RBD: Gender Implications

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16.1 Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) has historically been reported more frequently in men, starting with the first report of the disorder which identified four men and one woman [1]. This brings considerable inquiries specific to gender differences and their implications. RBD is associated with many neurologic disorders including narcolepsy and neurodegenerative disorders. Idiopathic RBD (iRBD) was thought to be a disorder unrelated to other neurological disorders or clinical syndromes. However, recent evidence supports that iRBD can be one of the early manifestations of a neurodegenerative disorder (Chaps. 4 and 36). As medical research continues to advance in the field of neurodegeneration, and as disease-modifying agents become a reality (Chap. 44), a better understanding of gender differences has treatment consequences. This chapter will discuss gender in RBD and the clinical and research implications.

16.2 Gender Prevalence

iRBD has been reported to be notably male predominant, with the reported range extending up to 90% male [2, 3]. However, more recent studies either fail to demonstrate statistical gender differences [4, 5] or demonstrate overall male to female ratio of RBD closer to 2:1 [6, 7] compared to older series ranging 5:1–8:1 [8–13]. The discrepancy between recent studies compared to older series may relate to increased awareness about RBD, the higher volume of younger patients included in recent studies and/or increased access to video-polysomnography (vPSG). vPSG

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can help diagnose unrecognized RBD, as only 30–40% of patients with RBD in one study had a chief complaint suggestive of RBD [5].

16.2.1 Gender Differences of RBD Among Synucleinopathies

There is a strong association between synucleinopathies and RBD, with the most common synucleinopathy being Parkinson's disease (PD), which has a 1:5 male to female ratio in western populations [14]. Gender distribution of RBD or probable RBD (pRBD) in PD has recently demonstrated a closer balance with 31–40% women and 43–49% men [15–17]. A cross-sectional evaluation of patients with idiopathic PD demonstrated higher phasic electromyographic metric (PEM) in men compared to women in NREM and REM sleep despite no difference in dream enactment behavior [18]. However another study with RBD failed to demonstrate differences in EMG activity during REM sleep regardless of women having fewer behaviors [19]. Interestingly, a gender difference is not seen in multiple system atrophy (MSA) where almost all patients have RBD [3]. In patients with PD, women with pRBD tend to be older, with a shorter duration of PD symptoms, with higher levels of anxiety and depression, and with more sleep disturbances and decreased hours of sleep [20].

16.2.2 Gender Differences of RBD Among Other Disorders

Outside of the synucleinopathies, there is less male predominance with RBD in neurological disorders. Similar gender frequencies are seen in narcolepsy and multiple sclerosis [21]. RBD was reported in 12% (5/34) of patients with Wilson's disease, 4 of them being women [22], in contrast to the higher prevalence of Wilson's disease in men [23].

Autoimmune disorders and paraneoplastic disorders have also been linked to RBD. RBD has been reported with paraneoplastic cerebellar syndrome. Both cases were women with breast cancer and negative paraneoplastic antibodies [24]. Limbic encephalitis with potassium channel antibody has been associated with RBD; however all six cases were men [25].

16.2.3 Gender Differences of RBD with Age and Type of Disorders

Gender differences vary by age. Compared to women in the older age groups, women had a higher rate of RBD in early-onset RBD (before age 50 years), with a range of 41–45% compared to late-onset RBD of 11–25% [6, 7, 26]. Early-onset RBD had a higher rate of psychiatric diagnosis, antidepressant use, autoimmune disease, and narcolepsy, with neurodegenerative disease reported less often (2.6% compared to about 18% overall) [6, 7, 19, 26]. The high rate of autoimmune disease among female patients could account for the higher percentage of RBD in women

under age 50 [6]. Referral bias may also play a role given that psychiatric and rheumatologic patients frequently have fatigue and tiredness, which are common indications for referrals to sleep centers and sleep studies.

16.3 Gender Differences in RBD Dreams

Gender differences in dreaming are noted among patients with PD. Males with PD had more dreams involving aggression, work, adventure, and sports compared to women who had more dreams about family, friends, and daily activities [27]. However, when comparing patients with RBD or pRBD and PD, gender differences were not always noted [19, 27] or investigated [28]. A small reported series found that women had more victim dreams with no violent behaviors [29]. In patients with PD and pRBD, the women were all able to recall dreams, with content of being chased with 40% flight response, 40% fight response, and 20% with both responses [20]. Aggression and violence were significantly higher among RBD-PD men than with non-RBD-PD men. RBD patients' dreams were described as more often being chased, being defensive, or being aggressive and did not reflect daily life [27].

