REM Sleep Behavior Disorder in Patients With Guadeloupean Parkinsonism, a Tauopathy

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Study objective: To describe sleep characteristics and rapid eye movement (REM) sleep behavior disorder in patients with Guadeloupean atypical parkinsonism (Gd-PSP), a tauopathy resembling progressive supranuclear palsy that mainly affects the midbrain. It is possibly caused by the ingestion of sour sop (corossol), a tropical fruit containing acetogenins, which are mitochondrial poisons.

Design: Sleep interview, motor and cognitive tests, and overnight video-polysomnography.

Patients: Thirty-six age-, sex-, disease–duration- and disability-matched patients with Gd-PSP (n = 9), progressive supranuclear palsy (a tauopathy, n = 9), Parkinson disease (a synucleinopathy, n = 9) and controls (n = 9).

Settings: Tertiary-care academic hospital.

Results: REM sleep behavior disorder was found in 78% patients with Gd-PSP (43% of patients reported having this disorder several years before the onset of parkinsonism), 44% of patients with idiopathic Parkinson disease, 33% of patients with progressive supranuclear palsy, and no controls. The percentage of muscle activity during REM sleep was greater in patients with Gd-PSP than in controls (limb muscle activity, 8.3%±8.7% vs 0.1%±0.2%; chin muscle activity, 24.3%±23.7% vs 0.7%±2.0%) but similar to that of other patient groups. The latency and percentage of REM sleep were similar in patients with Gd-PSP, patients with Parkinson disease, and controls, whereas patients with progressive supranuclear palsy had delayed and shortened REM sleep.

Conclusion: Although Gd-PSP is a tauopathy, most patients experience REM sleep behavior disorder. This suggests that the location of neuronal loss or dysfunction in the midbrain, rather than the protein comprising the histologic lesions (synuclein versus tau aggregation), is responsible for suppressing muscle atonia during REM sleep. Subjects with idiopathic REM sleep behavior disorder should avoid eating sour sop.

Keywords: Synucleinopathy, tauopathy, REM sleep behavior disorder, parasomnia, REM sleep without atonia, parkinsonism, Guadeloupean PSP-like parkinsonism, progressive supranuclear palsy, Parkinson's disease, annonacin

Citation: Cochen de Cock V; Lannuzel A; Verhaeghe S; Roze E; Ruberg M; Derenne JP; Willer JC; Vidailhet M; Arnulf I. REM sleep behavior disorder in patients with guadeloupean parkinsonism, a tauopathy. *SLEEP* 2007;30(8):1026-1032.

INTRODUCTION

A NEW, ABNORMALLY FREQUENT, FORM OF ATYPICAL PARKINSONISM WAS DESCRIBED IN 1999 ON THE FRENCH CARIBBEAN ISLAND OF GUADELOUPE.[1, 2] A detailed clinical analysis of 160 successive patients seen in the neurology department of the University Hospital in Pointe-à-Pitre, Guadeloupe, showed that one third of the patients had a progressive supranuclear palsy-like syndrome (Gd-PSP), consisting of levodopa-resistant parkinsonism associated with early postural instability and supranuclear oculomotor dysfunction.[3] These patients differed, however, from patients with classic progressive supranuclear palsy by the frequency of tremor (> 50%), dysautonomia (50%), and the occurrence of complex visual hallucinations (59%). The neuropathologic profiles of 3 Gd-PSP cases that had come to autopsy were also reminiscent of progressive supranuclear palsy. There was diffuse accumulation of tau protein and threads in the deep layers of the isocortex, anterior cingulum, hippocampus, parahippocampal gyrus, striatum, thalamus, nucleus basalis of Meynert, subthalamic nucleus, mesencephalic tegmentum, locus coeruleus, nuclei pontis, transverse fibers of the pons, cerebellum, and dentate nucleus.[2] Interestingly, Gd-PSP was related to the ingestion of mitochondrial respiratory inhibitors (acetogenins) contained in the fruit and infusions of leaves of *Annona muricata* (corossol, sour sop).[4-6] Infusions of sour-sop leaves and sour-sop extracts, including widely available commercial preparations, are traditionally used in Guadeloupe and other tropical countries against fatigue and impotence (Figure 1). Rats intoxicated with annonacin, the major acetogenin in sour sop, develop a neurodegeneration in the basal ganglia reminiscent of atypical parkinsonism.[7]

