Absence of Alterations in Serum Sex Hormone Levels in Idiopathic REM Sleep Behavior Disorder

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Study objectives: More than 85% of the patients presenting to sleep centers with idiopathic REM sleep behavior disorder (RBD) are men. It has been hypothesized that sex hormone abnormalities may be related to this male predominance. The aim of our study was to determine the serum sex hormone levels in consecutive idiopathic RBD male patients who presented to our sleep center.

Setting: University hospital sleep disorders center. Participants: Fourteen male idiopathic RBD patients and 16 healthy matched controls.

Interventions: NA.

Measurements and Results: Serum levels of total testosterone, calculated free testosterone, calculated bioavailable testosterone, luteinizing hormone, follicle stimulating hormone, estradiol-17 beta, sex-hormone binding globulin, and prolactin were not different between idiopathic RBD patients and controls.

Conclusion: Serum sex hormone levels are normal in idiopathic RBD, indicating that androgenic abnormalities may not account for its male predominance and pathophysiology.

Keywords: Idiopathic REM sleep behavior disorder, sex hormones

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REM SLEEP BEHAVIOR DISORDER (RBD) IS A PARASOMNIA CHARACTERIZED BY VIGOROUS DREAM-ENACTING BEHAVIORS RELATED TO LACK OF MUSCLE ATONIA during REM sleep.[1,2] Patients recall dreams with violent content, such as being attacked and threatened by people or animals, and display aggressive dream-enacting behaviors including punching, kicking, and shouting.[1,2] RBD may be idiopathic or associated with neurological diseases.[1-7] For unknown reasons, more than 85% of the subjects presenting to sleep centers with idiopathic RBD are men.[4-6]

It has been hypothesized that sex hormone abnormalities might account for this male predominance and the violent nature of the RBD-associated behaviors.[2] This is based on the following observations. First, testosterone exerts neuroprotective effects,[8] and testosterone deficiency occurs in Parkinson disease,[9] a neurodegenerative condition in which RBD is common.[3,5,6] Second, androgen receptors are distributed in the brain structures that modulate both REM sleep and aggressiveness, such as the subceruleus nucleus, periaqueductal gray, amygdala, and frontal lobe.[10,11] Third, data from both humans and animals indicate that high testosterone levels are related to increased physical aggressiveness.[12]

The aim of our study was to determine the serum sex hormone levels in consecutive idiopathic RBD male patients who presented to our sleep center.

Disclosure Statement

This was not an industry supported study. Drs. Iranzo, Santamaría, Vilaseca, and Martínez de Osaba have indicated no financial conflicts of interest.

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PATIENTS AND METHODS

Serum sex hormone levels were measured in idiopathic RBD patients and healthy matched controls. The study was approved by the ethics committee at our institution and informed written consent was obtained in all subjects.

Patient and Control Selection

Between September 2004, and November 2005, 53 consecutive idiopathic RBD male patients diagnosed and followed in our sleep center were examined and asked to participate in this study. They had been referred by primary care physicians, neurologists, or pulmonologists because of vigorous dream-enacting behaviors. At referral, diagnosis of idiopathic RBD required[1,2,6] 1) history of dream-enactment behaviors, 2) nocturnal video-polysomnographic demonstration of excessive tonic and/or phasic electromyographic activity associated with abnormal behaviors and absence of electroencephalographic epileptiform activity during REM sleep, 3) no temporal association of RBD onset with the administration or withdrawal of a medication, 4) absence of chronic alcoholism, 5) no clinical evidence of an underlying neurodegenerative disease, 6) unremarkable neurologic examination, and 7) Mini-Mental State Examination[13] score greater than 27.

Patients' serum sex hormone levels were compared with those of a group of healthy men of similar age and body mass index who had no sleep complaints (e.g., nightmares, restless sleep, abnormal sleep behaviors) and were free of psychoactive drugs. Control subjects were recruited through a local advertisement and from the relatives of the patients attending at our sleep center. Controls underwent all-night polysomnographic studies which were unremarkable showing 1) muscle atonia during REM sleep, and 2) absence of sleep abnormalities including parasomnias and an apnea-hyponea index greater than 10.