16.4 Gender Differences in RBD Behaviors

Gender differences in RBD behaviors are theorized to contribute to reporting bias, with men having more aggressive and violent behaviors. When comparing RBD behaviors in patients with Parkinson's disease, both men and women have vocalization, with men having more violent behaviors and women reporting more sleep disturbances, flailed arms, a tendency to use upper limbs, and run more than men [15, 20, 27]. One study demonstrated that only men had sleep-related injuries in patients with RBD and Parkinson's disease [30]. This male predominance with violent behaviors is seen with other disorders associated with RBD [22, 31]. Females have also been reported to have fewer RBD behaviors on vPSG [19, 32]. Higher muscle activity in REM sleep in the legs was found in men with RBD compared to higher muscle activity in REM sleep in the arms of women with RBD, in one study [29]. However, in a Chinese population study, no differences among behavioral symptoms or violence between men and women with RBD were noted, although 82% were men in that study [12].

Gender nonconformity (transsexual status) was mentioned in a study on the different manifestations of RBD in men and women [29]. One patient was transsexual, was born a male (with gender change surgery 13 years prior to vPSG), had arm movements in REM sleep that were much less than that usually found in women, and did not differ substantially from those of men. This particular patient was the only woman in the case series with violent behaviors associated with RBD. Dream content was not mentioned, which raises the question of whether dream content and/or behaviors would be more consistent with their gender at birth or with the gender identity (resulting in transsexual surgery). The abovementioned case appears

to be more consistent with birth gender. One unreported homosexual iRBD female identified herself as female but labeled herself as a "tomboy" (CL Bodkin, unpublished observation). She described dreams where she was protecting people and/or animals from an attacker. She herself was neither the victim nor the attacker, but the dreams and behaviors were violent to protect her loved ones. Therefore, questions regarding gender nonconformity should be included in future studies looking at gender differences in RBD.

16.5 Etiology of Gender Differences in RBD

Hormonal factors, other predisposition factors, referral bias, and decreased sensitivity of detecting RBD in woman from vPSGs may contribute to the reported male predominance of RBD. Testosterone is one hormone that has been implicated. However when comparing men with PD-RBD to men with PD-non-RBD, there was no difference in testosterone levels [33]. Estradiol has been proposed to be protective specifically in glutamate-induced toxicity in vitro [34]. Estrogen has been shown to have effects in the central nervous system with respect to serotonin, norepinephrine (NE), and dopamine [35]. It has been suggested that higher estrogen levels in women may lower NE neurotransmission leading to reduced phasic REM activity, based on a study in anesthetized rats [36]. However, there is a lack of evidence that estradiol or other sex hormones differ in male patients with or without RBD [33, 37]. Although the evidence argues against hormone status as a risk factor for RBD, it does not rule out a hormonal role in phenotypic differences between men and women, or violent vs. nonviolent behaviors, in RBD.

Men may be preferentially predisposed to RBD. When looking at REM sleep without atonia (RSWA) in a retrospective study in patients who underwent PSG evaluations, men had higher phasic muscle activity in the leg compared to women [38]. Undiagnosed neurodegenerative diseases in men could explain some of this difference. When looking at small movements during NREM and REM sleep in a prospective study with healthy volunteers, women were found to have shorter duration of movements, and men had greater movement indices in the upper and lower extremities [39]. These findings suggest underlying gender differences with baseline sleep motor dyscontrol, which may place men at higher risk for RBD.

Given the strong relationship between RBD and neurodegenerative diseases, such as PD, the high rate of male RBD patients could in part be explained by the higher male incidence of PD. Male to female incidence of PD is estimated to be 1.5 with a male to female difference more evident in western populations and not demonstrated in Asian populations. The lack of gender difference in Asian populations also suggests genetics rather than hormonal factors, such as estradiol, in playing a role in the risk for PD [14].

Referral bias likely plays a partial role in gender incidences. Women, on average, live longer than men and therefore may not have a bed partner. This is supported by reports that men with RBD are more likely to have a bed partner [31]. If behaviors are less violent and women are not suffering injuries, and they are sleeping alone

(and unaware of their sleep behaviors and without a spouse who could complain of excessive movements during sleep), then they may be less likely to seek medical attention. The possibility of vPSG being less sensitive in women, especially if arm EMG electrodes are not used, could contribute to the underdiagnosis of RBD in women. The higher ratio of women in recent studies suggests a greater awareness of women with RBD. Only 10.4% of reported RBD patients between 1990 and 2003 were women, while 23.2% of reported RBD patients were women between 2004 and 2014 [31].