Patients with Gd-PSP and their spouses report insomnia and dream enactment and violence during sleep, which is suggestive of rapid eye movement (REM) sleep behavior disorder (RBD).[3] RBD is characterized by vigorous movements and increased muscle activity corresponding to enacted dreams and loss of normal atonia during REM sleep.[8] Chronic RBD can be idiopathic or symptomatic of other neurologic diseases, whether autoimmune (narcolepsy,[9] autoimmune encephalitis,[10] Guillain-Barré syndrome[11]), neurodegenerative (Parkinson disease,[12] multiple system atrophy,[13] dementia with Lewy bodies[14]) or genetic (*parkin* gene mutation,[15] spinocebellar ataxia[16]). As many as two thirds of middle-aged subjects with idiopathic RBD develop parkinsonism (mainly a synucleopa-

Disclosure Statement

This was not an industry supported study. Dr. Cochen De Cock has participated in speaking engagements for GlaxoSmithKline. Dr. Arnulf has received research support from GlaxoSmithKline, Bioproject, and Boehringer Ingelheim and has participated in speaking engagements for Cephalon and Schwartz Pharma. Drs. Lannuzel, Verhaeghe, Roze, Ruberg, Derenne, Willer, and Vidailhet have indicated no financial conflicts of interest.

Submitted for publication November, 2006
Accepted for publication March, 2007

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Table 1—Clinical Characteristics of Patients with Guadeloupean parkinsonism and Age-, Sex- and Disability-matched Patients with Progressive Supranuclear Palsy, Patients with Idiopathic Parkinson Disease, and Controls.

Patients	Gd-PSP	PSP	PD	Controls	P
No.	9	9	9	9	
Age, mean, y	66.6±10.1	66.1±8.8	69.8±7.2	66.9±9.5	NS
Sex, men, no.	6	6	6	6	NS
Body mass index, kg/m^2	24.2±3.6	23.7±3.0	19.6±9.7	26.8±6.0	NS
Disease duration, y	6.8±4.0	5.1±2.6	5.6±2.7	NA	NS
Motor disability, UPDRS-III	39±14	38±19	30±13	NA	NS
Use of dopamine agonists, %	33.3	22.2	55.6	NA	NS
Dopa-equivalent dose, mg/d	424±270	270±310	439±201	NA	NS
Use of benzodiazepine, %	33.3	33.3	33.3	33.3	NS
MMSE, score	21.4±5.7	21.6±6.2	27.1±1.7	NA	0.05
ESS, score	8.4±6.0	5.5±3.4	7.0±4.4	6.7±5.6	NS
Clinical RBD, %	77.8[ab]	11.1	44.4	0	0.002

Data are presented as mean ± SD unless otherwise indicated. PD refers to Parkinson disease; Unified Parkinson Disease Rating Scale, UPDRS; MMSE, Mini Mental State Examination; ESS, Epworth Sleepiness Scale; RBD, REM (rapid eye movement) sleep behavior disorder.
[a]$p < 0.01$ for a difference between patients with Guadeloupean parkinsonism (Gd-PSP) and progressive supranuclear palsy (PSP)
[b]$p < 0.01$ for a difference between patients with Gd-PSP and controls; UPDRS-III: Unified Parkinson's Disease Rating Scale-part III.

