BASIC SCIENCE

Increased Muscle Activity During Rapid Eye Movement Sleep Correlates with Decrease of Striatal Presynaptic Dopamine Transporters. IPT and IBZM SPECT Imaging in Subclinical and Clinically Manifest Idiopathic REM Sleep Behavior Disorder, Parkinson's Disease, and Controls

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Study Objectives: Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by complex behavior during REM sleep. The etiology of this disorder is still unknown, but a recent study showed that RBD precedes symptoms of Parkinson disease (PD) by several years, and in a previous study, we found reduced striatal dopamine transporters in idiopathic clinically manifest RBD.

Design: Hypothesizing that subclinical RBD shows a less severe reduction of striatal dopamine transporters than clinically manifest RBD, we studied striatal postsynaptic dopamine D2-receptors with (S)-2hydroxy-3iodo-6-methoxy-([1-ethyl-2-pyrrolidinyl]methyl) benzamide labeled with iodine 123 (IBZM) and the striatal presynaptic dopamine transporters with (N)-(3-iodopropene-2-yl)-2beta-carbomethoxy-3beta-(4-chlorophenyl) tropane labeled with iodine 123 (IPT) using single-photon emission computed tomography (SPECT) in the following groups: 8 patients with idiopathic subclinical RBD, 8 patients with idiopathic clinically manifest RBD, 11 controls, and 8 patients with PD stage Hoehn & Yahr I.

Results: The IPT uptake was highest in controls. There was a significant decrease in IPT uptake from controls to patients with subclinical RBD, from patients with subclinical RBD to clinically manifest RBD, and from patients with clinically manifest RBD to patients with PD (controls: right = 4.07 ± 0.29, left = 4.07 ± 0.30; subclinical RBD: right = 3.56 ± 0.21, left = 3.55 ± 0.25; clinically manifest RBD: right = 3.18 ± 0.43, left = 3.2 ± 0.43; PD: ipsilateral to the clinically affected body side = 3.25 ± 0.35, contralateral to the clinically affected body side = 2.51 ± 0.28). Muscle activity during REM sleep lasting persistently longer than 0.5 seconds was independently associated with reduction of striatal dopamine transporters (P=0.001). The IBZM uptake was not significantly different between the groups.

Conclusions: This study suggests that there is a continuum of reduced striatal dopamine transporters involved in the pathophysiologic mechanisms causing increased muscle activity during REM sleep in patients with subclinical RBD.

Key Words: presynaptic dopamine transporter, postsynaptic D2-receptor, REM sleep behavior disorder, Parkinson disease

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INTRODUCTION

RAPID EYE MOVEMENT (REM) SLEEP BEHAVIOR DISORDER (RBD) INVOLVES COMPLEX BEHAVIOR AND A LOSS OF SKELETAL MUSCLE ATONIA DURING REM SLEEP. This parasomnia was first described in 1986 by Schenck et al.[1] The minimal diagnostic criteria for RBD according to the *International Classification of Sleep Disorders* include movements of limbs or body associated with dream mentation and at least 1 of the following criteria: potentially harmful sleep behavior, dreams that appear to be "acted out," or sleep behavior that disrupts sleep continuity.[2] Patients often recall aggressive or violent dreams and sometimes injure their bed partner or themselves during episodes of RBD. The underlying cause of RBD is still unknown. Experimental lesions of the dorsolateral pontine tegmentum in animals have been reported to cause a loss of normal REM muscle atonia.[3] A recent prospective study showed that 38% of the patients with RBD eventually developed Parkinson disease (PD).[4] Another study showed that clinical symptoms of RBD preceded the onset of multiple system atrophy by more than 1 year in 44% of the patients examined.[5] Patients with PD consistently have reduced presynaptic dopamine transporters and normal D_2-receptor binding,[6] whereas patients with multiple system atrophy often show reduced presynaptic dopamine transporters and reduced dopamine D_2-receptor binding.[7] We conducted single-photon emission computed tomography (SPECT) studies using (N)-(3-iodopropene-2-yl)-2beta-carbomethoxy-3beta-(4-chlorophenyl) tropane labeled with iodine 123 (IPT) and (S)-2hydroxy-3iodo-6-methoxy-([1-ethyl-2-pyrrolidinyl]methyl) benzamide labeled with iodine 123 (IBZM) in patients with idiopathic clinically manifest RBD and found the number of their dopamine transporters to be higher than in patients with PD but lower than in controls.[8] We carried out additional IPT-SPECT and IBZM-SPECT studies in patients with idiopathic subclinical RBD to determine whether increased muscle activity during REM sleep *without* potentially locomotor behavior is associated with an abnormality of the presynaptic dopamine transporters or the dopamine D_2 receptors.

