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Abnormal Findings in Polysomnographic Recordings of Patients with Spinocerebellar Ataxia Type 2 (SCA2)

Alessandra Zanatta[1] · Carlos Henrique Ferreira Camargo[2] · Francisco Manoel Branco Germiniani[1] · Salmo Raskin[3] · Ana Chrystina de Souza Crippa[4] · Hélio Afonso Ghizoni Teive[1]

Abstract

Spinocerebellar ataxia type 2 (SCA2) is characterized by a progressive cerebellar syndrome, and additionally saccadic slowing, cognitive dysfunction, and sleep disorders. The aim of this study was to assess the frequency of abnormal findings in sleep recordings of patients with SCA2. Seventeen patients with genetically confirmed SCA2 from the Movement Disorders Outpatient group of the Hospital de Clínicas da UFPR were evaluated with a structured medical interview and the Scale for the Assessment and Rating of Ataxia (SARA). Polysomnographic recordings were performed and sleep stages were scored according to standard criteria. There were 10 male subjects and 7 females, aged 24–66 years (mean 47.44). A sex- and age-matched control group of healthy subjects was used for comparison. There was a reduction of rapid eye movement (REM) sleep in 12 (70.58%), increased REM latency in 9 (52.94%), increased obstructive sleep apnea-index in 14 (82.35%), absent REM density (REM density was calculated as the total number of 3-s miniepochs of REM sleep with at least 1 REM per minute) in 13 (76.47%), and markedly reduced REM density in 4 (23.52%). There was an indirect correlation according to the SARA scale and the REM density decrease ($r = -0.6$; $P = < 0.001$); and with a disease progression correlating with a reduction in the REM density ($r = -0.52$, $P = 0.03$). In SCA2, changes occur mainly REM sleep. The absence/decrease of REM sleep density, even in oligosymptomatic patients, and the correlation of this finding with disease time and with the SARA scale were the main findings of the study.

Keywords SCA · SCA2 · Spinocerebellar ataxia · Spinocerebellar ataxia 2 · Sleep disorders · REM sleep disorder · REM density · Polysomnography

Introduction

Autosomal dominant cerebellar degenerative diseases are known as spinocerebellar ataxias (SCAs) [1]. Currently, 43 types of SCAs have been described, with more than 30 loci identified [2], which were named according to the chronology of their description from SCA type 1 (SCA1) to SCA43 [3, 4]. Spinocerebellar ataxia type 2 (SCA2) is a polyglutamine disease caused by abnormal expansion of CAG triplet repetitions in the coding region of the *ATXN2* gene (12q24.1) [5]. It is the

✉ Alessandra Zanatta
lezanatta@yahoo.com

Carlos Henrique Ferreira Camargo
chcamargo@uol.com.br

Francisco Manoel Branco Germiniani
frankgerminiani@hotmail.com

Salmo Raskin
salmoraskin@icloud.com

Ana Chrystina de Souza Crippa
anacrippa@ufpr.br

Hélio Afonso Ghizoni Teive
hagteive@mps.com.br

[1] Movement Disorders Unit, Neurology Service, Hospital de Clínicas, Federal University of Parana, Rua General Carneiro, 181 - Alto da Glória, Curitiba 80060-900, Brazil

[2] Neurology Service, Hospital Universitário Regional dos Campos Gerais, State University of Ponta Grossa, Ponta Grossa, Brazil

[3] Advanced Molecular Research Center, Center for Biological and Health Sciences, Catholic University of Parana, Curitiba, Brazil

[4] Epilepsy and Sleep Disorders Unit, Hospital de Clínicas, Federal University of Parana, Curitiba, Brazil

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second most common autosomal dominant cerebellar ataxia worldwide [6–8], but in some countries like India, Cuba, South Korea, Italy, and Mexico, it is one of the most frequent forms. The province of Holguin in Cuba has the highest prevalence in the world of SCA2, about 40 cases per 100,000 inhabitants, associated with a founder effect [2, 9]. In Brazil, SCA2 is the second most commonly found type, accounting for about 4 to 8% of cases [6, 7].