thy rather than a tauopathy) within 5 to 13 years,[17,18] making neuroprotection a future challenge in these patients. However, the frequency of symptomatic RBD is variable in patients with neurodegenerative diseases. RBD occurs in 33% to 100 % of patients with synucleinopathies (the highest frequencies being observed in dementia with Lewy body disease and multiple system atrophy[14]) but are rare in patients with tauopathies such as Alzheimer disease,[19] frontotemporal dementia, corticobasal degeneration,[14] and familial pallidopontonigral degeneration.[20] However, we recently reported that 27% of patients with progressive supranuclear palsy, a tauopathy, had REM sleep without atonia and 13% had clinical RBD.[21] Since sleep has not yet been described in Gd-PSP patients, we conducted a prospective study of nighttime sleep in 9 patients with Gd-PSP, compared with the sleep of patients with other parkinsonian syndromes, the tauopathy progressive supranuclear palsy, and idiopathic Parkinson's disease, a synucleinopathy.

Figure 1—The fruits and leaves of sour sop (the green fruits with blunted prickles placed between tomatoes and bananas) are used for culinary and medicinal purposes. They contain annonacin, a mitochondrial poison associated with atypical parkinsonism (and rapid eye movement sleep behavior disorder) in the French West Indies.

METHODS

Subjects

Between December 2005 and March 2006, 10 African-Caribbean patients from Guadeloupe were brought to Paris, with their informed consent, for sleep monitoring in the sleep department of the Pitié-Salpêtrière University Hospital. Nine patients, 3 women and 6 men, completed the study. They were selected from a group of 51 patients (mean age 73.9± 1 years, 37 men) with Gd-PSP recruited prospectively in the neurology department of the University Hospital of Pointe-à-Pitre between September 2003 and September 2005 on their ability to travel from Pointe-à-Pitre to Paris without medical assistance. As previously described,[3] all of these patients had features characteristic of supranuclear palsy, such as (1) levodopa-unresponsive parkinsonism, (2) major frontal dysfunction, (3) early postural instability or falls, and (4) supranuclear oculomotor dysfunction; they also had (1) hallucinations and/or delusions or (2) severe autonomic dysfunction, which are considered exclusion criteria for progressive supranuclear palsy. One patient was subsequently excluded because she removed the electrodes after 1 hour of sleep monitoring and was too confused to continue the study. Patients with idiopathic Parkinson disease (n = 9) and progressive supranuclear palsy (n = 9) matched for age, sex and Unified Parkinson Disease Rating Scale-III scores were selected from groups of 200 and 30 patients, respectively, participating in a sleep research program on these diseases. Their characteristics are summarized in Table 1. Nine age- and sex-matched controls with no neurologic or known sleep diseases were selected from a series of 104 subjects seen in the department of internal medicine for a suspicion of pulmonary embolism that was not confirmed (Table 1). None of the patients or controls took antidepressants, which are known to induce RBD.

Table 2—REM Sleep Behavior Disorder as Reported by 7 of 9 Patients with Guadeloupean Parkinsonism and Observed by Videopolysomnography

Patient	Clinical RBD	Dream contents associated with RBD at home	Onset of RBD/ parkinsonism	RBD in VPSG	Enhanced muscle tone, % REM sleep	
					Chin	Limbs
1	Yes	I dreamed I was being attacked, I shouted in my sleep.	At the same time	Kicking, punching	5.7	10.5
2	Yes	A buffalo herd charged at me. I shouted and tried to flee.	Before	Laughing, talking Shouting	33.8	7.4
3	Yes	I have conversations, make gestures.	Before	Excessive jerking of body and limbs	34.8	18.0
4	Yes	I fought with my cousin using a wooden stick to pick some oranges from a tree.	Unknown	None	69.8	3.8
5	Yes	I fought, kicked and punched.	Before	Kicking, punching	13.7	7.6
6	Yes	I called my dead wife during the night.	Unknown	Shouting	14.6	1.5
7	Yes	I shouted and woke up sitting up on my bed, punching.	After	Kicking	46.2	25.6

RBD refers to rapid eye movement (REM) sleep behavior disorder (RBD); VPSG, videopolysomnography.