16.6 Gender Implications in RBD

It is important to recognize RBD in both men and women, for compelling reasons. In one study of 93 patients with iRBD, the 12-year risk for developing a neurodegenerative disease, from the time of iRBD diagnosis, was 52.4%, and the risk of progressing to a neurodegenerative disease was similar in men and women [2]. Also, more recent findings from a cohort of 174 iRBD patients at another center found the risk of a defined neurodegenerative disorder from the time of iRBD diagnosis to be 33% at 5 years, 76% at 10 years, and 91% at 14 years, with the median conversion time being 7.5 years [40].

Although currently there are no disease-modifying agents, clinical trials in this area are being developed. As disease-modifying agents become a reality, early recognition of RBD will be of upmost importance. Healthcare providers across a wide range of specialties will need to be made aware of RBD and its strong link with parkinsonian neurodegenerative disorders in both women and men and be mindful of the gender differences in RBD and their different clinical profiles. The recent trend toward home sleep testing (HST), which is not indicated for nor sensitive in diagnosing RBD, could greatly underdiagnose RBD. In two reports, only 30–40% of patients with RBD had presented to a sleep center with a chief complaint suggestive of RBD [5, 6]. Therefore, healthcare providers need to carry out a detailed sleep evaluation prior to and/or after HST, as well as after treatment of any diagnosed sleep disorder breathing.

Besides the risk of developing a neurodegenerative disorder, there are social and physical implications to the bed partner. Women and children can be victims of violent RBD behaviors, which can include choking, headlocks, and punching [41]. This often leads to spouses sleeping in a different bed and/or room. Despite spouses often being victims of repeated injuries from RBD behaviors, necessitating sleeping in a different room, only two cases with divorces related to RBD have been reported [42, 43]. This most likely reflects how the majority of RBD reported cases involve older men who have been married for decades, and so their spouses understand that the sleep violence is completely out of character from the waking personality.

RBD is a treatable and important disorder to recognize, given the risk of future neurodegenerative disorder and the psychosocial implications. Some women and men may have similar presentations. However, women may present with less violent dreams and behaviors, have less tonic and phasic EMG activity during REM

sleep and less behavioral abnormalities during REM sleep, and also have a chief complaint with symptoms other than a parasomnia. A detailed history and the use of a screening questionnaire are important for both genders and should include an assessment of any impact to the bed partner and the relationship, if appropriate. Management should also include monitoring for resolution of all sleep symptoms in the setting of comorbid sleep disorder.

Note Added in Proof: Equal RBD gender ratio was recently found in the first general population-based study of PSG-confirmed RBD (in contrast to male gender predominance in RBD patients presenting to sleep clinics): Haba-Rubio J, Frauscher B, Marques-Vidal P, et al. Prevalence and determinants of REM sleep behavior disorder in the general population. Sleep 2017; doi: 10.1093/sleep/zsx197.