Exclusion criteria for patients and controls were 1) use of any medication known to affect sex hormone levels (e.g., androgen replacement or deprivation therapy, cimetidine, ketoconazol, spironolactone); 2) alcohol abuse; 3) prostatic and gonadal disorders (e.g.,

benign prostatic hyperplasia, carcinoma of the prostate, prostatectomy, tumors of the testis, orchiectomy); and 4) liver, kidney, and thyroid disorders. Subjects with elevated serum levels of aspartate aminotransferase, alanine aminotransferase, creatinine, free thyroxine, and thyroid-stimulating hormone were also excluded because liver, kidney, and thyroid dysfunction may modify the metabolism and serum concentrations of sex hormones.[14] Subjects with an apnea-hyponea index greater than 10 were excluded, since obstructive sleep apnea has been associated with low serum testosterone concentrations.[15] Subjects with sleep apnea treated with continuous positive airway pressure were also excluded because this therapy is associated with increased testosterone levels.[15] Patients taking clonazepam were not excluded from this study because this medication does not influence serum sex hormone levels.[16,17]

Hormone Assays

Serum levels of total testosterone, free testosterone, bioavailable testosterone, luteinizing hormone, follicle stimulating hormone, estradiol-17 beta, sex-hormone binding globulin, prolactin, aspartate aminotransferase, alanine aminotransferase, creatinine, free thyroxine, and thyroid-stimulating hormone were determined in patients and controls. Blood samples were taken by venipuncture between 08:30 and 10:00, after an overnight fast. Hormones were measured using commercially available kits. Serum total testosterone was measured by immunoenzymatic assay (Immuno 1; Technicon, Bayer, Tarrytown, NY, USA). The intra-assay coefficient of variation was 8.3%. Serum free testosterone and bioavailable testosterone levels were calculated based on equations derived from the laws of mass action, as reported previously.[18] Serum levels of estradiol-17 beta were analyzed by radioimmunoassay (Estradiol 3rd Generation, DSL, Webster, TX, USA) and the intra-assay coefficient of variation was 11%. Concentrations of sex-hormone binding globulin were determined by electrochemiluminiscence immunoassay (Roche Elecsys, Mannheim, Germany). The intra-assay coefficient of variation was 6.6%. Chemiluminiscent enzyme immunoassays were performed to measure serum levels of luteinizing hormone, follicle stimulating hormone, prolactine, free thyroxine and thyroid-stimulating hormone (ADVIA-Centaur, Bayer, Tarrytown, NY, USA) and the intra-assay coefficients of variation were 4.5%, 3%, 3.9%, 4.2%, and 4.1%, respectively.

Statistical Analysis

Between-group differences in serum sex hormone levels, age, and body mass index were assessed by the Mann-Whitney *U* test.

RESULTS

Thirty-nine out of 53 idiopathic RBD male subjects were excluded from the study because coexistent prostate disorders (n=15), apnea-hypopnea indexes >10 (n=14), prostate disorders plus apnea-hypopnea index >10 (n=6), and refusal to participate (n=4). Sex hormone levels were determined in the remaining 14 male patients and compared to those of 16 healthy age-matched male controls.

At the time of RBD diagnosis, all 14 patients reported both frequent fearful dreams and violent behaviors during sleep. Abnormal behaviors were punching (92.9%), kicking (78.6%), knocking off the nightstand (57.1%), assaulting the bed partner (42.9%) and biting the bed partner (14.3%). Eleven (78.6%) patients fell out of bed. Ten (71.4%) patients had injured themselves and 3 (21.4%) had injured their bed partners. Injuries included lacerations in 5, ecchymosis in 7, and fractures in the remaining subject. Three (21.4%) spouses chose to sleep in a separate room, and 7 (50%) patients self-protected from injury by placing a mattress on the floor or removing pieces of furniture from the room.

At the time of this study, patients had a mean age of 70.79 ± 4.71 (range, 64-77) years. The mean age of onset of RBD symptoms was 62.57 ± 7.51 (range, 45-72) years. Duration of RBD (time between reported onset of RBD and serum sex hormones measurement) was 8.21 ± 5.01 (range, 2-19) years. Eleven (78.6%) patients were treated with clonazepam, and this medication was considered efficacious in each. Mean clonazepam dose was 1.08 ± 0.78 (range, 0.5-3) mg, and mean treatment duration was 2.28 ± 2.01 (range, 0-5) years.

No significant differences between patients and controls were found in serum concentrations of total testosterone, calculated

Table 1—Demographics and Serum Level Comparisons Between Patients and Controls.