Study Design

Each patient was examined in the sleep laboratory. The protocol included (1) a motor interview and evaluation of the part III of the Unified Parkinson's Disease Rating Scale;[22] (2) a semistructured sleep interview of the patient and his or her caregiver, based on the sleep disorder diagnosis criteria,[23] including the Epworth Sleepiness Scale,[24] and a semistructured interview about clinical RBD; (3) a cognitive examination, including the Mini-Mental State Examination[25] and the frontal assessment battery;[26] (4) and nighttime sleep monitoring. The controls had the sleep interview, the Mini-Mental State Examination and nighttime sleep monitoring. Nighttime videopolysomnography included Fp1-Cz, O2-Cz, and C3-A2 electroencephalography (EEG); right and left electrooculograms; surface electromyogram of the levator menti, right and left tibialis anterior, right extensor radialis muscles; nasal pressure through cannula; tracheal sounds through a microphone; thoracic and abdominal belts to assess respiratory movements; electrocardiography; pulse oximetry; EEG-synchronized infrared videography; and ambiance microphone. The sleep stages, arousals, periodic leg movements, and respiratory events were scored by visual inspection according to standard criteria, as previously described.[21] REM sleep was scored in all subjects on the basis of EEG (theta-alpha mixed background with saw-tooth waves) and eye movements, since the absence of muscle atonia in patients with RBD may lead to an underestimation of REM sleep. Background EEG activity during wakefulness on O2-Cz EEG and chin and limb muscle activity were also quantified in the evening during a period of quiet wakefulness, with the occipitocentral lead using a fast Fourier transformation. Since there is no consensus as to how to measure enhanced muscle activity during REM sleep,[23] we quantified, second by second, tonic or phasic muscle activity on chin electromyogram with amplitudes greater than or equal to the amplitude observed during quiet wakefulness. We excluded muscle arousals (spontaneous or secondary to sleep apnea) and asymptomatic motoneuron discharges. None of the patients had "snoring artifacts," which are inspiration-associated chin-muscle bursts during snoring. The duration of REM sleep with enhanced muscle activity was then divided by the total duration of REM sleep to obtain the percentage of REM sleep without chin atonia. Limb muscle activity (by definition phasic rather than tonic, but all activities were counted) was measured second by second on the leg (tibialis anterior) and the arm (extensor radialis) electromyograms as a transient and frank elevation of muscle tone. Leg muscle activity, defined as aperiodic nonstereotyped movements, was distinguished from periodic leg movements. The duration of limb muscle activity was also divided by total REM sleep to obtain the percentage of limb muscle activity during REM sleep. This method of scoring that measures muscle activity, second by second, may detect differences between controls and patients that would not be observed with other methods, such as that of Lapierre and Montplaisir.[27] We defined RBD on videopolysomnographies as purposeful complex movements and speech during REM sleep or as enhanced chin muscle activity during at least 20% of REM sleep, associated with a clinical history of enacted dreams, in accordance with the diagnostic criteria for RBD in the *International Classification of Sleep Disorders -2*.[23] Subclinical RBD was defined as enhanced chin muscle activity during at least 20% of REM sleep without history (or video) of enacted dreams.

Data Analysis

Analysis of variance was used to compare continuous measures in the 4 groups and between the Gd-PSP and control groups. The χ^2 test was used for noncontinuous measures. When the analysis of variance was significant (P less than 0.05), we performed a posthoc analysis by Bonferroni corrected t tests. Results were reported as mean ± SD (ranges).