Disclosure Statement
No significant financial interest/other relationship to disclose.

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METHODS

Study Population

Eight patients with polysomnographically confirmed clinically manifest RBD; 8 age- and sex-matched patients with subclinical RBD, which was defined as more than 15% of REM sleep being associated with long-lasting muscle activity in the polysomnogram (PSG), as described later, but without any visible movements in the synchronized videotape; 11 age- and sex-matched controls without a history of parasomnias or any detectable movements during REM sleep and with less than 15% of their REM sleep being associated with long-lasting muscle activity; and 8 patients with PD (Hoehn and Yahr I) participated in the study (Table 1). The results of the SPECT imaging studies of the subjects with subclinical RBD were compared with those of the group with clinically manifest RBD (complex behavior during REM sleep) and with those of the control group and the IPT-SPECT results of the group of patients with PD. All patients diagnosed with idiopathic clinically manifest RBD had a history of several years of violent behavior during sleep associated with screaming, aggressive dream contents, and self injury or injury of the bed partner. Only 1 of the patients reported a family history of parasomnias (his father reportedly has exhibited violent behavior during sleep), and the results of neurologic examination of all patients with RBD and controls were normal. None of the controls or patients with subclinical RBD had a history or PSG results (increased muscle activity during REM sleep with associated movements in the synchronized videotape) typical for RBD.[9,10] Four healthy controls were recruited from our staff for the purpose of the study. Control subjects referred to the sleep laboratory because of excessive daytime sleepiness had normal results on their Multiple Sleep Latency Tests and turned out to have minor depression or exhaustion syndrome. Patients with PD did not have a PSG. One control (59-year-old man) and 1 patient with subclinical RBD (74-year-old woman) suffered from mild RLS, which was shown to not be associated with striatal dopaminergic dysfunction.[11] The subclinical RBD, clinically manifest RBD, control, and PD groups did not differ significantly in age and sex distribution. All 8 patients with PD fulfilled the clinical criteria steps 1 and 2 established by the PD Society Brain Tissue Bank [12] indicating that all patients had at least bradykinesia and at least 1 of the other features of PD such as resting tremor, rigidity, or impairment of postural reflexes. According to the prospective supportive criteria, all PD patients had a progressive disorder, resting tremor, unilateral onset, or persisting asymmetry or a combination thereof and were rated as stage Hoehn and Yahr I. Disease duration was 20 ± 11 months (range, 12 to 48 months). Our patients with PD had been part of another study that had systematically looked for IPT-SPECT changes in PD.[13] Patients with clinically manifest RBD, patients with subclinical RBD, and controls underwent high-resolution cranial magnetic resonance imaging (MRI) studies. Informed consent was obtained from each subject, and the institutional ethics committee approved the study. The study conformed to the Declaration of Helsinki. None of the patients (clinically manifest RBD, subclinical RBD, and PD) or controls was on medication known to affect the dopaminergic system at least 5 days prior to the SPECT study. Other medications remained stable at the time of SPECT and PSG.

Single-Photon Emission Computed Tomography Studies

We studied striatal presynaptic dopamine transporter binding in patients and controls with ^{123}I IPT-SPECT according to a method described in detail previously.[8] We also studied striatal dopamine D_2-receptor binding in controls and patients with subclinical and clinical RBD with ^{23}I IBZM-SPECT according to a method described elsewhere in detail.[8] One 44-year-old healthy male control did not undergo an ^{123}I IBZM-SPECT examination.