References

1. Schenck CH, Bundlie SR, Ettinger MG, Mahowald MW. Chronic behavioral disorders of human REM sleep: a new category of parasomnia. Sleep. 1986;9:293–308.
2. Postuma RB, Gagnon JF, Vendette M, Fantini ML, Massicotte-Marquez J, Montplaisir J. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. Neurology. 2009;72:1296–300.
3. Iranzo A, Santamaria J, Rye DB, Valldeoriola F, Marti MJ, Munoz E, Vilaseca I, Tolosa E. Characteristics of idiopathic REM sleep behavior disorder and that associated with MSA and PD. Neurology. 2005;65:247–52.
4. Wong JC, Li J, Pavlova M, Chen S, Wu A, Wu S, Gao X. Risk factors for probable REM sleep behavior disorder: a community-based study. Neurology. 2016;86:1306–12.
5. Frauscher B, Gschliesser V, Brandauer E, Marti I, Furtner MT, Ulmer H, Poewe W, Hogl B. REM sleep behavior disorder in 703 sleep-disorder patients: the importance of eliciting a comprehensive sleep history. Sleep Med. 2010;11:167–71.
6. Ju YE, Larson-Prior L, Duntley S. Changing demographics in REM sleep behavior disorder: possible effect of autoimmunity and antidepressants. Sleep Med. 2011;12:278–83.
7. Bonakis A, Howard RS, Ebrahim IO, Merritt S, Williams A. REM sleep behaviour disorder (RBD) and its associations in young patients. Sleep Med. 2009;10:641–5.
8. Schenck CH, Hurwitz TD, Mahowald MW. Symposium: normal and abnormal REM sleep regulation: REM sleep behaviour disorder: an update on a series of 96 patients and a review of the world literature. J Sleep Res. 1993;2:224–31.
9. Sforza E, Krieger J, Petiau C. REM sleep behavior disorder: clinical and physiopathological findings. Sleep Med Rev. 1997;1:57–69.
10. Olson EJ, Boeve BF, Silber MH. Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases. Brain. 2000;123(Pt 2):331–9.
11. Iranzo A, Molinuevo JL, Santamaria J, Serradell M, Marti MJ, Valldeoriola F, Tolosa E. Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study. Lancet Neurol. 2006;5:572–7.
12. Wing YK, Lam SP, Li SX, Yu MW, Fong SY, Tsoh JM, Ho CK, Lam VK. REM sleep behaviour disorder in Hong Kong Chinese: clinical outcome and gender comparison. J Neurol Neurosurg Psychiatry. 2008;79:1415–6.
13. Okura M, Taniguchi M, Sugita H, Ohi M, Tachibana N. [Demographic characteristics of RBD patients at a sleep center—with special emphasis on neurodegenerative diseases as the background condition]. Brain Nerve. 2007;59:1265–71.
14. Taylor KS, Cook JA, Counsell CE. Heterogeneity in male to female risk for Parkinson's disease. J Neurol Neurosurg Psychiatry. 2007;78:905–6.

15. Bjornara KA, Dietrichs E, Toft M. REM sleep behavior disorder in Parkinson's disease—is there a gender difference? Parkinsonism Relat Disord. 2013;19:120–2.
16. Szewczyk-Krolikowski K, Tomlinson P, Nithi K, Wade-Martins R, Talbot K, Ben-Shlomo Y, Hu MT. The influence of age and gender on motor and non-motor features of early Parkinson's disease: initial findings from the Oxford Parkinson Disease Center (OPDC) discovery cohort. Parkinsonism Relat Disord. 2014;20:99–105.
17. Bjornara KA, Dietrichs E, Toft M. Clinical features associated with sleep disturbances in Parkinson's disease. Clin Neurol Neurosurg. 2014;124:37–43.
18. Bliwise DL, Trotti LM, Greer SA, Juncos JJ, Rye DB. Phasic muscle activity in sleep and clinical features of Parkinson disease. Ann Neurol. 2010;68:353–9.
19. Zhou J, Zhang J, Li Y, Du L, Li Z, Lei F, Wing YK, Kushida CA, Zhou D, Tang X. Gender differences in REM sleep behavior disorder: a clinical and polysomnographic study in China. Sleep Med. 2015;16:414–8.
20. Mahale RR, Yadav R, Pal PK. Rapid eye movement sleep behaviour disorder in women with Parkinson's disease is an underdiagnosed entity. J Clin Neurosci. 2016;28:43–6.
21. Bodkin CL, Schenck CH. Rapid eye movement sleep behavior disorder in women: relevance to general and specialty medical practice. J Womens Health (Larchmt). 2009;18:1955–63.
22. Tribl GG, Trindade MC, Bittencourt T, Lorenzi-Filho G, Cardoso Alves R, Ciampi de Andrade D, Fonoff ET, Bor-Seng-Shu E, Machado AA, Schenck CH, et al. Wilson's disease with and without rapid eye movement sleep behavior disorder compared to healthy matched controls. Sleep Med. 2016;17:179–85.
23. Litwin T, Gromadzka G, Czlonkowska A. Gender differences in Wilson's disease. J Neurol Sci. 2012;312:31–5.
24. Vale TC, Fernandes do Prado LB, do Prado GF, Povoas Barsottini OG, Pedroso JL. Rapid eye movement sleep behavior disorder in paraneoplastic cerebellar degeneration: improvement with immunotherapy. Sleep. 2016;39:117–20.
25. Iranzo A, Graus F, Clover L, Morera J, Bruna J, Vilar C, Martinez-Rodriguez JE, Vincent A, Santamaria J. Rapid eye movement sleep behavior disorder and potassium channel antibody-associated limbic encephalitis. Ann Neurol. 2006;59:178–81.
26. Teman PT, Tippmann-Peikert M, Silber MH, Slocumb NL, Auger RR. Idiopathic rapid-eye-movement sleep disorder: associations with antidepressants, psychiatric diagnoses, and other factors, in relation to age of onset. Sleep Med. 2009;10:60–5.
27. Borek LL, Kohn R, Friedman JH. Phenomenology of dreams in Parkinson's disease. Mov Disord. 2007;22:198–202.
28. Valli K, Frauscher B, Peltomaa T, Gschliesser V, Revonsuo A, Hogl B. Dreaming furiously? A sleep laboratory study on the dream content of people with Parkinson's disease and with or without rapid eye movement sleep behavior disorder. Sleep Med. 2015;16:419–27.
29. Tatman JE, Sind JM. REM behavior disorder manifests differently in women and men. Sleep Res. 1996;25:380.
30. Comella CL, Nardine TM, Diederich NJ, Stebbins GT. Sleep-related violence, injury, and REM sleep behavior disorder in Parkinson's disease. Neurology. 1998;51:526–9.
31. Fernandez-Arcos A, Iranzo A, Serradell M, Gaig C, Santamaria J. The clinical phenotype of idiopathic rapid eye movement sleep behavior disorder at presentation: a study in 203 consecutive patients. Sleep. 2016;39:121–32.
32. Mattarozzi K, Bellucci C, Campi C, Cipolli C, Ferri R, Franceschini C, Mazzetti M, Russo PM, Vandi S, Vignatelli L, et al. Clinical, behavioural and polysomnographic correlates of cataplexy in patients with narcolepsy/cataplexy. Sleep Med. 2008;9:425–33.
33. Chou KL, Moro-De-Casillas ML, Amick MM, Borek LL, Friedman JH. Testosterone not associated with violent dreams or REM sleep behavior disorder in men with Parkinson's. Mov Disord. 2007;22:411–4.
34. Sawada H, Ibi M, Kihara T, Urushitani M, Akaike A, Shimohama S. Estradiol protects mesencephalic dopaminergic neurons from oxidative stress-induced neuronal death. J Neurosci Res. 1998;54:707–19.