SCA2 is clinically characterized by a progressive cerebellar syndrome, as all patients present with gait ataxia, postural instability, dysmetria, cerebellar dysarthria, and dysdiadochokinesia, features that can be accompanied by slowing of horizontal saccadic eye movements [10, 11]. Slowing saccadic movements may be associated with injury to the pons reticulotegmental nucleus (PRTN) or Bechterew nucleus. PRTN is an important precerebellar nucleus and is part of the oculomotor circuit responsible for the generation and accuracy of horizontal saccadic movements. The neuropathological hallmark of SCA2 is early olivopontocerebellar atrophy associated with changes in the basal ganglia, brainstem, spinal cord, optic nerves, retina, and peripheral nerves [10–14].

Other commonly described signs and symptoms are cognitive impairment, peripheral neuropathy with fasciculations, and sleep disorders. Sleep disturbances are common in neurodegenerative diseases such as spinocerebellar ataxias [15–17].

In patients with SCA3, REM sleep behavior disorder (RBD) is highly prevalent, present in up to 50% of individuals throughout the disease, and may even precede the onset of cerebellar symptoms, and the frequency of excessive daytime drowsiness (EDD) is high. In addition, other sleep disorders have been reported, such as obstructive sleep apnea, insomnia, nocturia, and hallucinations hypnagogic [18]. Rueda et al. [19] in a study with 12 patients with SCA6 found greater incidence of sleep respiratory disorders in patients than in controls. The restless leg syndrome (RLS) and periodic leg movement (PLM) have been described in some forms of SCA, with a higher prevalence in SCA1, SCA2, SCA3, SCA4, and SCA6 [20]. Moro et al. [21] studied the incidence of non-motor symptoms in SCA10 and found that RBD and RLS were unusual in SCA10.

The aim of this study was to assess the frequency of abnormal findings in sleep recordings of patients with SCA2 in our group.

Methods

Seventeen patients with genetically confirmed SCA2 from the Movement Disorders Outpatient Group of the Hospital de Clínicas of the Federal University of Paraná selected between March 2015 and May 2016 were evaluated. The study procedures were approved by the HC-UFPR University Ethics Committee, and informed consent was obtained from all participants. SCA2 patients with respiratory diseases or cognitive or behavioral alterations were not included because these disorders would not allow for a technically adequate polysomnography performance.

A control group for the polysomnography examination consisted of 17 healthy volunteers with no history of neurological disease or complaints of sleep disorders, matched for gender, age, and body mass index (BMI).

Clinical Evaluation

All the subjects and their bed partners were interviewed with regard to their subjective sleep quality, nocturnal cramps, dream recall and content (nightmares), complex or aggressive behavior during sleep, sensory and motor complaints during sleep, sleep-related self-injuries or injuries to their bed partners, vocalizations, somniloquy, bruxism, and snoring. Patients completed the REM Sleep Behavior Disorder Single-Question Screen (RBD1Q) [22] and the Epworth Sleepiness Scale (ESS) [23] to document daytime sleepiness. Physical and neurological examination was performed by a certified neurologist and sleep physician; the patients were scored for the severity of their ataxia according to the Scale for the Assessment and Rating of Ataxia (SARA), which ranged from a total score of 0 (no ataxia) to 40 (most severe ataxia) [24].

Polysomnography

Polysomnography (PSG) was performed with a standardized 21-channel montage (Polysmith Software, QP-260AK, Nihon Kohden), 2 electrooculogram channels, 1 electromyogram channel, 6 electroencephalogram channels, 2 nasal airflow channels, 2 respiratory effort channels, 1 oximetry channel, 2 snore detector channels, 1 electrocardiography channel, 1 pulse transit time channel, 1 body position channel, and 2 limb movement sensors placed on the right and left leg. Video-polysomnographic (VPSG) recordings were performed with a digital polygraph (polysmith) using a standard montage which included electroencephalographic (EEG) recording with a montage using F3, F4, C3, C4, O1, and O2 electrodes referred to the contralateral ear, vertical e horizontal electrooculography, electrocardiography and electromyography (EMG) of mental and both tibialis anterior muscles. Respiration monitoring included nasal airflow, tracheal microphone, thoracic and abdominal respiratory effort bands, and oxygen saturation. Analysis of polysomnographic data was made according to standard criteria [25–28]. REM sleep was scored if signs of REM sleep were present (e.g., rapid eye movements, typical mixed frequency, low amplitude EEG, or sawtooth waves). Eye movements in REM sleep