Sleep Studies

All patients with clinically manifest RBD underwent a PSG to confirm the previously clinically suggested diagnosis of RBD. Patients were diagnosed with subclinical RBD if they had no history of RBD and if more than 15% of their REM sleep was associated with long-lasting muscle activity (as described below), in the absence of arousal in the

Table 1—Description of the study populations

	Subclinical RBD	Clinically manifest RBD	PD	Controls
N	8	8	8	11
Age in years ± SD (range)	62.3 ± 13.5 (35-79)	69.2 ± 7.6 (60-78)	57.2 ± 6.6 (50-68)	61.6 ± 8.2 (44-74)
Men, N	6	7	5	9
Results of cranial hr-MRI, N	Normal, 7; pineal cyst, 1	Normal, 5; white matter lesions, 2; frontobasal meningioma, 1	NA	Normal, 8; white matter lesions, 3
History of complex behavior during sleep, N	0	8	NA	0
Reason for initial PSG, N	EDS, 1; insomnia, 1; mild RLS, 1; control of previously adjusted nCPAP, 2; snoring, 3	Violent behavior during sleep (n=8)	NA	EDS, 3; mild RLS, 1; snoring, 3; true controls, 4
Medications	Tricyclic antidepressant, 1; SSRI, hydrocortisone, valproic acid, l-thyroxine, iron, pirenzepine,1; estrogen, 2; glibenclamid, simvastatine, 1; allopurinole, triamteren, 1; lacidipine, 1; none, 1	Tricyclic antidepressant, tilidine, gabapentin, ACE-inhibitor, hydrochlorthiazide, piroxicame, rofecoxibe, theophylline, 1; Verapamil, 1; bezafibrate, fendiline, cocculus, beta-acetyldigoxine, piracetame, gingko-biloba, 1; valproic acid, 1; propiverine, 1; none, 3	acetylsalicylic acid, 1 magnesium, 1 none, 6	beta-blocker, 1; nifedipine, 1; baldrian, 1; none, 8

PD, Parkinson disease (Hoehn and Yahr I); hr-MRI, high-resolution magnetic resonance imaging; NA, not assessed; PSG, polysomnogram; EDS, excessive daytime sleepiness; nCPAP, nasal continuous positive airway pressure; RBD, rapid eye movement-sleep behavior disorder; RLS, restless legs syndrome; SSRI, selective serotonin reuptake inhibitor

electroencephalogram or any visible movement in the synchronized videotape.

We arbitrarily chose 15% of 10-second REM epochs as the threshold for controls versus subclinical RBD because, to date, no definition for such threshold has been defined. There is also no definition for pathologically increased phasic muscle events. Twitching during REM sleep is supposed to be normal. But no one has defined to what extent it is normal and when excessive twitching begins to be pathologic. We intended to measure nonnormal increased rather than normal (eg, moderate phasic) muscle activity during REM sleep because we hypothesized that pathologically increased muscle activity or long-lasting muscle activity during REM sleep, which is potentially associated with complex movements, is related to the dopaminergic striatal system. Since excessive short-lasting muscle activity, or in other words excessive twitching, is not defined, we again arbitrarily declared more than 10 short-lasting muscle events per 10-second REM epoch as pathologically increased. Of course, with this method, we did not detect short-lasting muscle activity that appeared less than 10 times per 10-second REM epoch, which potentially is a normal phenomenon during REM sleep, especially if it occurs with phasic eye movements. But again, we were interested in measuring pathologically increased muscle activity during REM sleep. We felt that the methods described thus far in the literature[14,15] were not suitable to reach this aim. The method described by Lapierre and Montplaisir misses muscle activity during REM sleep that lasts between 5 and 10 seconds; it also misses muscle activity of the extremities and phasic muscle activity (of a duration of 0.1 to 5 seconds) and includes potentially locomotor behavior and simple twitching. The method of analyzing muscle activity during REM sleep described by Kohayama[15] also does not measure muscle activity of the extremities or muscle activity lasting longer than 2 seconds.