Table 3—Nighttime Sleep in Controls and in Patients with Guadeloupean Parkinsonism, Progressive Supranuclear Palsy and Parkinson's Disease

Sleep measure	Gd-PSP	PSP	PD	Controls	P Value
Occipital alpha EEG rhythm, mean, Hz	8.1±1.4	8.9±1.5	9.5±0.7	10.0±2.4	0.16
Nighttime sleep, min					
Total sleep period	603±103[a]	544±53	510±86	477±77	0.02
Total sleep time	331±154	335±81	372±140	393±83	0.64
WASO	212±152	209± 101	138±71	84±84	0.046
Sleep efficiency%	55.2±22.4[a]	62.3±16.8	70.9±18.7	83.0±14.3	0.018
Latency to, min					
Sleep onset	73±120	27±31	45±34	27±22	0.40
REM sleep	138±155	266±135[c]	163± 126	93±47	0.04
Sleep stages, % total sleep time					
1	11.8±17.1	27.9±10.4[b,c,d]	7.3± 10.4	6.2±5.4	0.001
2	50.3±17.0	44.5± 15.3	53.5± 13.1	49.5± 16.6	0.67
3-4	23.9±15.9	21.1± 9.2	19.7± 5.8	21.2 ±14.3	0.90
REM	14.0±7.1	6.6± 5.2[c]	18.6± 9.4	19.1± 5.5	0.002
Sleep fragmentation with					
Arousals, no./h	23.0±29.6	54.5±29.7[d]	13.6± 15.1	29.9± 27.1	0.015
PLM, no./h	11.1±21.0	36.9± 35.1	20.2± 26.0	4.9± 10.4	0.08
AHI, no./h	5.8±13.9	24.4± 13.3	17.4± 19.2	5.8±10.0	0.02
Enhanced muscle tone during REM sleep					
Chin EMG, % REM sleep	24.3± 23.7[a]	24.9± 35.6	18.7± 24.9	0.7 ±2	0.15
Limb EMG, % REM sleep	8.3± 8.7[a]	2.6± 1.2	4.0± 8.2	0.1 ±0.2	0.005
Percentage of patients with					
Subclinical RBD	0	22.2	0	0	NA
History of RBD	77.8[b]	11.1	44.4	0	0.002
Video-RBD	77.8	33.3	44.4	0	0.008

P Value in the analysis of variance of the 4 conditions; $P < 0.05$ for a difference between patients with Guadeloupean parkinsonism (Gd-PSP) and [a]controls or [b]patients with progressive supranuclear palsy (PSP); $P < 0.05$ for a difference between patients with PSP and [c]controls, or [d]patients with Parkinson disease (PD). EEG refers to electroencephalogram; WASO, wake after sleep onset; REM, rapid eye movement; PLM, periodic limb movements; AHI, apnea-hypopnea index; EMG, electromyogram; RBD, REM sleep behavior disorder. Sleep efficiency: is the total sleep time divided by the total sleep period.

RESULTS

Clinical Interview and Examination

The main clinical characteristics of the patients and controls are summarized in Table 1. The patients with Gd-PSP (3 women and 6 men) were 53 to 83 years of age and had parkinsonism for 2 to 13 years. They were severely disabled, as shown by Unified Parkinson Disease Rating Scale-III scores of 39±14 (15-62) when optimally treated and had a less than 50% response to an acute challenge with levodopa. Four patients were treated with levodopa alone and 2with a combination of levodopa and dopamine agonists (1 with apomorphine and piribedil, and 1 with ropinirole). Two thirds of the patients had cognitive defects, defined by a score on the Mini-Mental State Examination less than or equal to 24 (range 9-22). All patients had clinical frontal signs, including grasping, imitation, and perseveration. Their score on the frontal assessment battery was 12±4.6 (3-16). Four patients had frontal scores less than or equal to 12.

By definition, age, sex, and motor disability were identical in all 3 patient groups (Table 1), as were disease duration and daily doses of levodopa equivalents. Patients with Gd-PSP and supranuclear palsy were less often treated with dopamine agonists than were patients with Parkinson disease, and they had more severe cognitive deficits. The scores on the Epworth Sleepiness Scale were similar in all groups. Three patients with Gd-PSP, 1 patient with supranuclear palsy, 1 with Parkinson disease, and 3 controls had scores higher than 10, indicating pathologic sleepiness.