were counted visually. REM density was calculated as the total number of 3-s miniepochs of REM sleep with at least 1 REM per minute [29, 30].

All patients were free of medications known to influence either sleep architecture, EEG, or motor activity. Three patients were using antidepressants (amitriptyline, bupropion, and fluoxetine), and one of them was also using clonazepam. They were instructed to tapper off these medications and stop them completely a fortnight prior to the sleep study. All data were scored independently by two experienced board certified sleep physicians (interrater agreement > 90%).

For the calculation of REM sleep density, the procedures described by Tuin et al. (2006) were modified [29]. Each 30-s time or page of the REM sleep polysomnographic examination was divided into ten miniepochs of 3 s (ten periods of 3 s in each epoch). Rapid eye movements (REM) were visually identified, and all REMs that occurred in each miniepoch were counted as a single REM. The total number of these eye movements was divided by the time in minutes of REM sleep. Thus, the term "REM sleep density" in the study means the number of miniepochs with rapid eye movements per minute of REM sleep (Fig. 1).

AASM criteria and ICSD-3 were used to assess REM sleep atonia, RBD, RLS, PLM, and sleep respiratory disorders [26, 31].

Statistical Analysis

The data were stored in a database of the program Microsoft Excel 2015. For the statistical analysis, the software SPSS 19.0 for Windows was used. With the Shapiro Wilk and Komogorov Smirnov tests, the variables were analyzed in relation to the distribution pattern. In the description of quantitative variables with normal distribution, mean and standard deviation (SD) or median and interquartile range (IR) were used in the non-normal distribution variables. For qualitative variables, absolute numbers and percentage frequencies were used. In the comparative analysis of the qualitative variables in the two groups, Fisher's exact test was used, whereas for comparison of the variables in the two groups, the Student's *t* test was used for the continuous variables with normal distribution. The Mann-Whitney test was applied in the evaluation of continuous variables with non-normal distribution. Pearson's coefficient was used for correlation. The level of significance was set at 5% ($p < 0.05$).