A digital system (Brainlab, Schwarzer, Munich, Germany) was used to record the PSGs. The study began at approximately 10 PM and ended at 6 AM; during this time electroencephalogram, electrooculogram, and mental and submental electromyograms (EMG) were recorded. The surface EMGs of both anterior tibialis muscles were recorded as described by Coleman.[16] In addition, the EMGs of both musculi brachioradiales were recorded. Breathing parameters and electrocardiogram were recorded and scored as described previously.[17] Sleep staging followed the recommendations of Rechtschaffen and Kales.[18] Arousal and periodic limb movement (PLM) scoring followed the guidelines suggested by the Atlas Task Force of the American Sleep Disorders Association.[19,20] Muscle activity during REM sleep was analyzed quantitatively in controls and in patients suggested to have subclinical RBD on the basis of their PSG. At present there is no widely accepted definition for the diagnosis of subclinical RBD. Therefore, we scored muscle activity during REM sleep according to the following criteria: 10-second epochs of REM sleep were scored; the percentage of the 10-second REM epochs associated with increased chin- or limb-muscle activity (long-lasting muscle activity or short-lasting muscle activity) was analyzed; muscle activity during REM sleep was considered increased if there was an increase in EMG amplitude of at least 50% compared with the immediately preceding atonic EMG baseline; long-lasting muscle activity during REM sleep was scored for each 10-second epoch in which persistently increased muscle activity lasted at least 1 second; each single persistent increase of muscle activity lasted at least 0.5 seconds. We chose the 0.5-second criterion according to the definition of a PLM during sleep, since this, at present, is the only commonly accepted time criterion for movements during sleep. Therefore, long-lasting muscle activity according to our criteria is more likely to potentially be associated with locomotor behavior, which is a feature of RBD, than is short-lasting muscle activity. An increase in muscle activity of less than 0.5 seconds was defined as short-lasting muscle activity. Short-lasting muscle activity was scored for one 10-second epoch if at least 10 short-lasting muscle activities occurred during this epoch. Long- and short-lasting muscle activities were analyzed for chin muscles and extremity muscles separately. Two 30-second epochs of a PSG, showing examples for long-lasting and short-lasting muscle activity, are presented in Figure 1. Because there is no widely accepted definition of different kinds of muscle activity during REM sleep, we avoided using the potentially misleading term *phasic* or *tonic* muscle activity and separated long-lasting muscle activity, which is more likely to be associated with complex movements, from short-lasting muscle activity, which more likely represents uncoordinated twitches (C. Schenck, MD, M. Mahowald, MD, and Y-Y. Lai, MD personal oral communications at the meeting of the American Professional Sleep Societies in Seattle, June 2002). The person who analyzed the PSGs had no knowledge of the SPECT results.

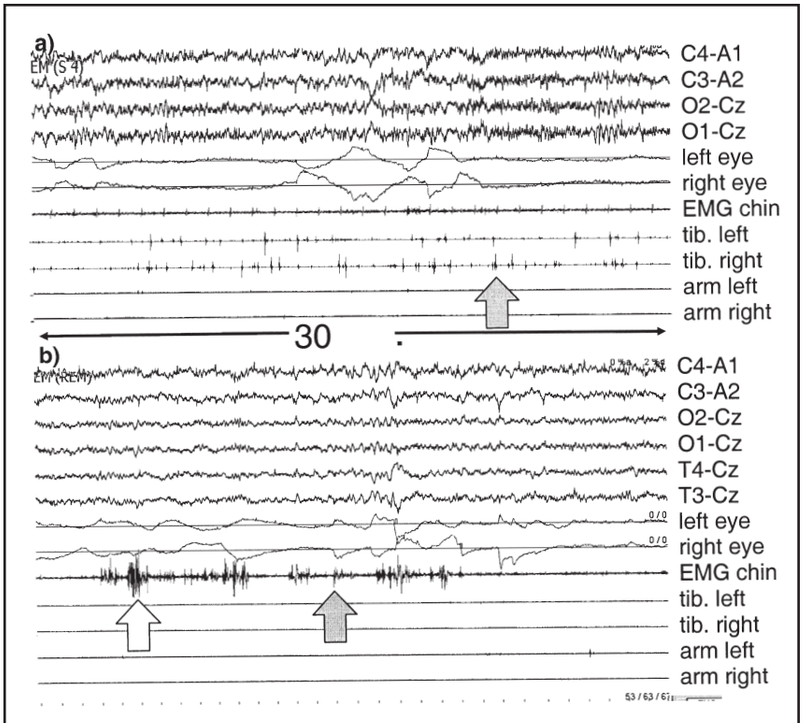

Figure 1—Muscle activity during rapid eye movement (REM) sleep, with two 30-second REM epochs, 1 (a) with short-lasting muscle activity of the legs and the other (b) with long- and short-lasting muscle activity of the chin. The grey arrows mark short-lasting muscle activity; the white arrow marks long-lasting muscle activity.
left eye, left lateral eye to left ear (A1); right eye, right lateral eye to right ear (A2); EMG, electromyogram; tib, EMG of the anterior tibialis muscle; arm: EMG of the forearm flexor