Seven patients with Gd-PSP (78%, 5 men and 2 women) had clinical RBD (Table 2). Some examples of dreams reported by Gd-PSP patients when awakened during nighttime episodes of REM sleep behavior disorder at home are summarized in Table 2. Three of 7 Gd-PSP patients (43%) had experienced clinical RBD for several years before the onset of parkinsonism, although they could not say exactly when the RBD began. History of RBD was more frequent in patients with Gd-PSP than in those with progressive supranuclear palsy (11%, 1 man) or in controls (0%, Table 1) and was similar to the frequency in patients with Parkinson disease (44% patients, 3 men, 1 woman).

Waking EEG and Nighttime Sleep

Although the occipital alpha rhythm on waking EEG was similar in the different patient groups (Table 3), it was more often abnormally slow (< 8 Hz) in patients with Gd-PSP (78%) than in patients with Parkinson disease (22%), in patients with supranuclear palsy (22%), and in controls (0%, $P = 0.003$). Four patients with Gd-PSP, 3 patients with Parkinson disease, and 3 with supranuclear palsy, but no controls, slept less than 5 hours. Sleep efficiency (total sleep time/total sleep duration) was reduced in Gd-PSP patients compared with controls. Only patients with progressive supranuclear palsy had delayed, shortened REM sleep, increased percentages of stage 1 non-REM sleep, and increased

sleep fragmentation. The sleep characteristics of patients with Gd-PSP were similar to those or patients with Parkinson disease, except for a reduced sleep efficiency.

Motor Activity and Speech During Sleep

The percentage of REM sleep with enhanced limb and chin muscle activity was greater in patients with Gd-PSP than in controls (Table 3) but did not differ among the 3 groups of patients (Figure 2). In 4 patients with Gd-PSP (44%), the percentage of REM sleep without atonia (chin muscle) was greater than 20% of REM sleep time. This was also the case in 3 patients (33%) with Parkinson disease and 3 patients (33%) with supranuclear palsy but never in controls. Subclinical RBD was observed in 22.2% of patients with supranuclear palsy and in no patient with Gd-PSP or Parkinson disease. In the group with supranuclear palsy, the mean disease duration was 4.5 years in patients with no RBD, 6 years in those with subclinical RBD, and 8 years in the single patient with a history of RBD. In patients with Gd-PSP, the percentage of REM sleep with enhanced chin muscle tone tended to be higher than that of controls ($P = 0.051$), but it was not different from that of patients with Parkinson disease ($P = 0.64$) and supranuclear palsy ($P = 0.96$). Gd-PSP patients had higher limb muscle activity during REM sleep than did controls ($P = 0.006$) and patients with supranuclear palsy ($P = 0.053$) muscle activity was not different from that of patients with Parkinson disease ($P = 0.14$). The index of periodic leg movements during sleep was similar in the 4 groups using analysis of variance. Patients with Gd-PSP had periodic leg movement indexes lower than those of patients with supranuclear palsy ($P = 0.04$) but not different from that of patients with Parkinson disease ($P = 0.63$) and controls ($P = 0.46$). Video recordings showed that patients with Gd-PSP made simple and complex nonstereotyped movements of the hands, arms, and legs during REM sleep, including kicking and punching (Table 2). Some patients talked while making these movements, and 1 patient laughed out loud. Their speech during REM sleep contained correctly articulated and accented words, forming sentences with normal prosody and syntax that were suddenly interrupted either by silence or groaning. Of interest, some patients spoke easily during REM sleep, although they were dysarthric and hypophonic during the day.

Sleep-disordered Breathing

The apnea-hypopnea index tended to be greater in patients with supranuclear palsy than in the other groups. It was abnormal (> 10 per hour) in 1 patient with Gd-PSP, 6 patients with Parkinson disease, and 7 patients with progressive supranuclear palsy, but was abnormal in only 2 controls. The apnea-hypopnea indexes were not different in patients with Gd-PSP, as compared with controls ($P = 0.99$) and patients with Parkinson disease ($P = 0.1$), but they were lower than in patients with supranuclear palsy ($P = 0.01$).