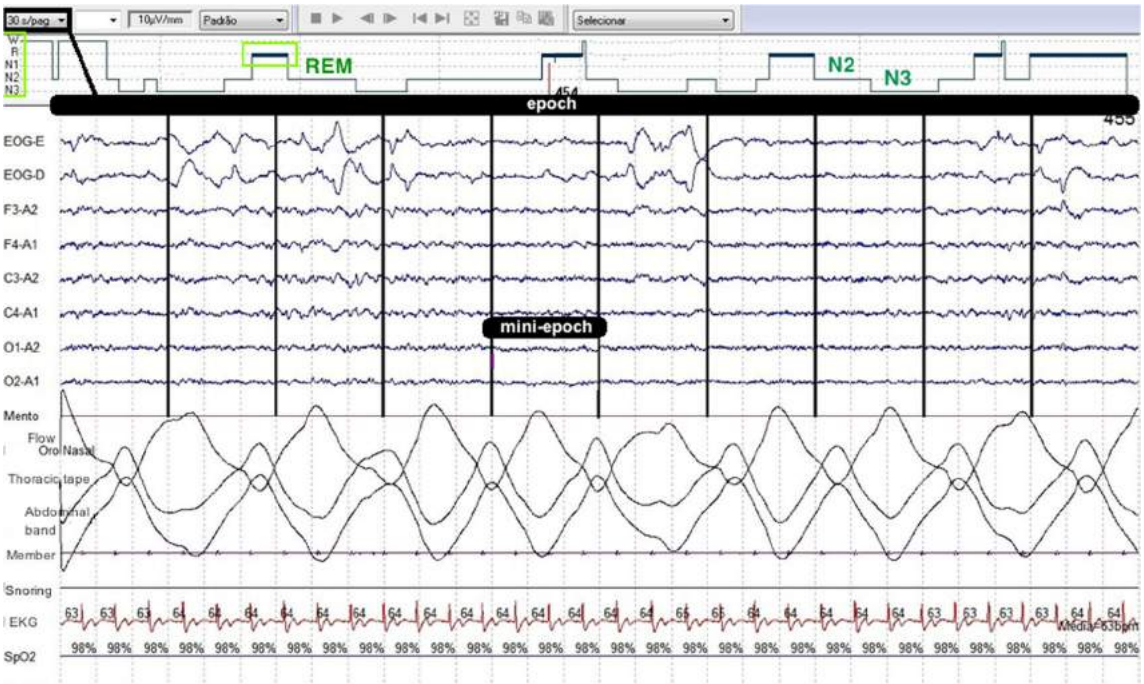

Fig. 1 Fragment with miniepochs divisions used for analysis of sleep parameters. EOGe and EOGd = left and right electrooculogram channel; electroencephalogram (EEG) channels = F3, F4, C3, C4, O1, and O2; F3 = EEG electrode located on the left frontal region; F4 = EEG electrode located on right frontal region; C3 = EEG electrode located on the left central region; C4 = EEG electrode located on the right central region; O1 = EEG electrode located on the central region; A1 and A2 = electrodes used as reference, A1 = left ear and A2 = right ear; Mento = submental electromyography; Oro/nasal flow = channel for air flow; thoracic tape = channel shows the signal of the type sensor placed in the chest, evaluates the respiratory effort; abdominal band = channel shows the signal of the band-type sensor placed in the abdomen, evaluates the respiratory effort; member = channel of electromyogram of lower limbs; snoring = snoring sensor channel; ECG = electrocardiogram lead channel; SpO2 = oxyhemoglobin saturation channel; miniepochs are brief periods of consecutive 3 s sampled from each epoch of polysomnographic tracing. SOURCE: the author

Results

Clinical Characteristics Seventeen patients with SCA2 who belonged to seven different families were studied. Family history could not be confirmed for patient 15, as she had been adopted. All subjects presented with ataxia and reported cramps predominantly nocturnal, 14 with dysarthria, 11 with dysmetria and dysdiadochokinesia. Cerebellar tremor was present in 10 cases. No patient had symptoms of parkinsonism. Slow horizontal saccades were observed in 11 patients; however, nystagmus was absent in all of the study subjects. Additionally, 14 patients (82.35%) had either absent or reduced deep tendon reflexes on neurological examination. SARA scores ranged from 2 to 26 (Table 1). Fifteen cases reported good sleep quality, six patients complained of excessive daytime sleepiness, but the Epworth daytime sleepiness scale showed a score above the 10 points cutoff in only three cases.

Five (29.41%) patients reported having had the sensation of experiencing (acting-out) their dreams while they slept and three of these patients reported having already caused injury to the bed partner. Nevertheless, none had presented these events in the last 6 months.

VPSG Measures REM sleep presented some abnormal findings in all patients in the study group: reduction of REM sleep in 12 (70.58%), increased REM latency in 9 (52.94%), absent REM density in 13 (76.47%), and markedly reduced REM density in 4 (23.52%). Increased arousal index was observed in 12 (70.58%), there was no statistical difference between spontaneous and apnea-related arousals, increased obstructive sleep apnea-index in 14 (82.35%), and increased latency of sleep in 13 patients (76.47%). No patient showed abnormal PLM indexes or increased muscle-tone during REM sleep. Higher numbers of abnormalities in polysomnographic recordings were found in more severely compromised subjects according to the SARA scale. Table 2 shows the demographic characteristics and the sleep scoring parameters measured in both SCA2 patients and healthy controls. Disease duration had a highly significant correlation with the decrease in the percentage of REM.