35. McEwen BS, Alves SE. Estrogen actions in the central nervous system. Endocr Rev. 1999;20:279–307.
36. Schwarz PB, Yee N, Mir S, Peever JH. Noradrenaline triggers muscle tone by amplifying glutamate-driven excitation of somatic motoneurones in anaesthetized rats. J Physiol. 2008;586:5787–802.
37. Iranzo A, Santamaria J, Vilaseca I, de Osaba MJ. Absence of alterations in serum sex hormone levels in idiopathic REM sleep behavior disorder. Sleep. 2007;30:803–6.
38. McCarter SJ, St Louis EK, Boeve BF, Sandness DJ, Silber MH. Greatest rapid eye movement sleep atonia loss in men and older age. Ann Clin Transl Neurol. 2014;1:733–8.
39. Stefani A, Gabelia D, Mitterling T, Poewe W, Hogl B, Frauscher B. A prospective video-polysomnographic analysis of movements during physiological sleep in 100 healthy sleepers. Sleep. 2015;38:1479–87.
40. Iranzo A, Fernandez-Arcos A, Tolosa E, Serradell M, Molinuevo JL, Valldeoriola F, Gelpi E, Vilaseca I, Sanchez-Valle R, Llado A, et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. PLoS One. 2014;9:e89741.
41. Schenck CH, Lee SA, Bornemann MA, Mahowald MW. Potentially lethal behaviors associated with rapid eye movement sleep behavior disorder: review of the literature and forensic implications. J Forensic Sci. 2009;54:1475–84.
42. Ingravallo F, Schenck CH, Plazzi G. Injurious REM sleep behaviour disorder in narcolepsy with cataplexy contributing to criminal proceedings and divorce. Sleep Med. 2010;11:950–2.
43. Zhou J, Liang B, Du L, Tan L, Tang X. A patient with childhood-onset aggressive parasomnia diagnosed 50 years later with idiopathic REM sleep behavior disorder and a history of sleepwalking. Clin Neurol Neurosurg. 2017;160:105–7. https://doi.org/10.1016/j.clineuro.2017.07.001.