DISCUSSION

Most patients with Gd-PSP (78%) reported mild insomnia and a complex elaborate RBD, which was confirmed by monitoring. The main limitation of this study was the small size of the sample. Gd-PSP is a rare, newly described disease that has only been documented so far on a small island with 422,000 inhabitants, where specific video-sleep monitoring is not available. The observations were, however, representative of the sleep disorders reported by the larger group of 51 Gd-PSP patients that we interviewed in Guadeloupe.[3] The patients were matched for age, sex, and motor disability but not for depression, cognitive status, or the intake of benzodiazepines. Benzodiazepine intake (given for anxiety) turned out to be similar, however, in all the groups of patients and controls. Depression was not evaluated for the purposes of this study, but none of the patients were taking antidepressant drugs. In addition, although depression is known to increase insomnia, it has not, to our knowledge, been shown to be associated with RBD. Not unexpectedly, patients with Gd-PSP and patients with supranuclear palsy, but not patients with Parkinson disease, were cognitively impaired. Cognitive impairment is a documented early characteristic of progressive supranuclear disease,[28] whereas it develops later in patients with Parkinson disease. It was, therefore, difficult to match the patients for both cognitive and motor status.

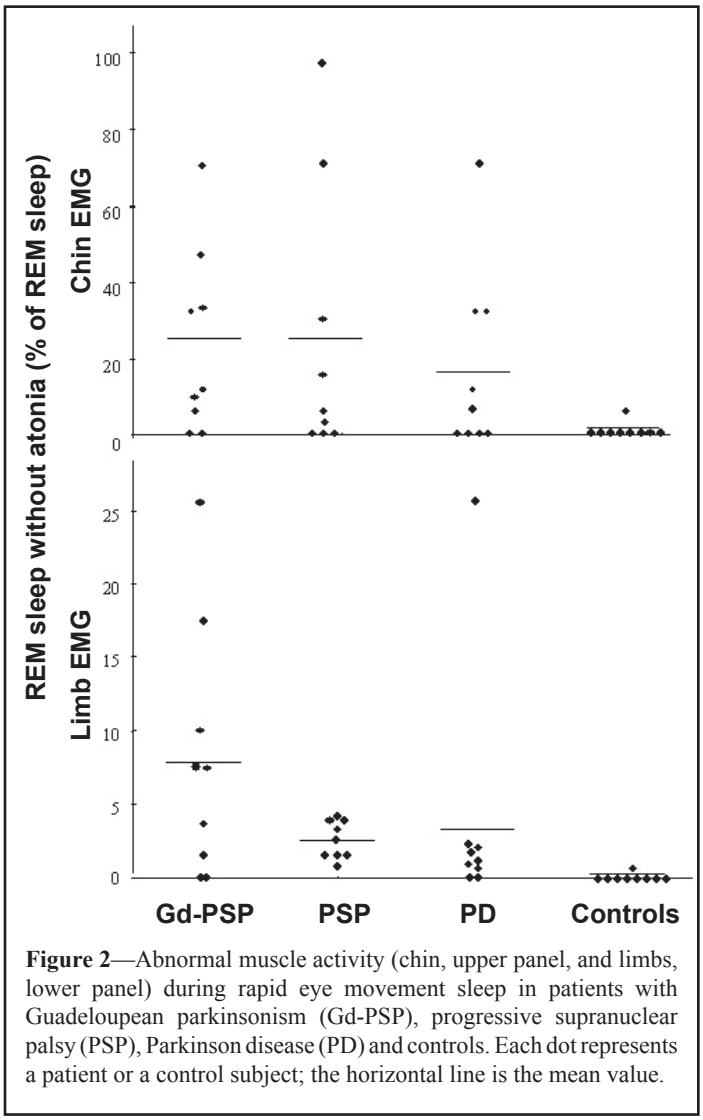

Figure 2—Abnormal muscle activity (chin, upper panel, and limbs, lower panel) during rapid eye movement sleep in patients with Guadeloupean parkinsonism (Gd-PSP), progressive supranuclear palsy (PSP), Parkinson disease (PD) and controls. Each dot represents a patient or a control subject; the horizontal line is the mean value.