Comparison of sleep parameters between SCA2 patients and controls demonstrated a significant reduction in total sleep time, sleep efficiency, sleep latency, sleep N3 latency, REM quantity, N2 quantity, and N3 quantity and markedly in REM density. Disease duration was correlated with decreased sleep efficiency ($p = 0.02$) and reduction of REM density ($p = 0.03$), so that the longer the disease, the more affected were these parameters; whereas the higher the scores in the SARA scale, the more pronounced was the reduction of REM density ($p = 0.0094$) (Table 3).

Discussion

The main finding of this study was the absence of REM density in 13 (76.47%) subjects and marked reduction of REM density in the remaining. Although few previous studies have reported abnormalities in REM sleep density in SCA2 patients [10, 29], none of them showed the important degree of REM reduction during REM sleep in patients with a short-time of disease evolution, and who presented mild clinical

Table 1 Data of the clinical history of patients with SCA2

Family	Patient	CAG repeats	Age on onset (years)	Disease duration (years)	SARA
Family 1	1	16/48	46	1	14
	2	20/46	38	10	13
	3	22/40	32	13	17.5
	4	21/38	49	0.5	7
	12	22/56	52	14	16.5
	17	22/48	33	21	18
Family 2	5	22/52	34	3	4.5
	6	20/39	26	4	9
	10	23/56	32	0.5	2
	11	23/54	45	17	18
Family 3	7	20/37	32	12	18
	16	22/48	49	2	4
Family 4	9	20/48	40	16	7.5
	13	23/52	38	3	12
Family 5	8	22/37	42	17	26
Family 6	14	22/58	30	14	13
Family 7	15	21/47	17	7	18

Table 2 Comparison between SCA2 patients and controls

	SCA2 patients $n = 17$	Controls $n = 17$	p
Sex			1
Male	10 (58.82%)	10 (58.82%)	
Female	7 (41.17%)	7 (41.17%)	
Age (mean/SE)	46.47 ± 11.41	46.05 ± 11.23	0.91
BMI (mean/SE)	28.44 ± 5.98	27.91 ± 5.48	0.79
Polysomnographic parameters			
PT (min)	460.85 ± 34.12	519.95 ± 19.75	< 0.001
TST (min)	335.59 ± 72.17	445.22 ± 47.62	< 0.001
Sleep efficiency (%)	70.07 ± 21.74	85.53 ± 7.58	0.03
WASO (min)	62.24 ± 34.06	69.29 ± 37.36	0.56
N1 sleep latency (min)	44.50 ± 47.05	5.26 ± 5.53	0.00
N2 sleep latency (min)	47.59 ± 48.34	6.47 ± 5.54	0.00
N3 sleep latency (min)	76.21 ± 57.55	26.09 ± 19.14	0.01
REM sleep latency (min)	147.54 ± 94.59	124 ± 64.78	0.61
Arousal index (events/h)	15.29 ± 9.07	8.89 ± 7.75	0.02
N1 (%)	2.42 ± 2.33	1.51 ± 1.20	0.24
N2 (%)	40.32 ± 9.51	45.94 ± 6.30	0.52
N3 (%)	28.68 ± 8.90	31.11 ± 8.13	0.41
REM (%)	12.59 ± 8.31	21.62 ± 4.50	< 0.001
Time N1 (min)	9.85 ± 10.19	1.55 ± 1.20	0.24
Time N2 (min)	162.29 ± 52.01	205.5 ± 41.65	0.01
Time N3 (min)	111.14 ± 27.27	137.72 ± 34.74	0.02
Time REM (min)	52.32 ± 38.14	96.38 ± 22.42	< 0.001
REM density	0.06 ± 0.12	3.87 ± 1.43	< 0.001
AHI (events/h)	15.29 ± 13.12	9.35 ± 10.40	0.11