Data Presentation and Statistics

Data were analyzed using the SPSS for Windows 10.0 statistical package. They are presented as mean and SD of the mean if not stated otherwise. The data were tested for normal distribution with the Kolmogorow-Smirnov test. Data points between the 4 study groups (clinically manifest RBD versus subclinical RBD versus controls versus PD) were compared using the χ^2 test for comparison of sex distribution, the Kruskal-Wallis Test and the Mann-Whitney *U* test, since data were consistently not normally distributed. Correlations were calculated using the Spearman correlation analysis. Multiple stepwise forward regression analysis was used controlling for percentage of REM sleep associated with long-lasting chin-muscle activity, percentage of REM sleep associated with long-lasting extremity-muscle activity, percentage of REM sleep associated with short-lasting chin-muscle activity, percentage of REM sleep associated with short-lasting extremity-muscle activity, age, and sex to identify independent influences on stri-

atal IPT-binding. A *P*-value less than 0.05 was considered significant.

RESULTS

Sleep Studies

The average duration of REM sleep per patient was 58.1 minutes (SD: 27.5 minutes, range, 12.2-106.8 minutes). Percentages of 10-second REM epochs associated with increased muscle activity are listed in Table 2. Muscle activity in REM sleep did not correlate with age in patients with subclinical RBD and controls. All patients with clinically manifest RBD had abnormal REM sleep with increased chin, leg, and arm EMG activity during REM episodes and complex behavior in the synchronized videotape. Six patients with clinically manifest RBD, 5 patients with subclinical RBD, and 5 control subjects showed more than 10 PLMs per hour of total sleep time (PLM index: clinically manifest RBD, 34.6 ± 31.8; subclinical RBD, 32.1 ± 45.2; controls, 24.2 ± 46.8). Six patients with clinically manifest RBD, 4 patients with subclinical RBD, and 3 control subjects showed more than 10 apneas or hypopneas per hour of total sleep time (apnea-hypopnea index: clinically manifest RBD, 23.2 ± 25.0; subclinical RBD, 12.7 ± 10.6; controls, 6.4 ± 9.4). Indexes for PLMs or apneas or hypopneas were not statistically different between the groups (clinically manifest RBD, subclinical RBD, or controls).

Single-Photon Emission Computed Tomography Studies

^{123}I IPT-SPECT

Significant asymmetries between right and left side were observed only in patients with PD (P=0.001). Results of the IPT-SPECT for the patients with subclinical RBD were significantly lower than those for the control subjects ($P \leq 0.001$) but significantly higher than those for patients with clinically manifest RBD and patients with PD stage Hoehn and Yahr I (contralateral to the clinically affected body side) (Table 3). Striatal IPT-binding ratios in clinically manifest RBD were not significantly different from IPT binding in the ipsilateral striatum of PD patients, reflecting the so-far nonaffected body side (Table 3). Striatal IPT-binding ratios in subclinical RBD patients were significantly lower than in the control subjects (Table 3). Excluding the patients who were taking central nervous system active medications (valproic acid, gabapentin, tricyclic antidepressants, selective serotonin reuptake inhibitors) from our analyses (subclinical RBD: N=2, clinically manifest RBD: N=2) did not change our results.

The percentage of REM sleep associated with long-lasting muscle activity (chin, extremities, or both) correlated significantly and negatively with IPT-binding ratios in the striatum of control subjects and patients with subclinical RBD (Spearman correlation coefficient: right striatum=-0.729, left striatum=-0.731, P<0.0001; Figure 2).

Table 2—Muscle-activity analyses during rapid eye movement sleep in patients with subclinical RBD and controls.

	Population	
	Subclinical RBD	**Controls**
Percentage of REM sleep	*% ± SD (range)*	*% ± SD (range)*
With long-lasting muscle activity	25.9 ± 5.0 (18.1-31.6)	8.9% ± 3.4 (3.1-14.1)
With short-lasting muscle activity	36.6 ± 35.0 (0.0 – 95.2)	9.0 ± 8.7 (0.0-30.4)
With long-lasting chin-muscle activity	17.1 ± 9.4 (6.9-31.2)	5.3 ± 3.3 (0.3-11.8)
With short-lasting chin-muscle activity	8.1 ± 10.3 (0.0-30.0)	2.5 ± 2.8 (0.0-8.3)
With long-lasting extremity-muscle activity	15.4 ± 10.6 (0.0-30.4)	4.0 ± 2.8 (0.8-9.4)
With short-lasting extremity-muscle activity	34.4 ± 34.8 (0.0-95.2)	7.2 ± 8.0 (0.0-24.9)