REM sleep structure was similar in patients with Gd-PSP and those with Parkinson disease, in sharp contrast to the fragmented, shallow sleep structure with delayed, shortened REM sleep observed in patients with supranuclear palsy in this and other studies.[21,29-31] Therefore, although Gd-PSP and supranuclear palsy have a number of clinical features in common,[2] their sleep

is different. Patients with supranuclear palsy mostly have REM sleep without chin atonia (a condition also called asymptomatic RBD). In contrast, patients with Gd-PSP had full-blown RBD, including tonic muscle activity and phasic movements, which means a suppression of axial atonia during REM sleep but also the facilitation (or disinhibition) of behavioral release in REM sleep that results in clinical RBD.

The high frequency of RBD in Gd-PSP, a tauopathy, is closer to the frequencies observed in synucleinopathies such as multiple system atrophy (90%)[13] and dementia with Lewy bodies (86%)[14] than to the frequencies usually observed in tauopathies, such as supranuclear palsy (13%),[21] genetic pallidopontonigral degeneration (0%),[20] and Alzheimer disease (2-6.6%).[14, 19] This suggests that the location of the lesions in the brain, rather than the protein that forms the neuropathologic hallmark of the disease, is important for the genesis of RBD.

The lesions responsible for RBD in Gd-PSP might affect neurons responsible for both axial and limb muscle tone during REM sleep but spare the executive system controlling REM sleep. The possible location of the lesions might be inferred from animal studies.[32, 33] In these models, glycinergic neurons located in the medulla block the discharge of lower motor neurons in the spinal cord, causing atonia. They are stimulated by glutaminergic neurons in the pedunculopontine tegmentum (locus coeruleus alpha and perialpha in the cat)[32] and in the sublaterodorsal nucleus of the rat,[33] which are stimulated by cholinergic and GABAergic neurons. Lesions affecting any of these neurons could cause RBD. It is of note that tau protein accumulates in the region of the locus coeruleus, possibly encompassing the subcoeruleus nucleus.[2] This area should therefore be explored in the brains of patients with Gd-PSP and RBD. In addition, since Guadeloupean parkinsonism is reminiscent of the one described in Guam (another atypical parkinsonism highly prevalent in a tropical island), it would be interesting to look for RBD in Guam.

Interestingly, intravenous infusions of annonacin, the major acetogenin in sour sop, induces, in rats, a significant loss of dopaminergic neurons in the substantia nigra and cholinergic and GABAergic neurons in the striatum, as well as a significant increase in the number of astrocytes and microglial cells in these regions.[7] Since the neurons responsible for REM sleep atonia in animal models contain choline[34] and GABA,[33] they may be particularly vulnerable to this putative toxin. It would be interesting to determine whether sleep is affected in annonacin-intoxicated rats, which might then provide a model of RBD. Available models reproduce either RBD (by acute focal lesions) with no parkinsonism[32, 33] or parkinsonism with sleep disorder but no RBD.[35-38]

Finally, RBD precedes the onset of Gd-PSP by several years in 43% of the patients, as in idiopathic Parkinson disease and multiple system atrophy. Sleep specialists diagnosing idiopathic RBD should, therefore, pay particular attention to patients of African-Caribbean origin and ask about culinary or medicinal use of sour sop. Although the role of sour-sop toxicity in Guadeloupean atypical parkinsonism is still hypothetical, the consumption of annonaceous products should probably be discouraged.

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