SPT sleep period time, *TST* total sleep time, *WASO* wake after sleep onset, *AHI* apnea-hypopnea index, *BMI* body mass index

Table 3 Pearson correlation coefficient in relation to SARA Scale and time of evolution of the disease

	Sara Scale			Time of evolution		
	r	p	IC (95%)	r	p	IC (95%)
DREM	*− 0.6*	*0.00*	− 0.84 a − 0.18	*− 0.52*	*0.03*	− 0.80 a − 0.06
SE%	− 0.4	0.1	− 0.74 a 0.09	*−0.55*	*0.02*	− 0.81 a − 0.10
Lat N1	*0.50*	*0.03*	0.03 a 0.79	0.42	0.08	− 0.06 a 0.75
Lat N2	*0.48*	*0.04*	0.00 a 0.78	0.47	0.05	− 0.01 a 0.77
Lat N3	*0.58*	*0.01*	0.14 a 0.83	0.37	0.13	− 0.12 a 0.72
Lat REM	*0.49*	*0.04*	0.01 a 0.78	0.31	0.21	− 0.19 a 0.69
AI	0.28	0.27	− 0.23 a 0.67	0.44	0.07	0.04 a 0.76
N1 (%)	− 0.35	0.15	− 0.71 a 0.14	− 0.12	0.64	− 0.56 a 0.38
N2 (%)	0.03	0.90	− 0.45 a 0.50	− 0.06	0.81	− 0.52 a 0.43
N3 (%)	0.23	0.35	− 0.27 a 0.64	− 0.03	0.88	− 0.51 a 0.44
REM (%)	− 0.28	0.26	− 0.67 a 0.22	− 0.38	0.88	− 0.51 a 0.45
N1	− 0.36	0.14	− 0.72 a 0.13	− 0.13	0.61	− 0.57 a 0.37
N2	− 0.03	0.88	− 0.50 a 0.45	− 0.06	0.81	− 0.52 a 0.43
N3	0.1	0.68	− 0.39 a 0.55	− 0.33	0.18	− 0.70 a 0.17
REM	− 0.29	0.25	− 0.67 a 0.22	− 0.02	0.93	− 0.49 a 0.46

DREM density of REM; *SE%* sleep efficiency; *Lat* latency; *AI* arousal index; *N1%, N2%, N3%, and REM%* percentage of sleep phases; *N1, N2, N3, REM* time in minutes of each stage of sleep. Note: data with statistical significance were italicized

impairment. REM sleep density is a measure that depends directly on ocular motility. However, six of our patients had normal saccadic eye movements on the standard neurological exam. Estrada et al. [13] performed a study based on autopsies and found two patients with normal saccadic eye movements, reflecting the early stage of disease, even though both of their subjects had marked reduction on neuron counts in the nuclei of the pons, which could explain the reduction on REM density. Neuroanatomically early REM density reduction can be easily associated with the pons degeneration at the initial SCA2 stage and can be further interpreted as a symptom reflecting the progressive loss of pontine REM-on neurons [13, 29]. The significant reduction of saccade peak velocity is suggestive of a progressive compromise of the paramedian pontine reticular formation and other structures of the premotor saccadic circuitry. As observed in autopsies of SCA2 patients, compromise of the reticulotegmental and precerebellar nuclei, as well as the cranial nerves, correlates with saccadic pathology [32, 33]. It is also known that during REM sleep, the cerebellum participates in both REM atonia and phasic activity of the lateral rectus muscles of the eyes [34]. Thus, the cerebellum plays an important role in maintaining the saccadic subsystem efficient for vision stabilization both by minimizing movement inaccuracy and by learning from endpoint errors. This ability is often disrupted in degenerative cerebellar diseases, as demonstrated by saccade-kinetic abnormalities [35]. Mutation carriers with a SARA score < 3 are commonly defined as being in a preclinical phase, and in our group, even those patients who had no clinical signs of ataxia had reduced REM density in polysomnographic studies [36]. These findings suggest REM sleep density might be a useful biomarker of SCA2.