REM, rapid eye movement, RBD, REM sleep behavior disorder

No significant correlation was found between the percentage of REM sleep associated with short-lasting muscle activity (chin, extremities, or both) and IPT-binding ratios. Multiple stepwise forward regression analysis controlling for short-lasting muscle activity of the chin, short-lasting muscle activity of the extremities, long-lasting muscle activity of the chin, long-lasting muscle activity of the extremities, age, and sex identified the percentage of REM episodes associated with long-lasting chin-muscle activity and the percentage of REM episodes associated with long-lasting extremity-muscle activity as variables being independently associated with striatal IPT binding. Age correlated with neither increased muscle activity during REM sleep nor the IPT-SPECT results.

^{123}I IBZM-SPECT

Significant asymmetries between the right and left side were not observed. Dopamine D_2-receptors were not significantly different between the groups (IBZM-SPECT: clinically manifest RBD, right=0.47 ± 0.09, left=0.4 ± 0.05; controls, right=0.46 ± 0.04, left=0.45 ± 0.05; subclinical RBD, right=0.46 ± 0.06, left=0.43±0.05). No significant correlation was found between muscle activity during REM sleep or age and the IBZM-SPECT results.

DISCUSSION

Our patients with subclinical RBD had reduced striatal dopamine transporters when compared with those of control subjects but higher striatal dopamine transporters when compared with those of patients with clinically manifest RBD. Patients with clinically manifest RBD had decreased striatal dopamine transporters when compared with those of control subjects and higher striatal dopamine transporters when compared with the striatum contralateral to the clinically affected body side of patients with PD. Patients with clinically manifest RBD were older than the control subjects, but it is unlikely that the decrease in presynaptic striatal dopamine transporters is due to age because the significant decrease in striatal dopamine transporters generally happens before the age of 40 years[21] and our patients and controls usually were older than 50 years with only 2 exceptions: one 44-year-old control subject and one 35-year-old patient with subclinical RBD. The amount of long-lasting

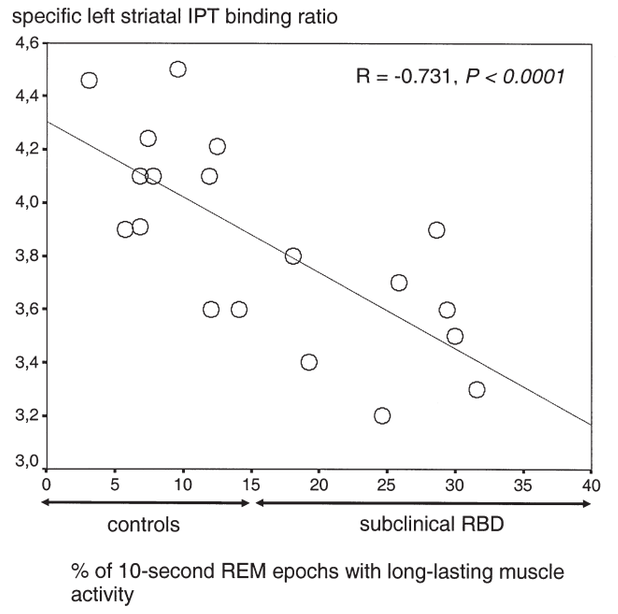

Figure 2—Muscle activity during rapid eye movement (REM) sleep and IPT [(N)-(3-iodopropene-2-yl)-2beta-carbomethoxy-3beta-(4-chlorophenyl) tropane labeled with iodine 123] binding ratio in patients with subclinical REM sleep behavior disorder and controls. Correlation of long-lasting muscle activity during REM sleep and IPT binding ratio (left striatum) in controls and patients with subclinical RBD. P, level of significance; R, Spearman correlation coefficient.