	Patients (n=14)	Controls (n=16)	P value
Age (years)	70.79 ± 4.71	68.69 ± 5.69	0.327
Body mass index (Kg/m^2)	26.26 ± 4.34	26.94 ± 2.93	0.589
Total testosterone (ng/dL)	476.88 ± 169.68	514.06 ± 174.12	0.360
Free testosterone (ng/dL)	7.99 ± 2.40	7.52 ± 2.79	0.493
Bioavailable testosterone (ng/dL)	187.21 ± 56.36	176.40 ± 65.37	0.492
Luteinizing hormone (U/L)	5.27 ± 2.74	5.97 ± 2.57	0.454
Follicle stimulating hormone (U/L)	7.42 ± 4.27	9.16 ± 5.86	0.406
Estradiol-17 beta (pg/mL)	41.03 ± 11.91	43.12 ± 10.54	0.771
Sex-hormone binding globulin (nmol/L)	46.83 ± 16.36	59.81 ± 24.75	0.158
Prolactin (ng/mL)	5.41 ± 1.89	6.97 ± 3.13	0.190
Aspartate aminotransferase (U/L)	25.14 ± 5.78	28.56 ± 10.55	0.287
Alanine aminotransferase (U/L)	29.14 ± 17.97	29.62 ± 19.48	0.819
Creatinine (mg/dL)	1.25 ± 0.17	1.13 ± 0.11	0.050
Free thyroxine (ng/dL)	1.24 ± 0.22	1.25 ± 0.12	0.245
Thyroid-stimulating hormone (mIU/L)	1.51 ± 0.58	1.55 ± 1.50	0.258

free testosterone, calculated bioavailable testosterone, luteinizing hormone, follicle stimulating hormone, estradiol-17 beta, sex-hormone binding globulin, prolactin, aspartate aminotransferase, alanine aminotransferase, creatinine, free thyroxine, and thyroid-stimulating hormone (Table 1).

DISCUSSION

To the best of our knowledge, this work is the first to evaluate the influence of sex hormones on the pathophysiology of RBD. We have shown that morning circulating sex hormone concentrations in male patients with idiopathic RBD are not different from those in healthy matched controls. Our finding does not provide evidence of an androgenic hormonal influence in the male predominance and pathogenesis of idiopathic RBD. However, impaired testosterone function cannot definitively be excluded since our results may be subject to false negative, or type II error, due to 1) a relatively small sample size, 2) abnormal serum testosterone secretion at night during different sleep stages,[19] 3) abnormal neuronal testosterone production within the brain, or 4) androgen receptor dysfunction.

Elevated serum testosterone is associated with the predatory-attack aggressive behavior. This subtype of behavior is characterized by goal-directed aggression performed in an emotional calm toward a non-threating victim.[12,20-22] The characteristic violent dream-enacting motor and vocal behaviors seen in RBD, however, may correspond to a different subtype of aggressive behavior, called defensive rage. In this subtype of aggressive behavior the attack is directed against a threat in the context of fear and anger.[20-22] Patients with RBD dream that they are defending themselves or their relatives from an attacker, are never the primary aggressors,[4-7] and exhibit normal levels of aggressiveness during wakefulness.[7] Thus, the vigorous behaviors displayed by RBD patients (e.g., prominent abrupt jerks, punching, kicking, shouting) may be the result of a defensive rage behavior. Compared with predatory-attack behavior, defensive rage has a different neuroanatomic and neurobiological basis, and it is not related to increased testosterone levels.[21,22]

In a significant majority of patients, RBD presages the development of a neurodegenerative disease such as multiple system atrophy, dementia with Lewy bodies, and Parkinson disease.[23,24] Interestingly, these diseases do not have the strong male predominance seen in idiopathic RBD.

It remains unclear why most patients diagnosed in sleep centers with idiopathic RBD are men. There are several possible explanations. First, a milder form of RBD may exist in women manifesting with less vigorous and disruptive behaviors, thereby making female patients less prone to seek medical help.[2,4] This is supported by 1) the finding that in Parkinson disease the mildest form of RBD (subclinical increased submental tonic REM sleep electromyographic activity) is equally frequent in men and women, whereas clinically evident RBD is more common in men,[3] and by 2) the result of an epidemiological study showing that subjects with a milder clinical form of RBD do not seek medical attention.[25] Since estrogens[26] and progesterone[27] exert protective effects in the brain, these hormones in women may be protective of developing a severe form of RBD. Second, RBD may manifest similarly in women and men, but women may be more embarrassed than men by their condition, and are ashamed to seek medical consultation. It is also possible that women are more capable than men of detecting sleep disorders in their bed partners (such as snoring, apneas, and abnormal sleep behaviors) and are more prompt in seeking medical attention for them. Finally, we cannot exclude that other yet to be defined biological and social factors may explain why most of the patients diagnosed with idiopathic RBD in sleep centers are men.

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