Reduction of REM sleep occurred in most SCA2 patients. Thalamic degeneration in the later course of SCA2 may contribute to the progression of REM pathology, as REM sleep is known to correlate with increased metabolic activities in both the pons and the thalamus. The relative sparing of brainstem raphe nuclei and the cerebral cortex in the degenerative process of SCA2 suggests the survival of REM-off neurons, who are responsible for the triggering of slow wave sleep (SWS) and may be the basis for the dominance of SWS stages in advanced SCA2 [29].

Changes in the quantity and density of REM sleep have not been described in other types of SCAs [30, 37]. These differences may be due to the fact that SCA2 is the only SCA that has an important olivopontocerebellar atrophy, which occurs already in early stages of the disease [13]. Patients with

idiopathic Parkinson's disease may also present reduction in REM sleep density, this alteration could lead to lower motor cortex activation during REM sleep. These changes may be similar to bradicinesia seen during wakefulness, in which there is less activation in motor cortex [38].

Paradoxically, the perceived sleep quality reported by most patients is better than would be expected by analysis of objective parameters of sleep. Similar to other groups, our data disclosed abnormalities associated with both REM and NREM stages. Five subjects answered "yes" in the RBD1Q [22], although no patient presented loss of REM atonia on polysomnographic recordings associated with either a self-reported history of dream-enactment, or objective documentation during REM sleep as recorded on video as part of the polysomnography. Absence of polysomnography confirmation was probably a result of a single-night study and/or the marked reduction in the quantity of REM sleep. Tuin et al. [29] reported no dream recall within the past year or years. The evidence of REM behavior disorder (RBD) events was scarce. SCA3 is a neurodegenerative disease involving the substantia nigra, locus cerulleus, other brain stem structures and cerebellum, locations typically involved in Parkinsonian disorders, whose association with RBD is well established [39]. This difference in anatomopathologic commitment could also explain why in SCA2 there is less incidence of RBD.

In addition to the decrease/absence of REM sleep, reduction of REM sleep time, the presence of cramps was an important marker found in patients with SCA2 in this group. All of our patients presented cramps predominantly nocturnal, a symptom that had already been reported by Velázquez-Pérez et al. [12], who found that muscle cramps and sensory symptoms were the earliest and most progressive complaints. Cramps have been physiopathologically related to collateral sprouting processes after initial axonal damage in motor neurons [12, 40].

Although a large part of the patients with SCA2 had an increased apnea-hypopnea index (AHI), this finding was not statistically significant when compared to the control group, which may have occurred due to the sample size in relation to the high prevalence of OSA in the population. Velázquez-Pérez et al. [10], in Cuba, found a significantly higher AHI in the patients compared to the control group. Snoring was recorded in the majority of the cases studied (88.23%). No patient in our group presented polysomnographic criteria for the diagnosis of PLM or met the clinical criteria for RLS and insomnia, only three cases presented evidence of a discrete EDD on the specific scale.

In our study, even patients with no clinical signs of cerebellar syndrome had significant reduction in REM sleep density. This early alteration could be used as a marker in asymptomatic patient carriers of SCA2. Therefore, our results suggest the importance of sleep research by means of polysomnography as an investigative tool not only for the diagnosis of sleep changes, but also as an aid for diagnosing carriers within kindreds with SCA2, who may have not yet have undergone genetic evaluation and even do not present the clinical signs of the disease, particularly in areas where genetic testing is not readily available.

Finally, a limitation of our study is the small sample size, which implies that our findings should be interpreted with caution and we cannot exclude the possibility that nonsignificant findings might be due to a lack of statistical power. We emphasize the rarity of SCA2, therefore, the importance of the presented data. We demonstrate in this study that sleep changes occur in patients with SCA2, as in other SCAs and other degenerative diseases. The differential findings, which might be important for future studies, were alterations in REM sleep, mainly the early alteration of REM sleep density, even in oligosymptomatic patients, and the correlation of this finding with disease time and with the SARA scale.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

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