muscle activity during REM sleep correlated significantly and negatively with IPT binding to presynaptic striatal dopamine transporters. Neurologic examination of control subjects and patients with subclinical and clinically manifest RBD identified no abnormalities that would suggest further brain pathology. Excluding patients on medications that affect the central nervous system (subclinical RBD, N=2; clinically manifest RBD, N=2) did not change our results, suggesting that our findings are not predominantly caused by central nervous system-active medications. Findings from experimental-lesion studies in animals or MRI studies in patients with secondary RBD suggest that degenerated brainstem nuclei are the anatomic basis for RBD.[22,23] Culebras et al[23] found small vascular periventricular lesions in 5 of 6 patients with RBD. Small vascular lesions are common in older patients with risk factors for stroke; however, only a few develop RBD. Four of our patients with clinically manifest RBD and 7 of our patients with subclinical RBD had normal cranial MRIs. High-resolution MRI did not detect any brainstem lesions in our patients with clinically manifest or subclinical RBD. There are several links between RBD and PD. On the one hand, about one third of patients with RBD develop PD later in life.[4] On the other, 15% to 47% of patients with PD suffer from RBD.[9,10] We previously found that patients with clinically manifest RBD had significantly reduced striatal dopamine transporters when compared with controls.[8] We were able to confirm these results in the present study in a larger group of patients with RBD. StriatаI IPT uptake in patients with subclinical and clinically manifest RBD was lower than in the control subjects but higher than in PD patients. StriatаI IPT uptake in patients with subclinical RBD was higher than in patients with clinically manifest RBD but lower than in control subjects. The IPT binding contralateral to the clinically symptomatic side in PD patients was significantly lower than the IPT binding in patients with subclinical and clinically manifest RBD. These results suggest that there is a continuum of dopaminergic dysfunction, with the mildest pathology occurring in patient with subclinical RBD, moderate dysfunction in patients with clinically manifest RBD, and the most severe dysfunction in patients with PD. The amount of long-lasting muscle activity during REM sleep in control subjects and patients with subclinical RBD correlated highly significantly and negatively with the IPT binding to striatal presynaptic dopamine transporters. Decreased IPT binding in RBD could result from either degeneration of presynaptic dopaminergic neurons or from intracellular trafficking of IPT-binding receptors to an intracellular compartment not accessible to IPT. The first explanation would support our previous hypothesis[8] that muscle activity in REM sleep is directly influenced by striatal presynaptic dopaminergic output; in the case of the latter plausible explanation, decreased IPT binding in RBD would reflect an epiphenomenon of another pathophysiologic process not affecting dopaminergic transmission in the nigrostriatal area. The fact that patients with clinically manifest RBD develop PD in the course of their disease[4] favors the hypothesis that decreased IPT binding in RBD reflects true degeneration of striatal dopaminergic neurons. Interestingly, we did not find any association between striatal dopaminergic function and short-lasting muscle activity, more or less resembling twitching, in contrast to long-lasting muscle activity during REM sleep. We assume, therefore, that the pathologic significance of short-lasting muscle activity is less than that of long-lasting muscle activity during REM sleep. We do not conclude that striatal dopamine transporters show no correlation with phasic measures in general; rather, we conclude that excessive short-lasting muscle activity during REM sleep is not related to striatal dopamine transporters. A recent work found decreased phasic EMG activity during REM sleep after dopaminergic treatment in Parkinson's disease.[24] This suggests an association between phasic muscle activity during REM sleep and the striatal dopaminergic system. However, phasic muscle activity in the abovementioned work was defined similar to the method of Lapierre and Montplaisir,[14] which was discussed above.

Rye[25] hypothesized that GABA-ergic basal-ganglia output targets the glutamatergic retrorubral field, neurons of the midbrain extrapyramidal area, or both, which, in turn, activate the ventromedial medullary zone, which promotes REM atonia. Dopamine cell loss in the substantia nigra occurs either transiently or persists in pathologic states such as PD.[26] One would expect heightened phasic discharge of the internal segment of the globus pallidus secondary to dopamine cell loss in the substantia nigra to excessively inhibit the midbrain extrapyramidal area, thereby allowing for the expression of increased muscle activity and even movements that overcome REM atonia. This hypothesis is supported by clinical experience in individual cases showing that excessive nocturnal movements[27] can be reversed by removing excessive inhibition of the midbrain extrapyramidal area by pallidotomy.[26] If reduced striatal dopaminergic neurons cause RBD, why do some patients with PD not suffer from RBD? Additional brainstem neurons that play significant roles in behavioral state control, particularly brainstem monoaminergic nuclei, also degenerate in PD.[28] There are 2 different glutamatergic receptors in the dorsolateral pons and the nucleus magnocellularis: 1 promotes REM sleep without atonia and with locomotion; the other promotes atonia during REM sleep.[29,30] The additional degeneration in PD of neurons in the brainstem, which promote REM sleep without atonia, might therefore cancel the effect of heightened phasic discharge of the internal segment of the globus pallidus secondary to

