower, on average, in early-onset RBD. A separate study found the same mean RWA of 41% in both idiopathic and secondary RBD; however, separate data for early- and late-onset RBD were not reported [11]. Future studies of RBD should incorporate RWA quantification to clarify the issue. Furthermore, RWA associated with narcolepsy may have distinct characteristics. A systematic study of RBD and RWA associated with narcolepsy identified ten individuals with definite narcolepsy and RBD; eight were early-onset. Six of the ten had preserved submental atonia, despite excessive phasic movements [18]. Again, since narcolepsy-associated RBD is relatively more common in early-onset RBD, there may be a higher proportion of early-onset RBD cases, which demonstrate motor dyscontrol of only the phasic, rather than tonic, motor component of REM sleep.

Clonazepam is an effective treatment for the disruptive behaviors in RBD in general [1]; however, treatment response has not been prospectively examined in the early-onset RBD population. Data from the single study which separately reported treatment response for early- and late-onset RBD, suggest that early-onset RBD may be more treatment-resistant, although this may be due to narcolepsy as a confounder. In this study, 18 of the early-onset RBD cases were treated with medication, 17 of these with clonazepam. Ten of the thirteen with idiopathic RBD improved. In contrast, only one of four who had RBD associated with narcolepsy had any improvement, and this was only after transition from clonazepam 2 mg to temazepam 10 mg [8]. A more detailed report from the same group reported that another case of early-onset RBD associated with narcolepsy did have response to clonazepam, however due to side effects, the medication was changed to zopiclone and there was a good response [21]. There are no other systematic studies of medication response in early-onset RBD, and additional investigation of optimal treatment strategies in early-onset RBD would be highly valuable for clinical practice.

9. Summary

A substantial proportion of RBD occurs in individuals less than 50 years old, and is characterized by near gender parity, increased proportion of idiopathic cases, and cases associated with narcolepsy, POD, and antidepressants, and may have less typical clinical presentations. Further investigation of early-onset RBD will be required to determine whether the age-adjusted risk of future neurodegenerative disease is increased, any potential autoimmune mechanisms, the long-term clinical course, and optimal treatment strategies.

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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]	N/A	N/A	73.1[b]	N/A	N/A	13
		secondary 59.9 (1.2)[a]						
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.