Table 3—Results of IPT-SPECT (IPT binding ratio) in patients with subclinical and clinically manifest RBD, PD, and controls. Results (mean±SD) of patients with subclinical RBD were compared with those of clinically manifest RBD, controls, and PD patients.

		Subclinical RBD N, 8	Clinically manifest RBD N, 8	Controls N, 11		PD N, 8
Brain region imaged					Contralateral	Ipsilateral
Striatum	R	3.56 ± 0.21	3.18 ± 0.43 P = 0.038	4.07 ± 0.29 P = 0.002	2.51±0.28 P* < 0.0001	3.25±0.35 P* = 0.065
	L	3.55 ± 0.25	3.20 ± 0.43 P = 0.083	4.07 ± 0.30 P = 0.001	P** < 0.0001	P** = 0.083
Caudate	R	3.95 ± 0.26	3.53±0.41 P = 0.028	4.38±0.38 P = 0.020	3.13±0.34 P* = 0.001	3.86±0.46 P* = 0.721
	L	3.85 ± 0.26	3.66±0.53 P = 0.382	4.46±0.32 P = 0.001	P** = 0.001	P** = 0.878
Putamen	R	3.48 ± 0.32	3.09±0.55 P = 0.161	4.02±0.20 P < 0.0001	1.86±0.31 P* < 0.0001	2.77±0.37 P* = 0.002
	L	3.45 ± 0.35	3.05±0.47 P = 0.130	3.97±0.37 P = 0.007	*P** < 0.0001*	P** = 0.002
Putamen/caudate	R	0.88 ± 0.07	0.87 ± 0.1 P = 0.574	0.91±0.07 P = 0.129	0.59 ± 0.06 P* < 0.0001	0.72 ± 0.09 P* < 0.0001
	L	0.90 ± 0.07	0.84 ± 0.11 P = 0.161	0.90 ± 0.01 P = 0.968	P** < 0.0001	P** < 0.0001

IPT-SPECT, (N)-(3-iodopropene-2-yl)-2beta-carbomethoxy-3beta-(4-chlorophenyl) tropane labeled with iodine 123 using single-photon emission computed tomography; REM, rapid eye movement; RBD, REM sleep behavior disorder; PD, Parkinson disease, stage Hoehn and Yahr I; R, right; L, left; P, comparison of patients with subclinical RBD to controls and patients with RBD; P*, comparison of the right side of patients with subclinical RBD to patients with PD; P**, comparison of the left side of patients with subclinical RBD to patients with PD; Ipsilateral, striatal IPT-binding reflecting the asymptomatic side of the body; Contralateral: striatal IPT-binding contralateral to the symptomatic side of the body

dopamine cell loss in the substantia nigra. Conversely, additional degeneration of neurons in the brainstem, which promote REM sleep with atonia, might promote RBD. This hypothesis might explain why only certain patients with PD are affected by RBD. The observation that multiple system atrophy is frequently associated with RBD[5] also supports the concept of degeneration. Our results demonstrate that striatal presynaptic dopamine transporters correlate significantly and negatively with long-lasting muscle activity during REM sleep. Moreover, reduced striatal dopamine transporters are not only relevant in patients with PD and clinically manifest RBD, but also in patients with subclinical RBD. The reduction of striatal dopaminergic neurons may play a role in the development of idiopathic clinically manifest RBD or subclinical RBD; the last is indicated solely by increased muscle activity during REM sleep. Of course, undetected pathologies occurring in parallel with nigrostriatal dopamine cell loss may be more relevant than what can be readily measured by imaging techniques. But, in spite of the latter hypothesis, our results of decreased IPT binding, which correlates with increased muscle activity during REM sleep, in combination with the results of Schenck and collegues,[4] suggest that subclinical RBD may be the initial manifestation of an otherwise asymptomatic phase of PD or multiple system atrophy. These patients need to be followed in a further study.

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