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Sleep disorders in spinocerebellar ataxia type 10

Ester London1 | Carlos H. F. Camargo2 | Alessandra Zanatta3 | Ana C. Crippa3 | Salmo Raskin4 | Renato P. Munhoz5 | Tetsuo Ashizawa6 | Hélio A. G. Teive1

1Movement Disorders Unit, Neurology Service, Internal Medicine Department, Hospital de Clínicas, Federal University of Paraná, Curitiba, Brazil
2Neurology Service, Hospital Universitário, State University of Ponta Grossa, Ponta Grossa, Brazil
3Polysomnography Unit, Neurology Service, Hospital de Clínicas, Federal University of Paraná, Curitiba, Brazil
4Group for Advanced Molecular Investigation, Graduate Program in Health Sciences, School of Medicine, Pontifícia Universidade Católica do Paraná, Curitiba, Brazil
5Movement Disorders Centre, Toronto Western Hospital, Toronto University, Toronto, ON, Canada
6Neuroscience Research Program, Methodist Hospital Research Institute, Houston, TX, USA

Correspondence
Carlos Henrique Ferreira Camargo, Hospital Universitário – Universidade Estadual de Ponta Grossa, Ponta Grossa, Brazil
Email: chcamargo@uol.com.br

Summary
As sleep disturbances have been reported in spinocerebellar ataxias (SCAs), including types SCA1, SCA2, SCA3, SCA6 and SCA13, identification and management of these disturbances can help minimise their impact on SCA patients’ overall body functions and quality of life. To our knowledge, there are no studies that investigate sleep disturbances in SCA10. Therefore, the aim of this study was to assess sleep disturbances in patients with SCA10. Twenty-three SCA10 patients and 23 healthy controls were recruited. Patients were evaluated in terms of their demographic and clinical data, including disease severity (Scale for the Assessment and Rating of Ataxia, SARA) and excessive daytime sleepiness (Epworth Sleepiness Scale, ESS), and underwent polysomnography. SCA10 patients had longer rapid eye movement (REM) sleep ($p = .04$) and more REM arousals than controls ($p < .0001$). There was a correlation of REM sleep onset with the age of onset of symptoms ($r = .459$), and with disease duration ($r = -.4305$). There also was correlation between the respiratory disturbance index (RDI) and SARA ($r = -.4013$), and a strong indirect correlation between arousal index and age at onset of symptoms ($r = -.5756$). In conclusion, SCA10 patients had sleep abnormalities that included more REM arousals and higher RDI than controls. Our SCA10 patients had sleep disorders related to shorter disease duration and lower severity of ataxia, in a pattern similar to that of other neurodegenerative diseases.

KEYWORDS
arousal index, rapid eye movement sleep disorders, respiratory disturbances, SCA10

1 | INTRODUCTION

Spinocerebellar ataxias (SCAs) comprise a large, complex group of heterogeneous autosomal dominant diseases characterised by progressive degeneration of the cerebellum and its afferent and efferent connections (Teive & Ashizawa, 2015). In most areas of the world where the condition has been studied, the prevalence of a particular SCA type varies widely according to the ethnic distribution (Teive & Ashizawa, 2015). An increasing number of SCA subtypes have been identified, and these have now been mapped to 43 different loci. The most common form of the disease worldwide is SCA3, or Machado-Joseph disease. SCA10 is a rare form found predominantly in regions of Latin America, particularly Mexico and Brazil, where it is the second most common type (Matsuurua et al., 2000; Teive & Ashizawa, 2013; Teive et al., 2004). SCA10 is caused by an ATTCT pentanucleotide repeat expansion in intron 9 of the ATXN10 gene on chromosome 22q 13.1. This gene encodes a 450 kD protein of largely undetermined function. In the normal population, the number of ATTCT repeats ranges from 10 to 32, whereas in SCA10 patients the abnormally expanded allele contains 800–4500 repeats (Matsuurua et al., 2000; Teive & Ashizawa, 2015; Teive et al., 2004). Clinically, SCA10 patients presented with cerebellar ataxia, dysarthria, abnormal eye movements and seizures. However, the main phenotype observed in Brazilian SCA10 patients is pure cerebellar ataxia (Matsuurua et al., 2000; Teive & Ashizawa, 2013; Teive & Ashizawa, 2015; Teive et al., 2004, 2011).
As sleep disturbances have been reported in SCAs, including types SCA1, SCA2, SCA3, SCA6 and SCA13, identification and management of these disturbances can help minimise their impact on SCA patients' overall body functions and quality of life (D’Abreu et al., 2009; Dang & Cunnington, 2010; Howell, Mahowald, & Gomez, 2006; Kapoor & Greenough, 2015; Pedroso, Braga-Neto, Felício, Aquion, et al., 2011; Pedroso, Braga-Neto, Felício, Dutra, et al., 2011; Pedroso, Braga-Neto, et al., 2013). D’Abreu et al. (2009) demonstrated that sleep disorders are common in patients with SCA3, particularly the presence of insomnia, restless legs syndrome (RLS) and REM sleep behaviour disorder (RBD), as well as nocturnal cramps, snoring and sleep obstructive apnea (SOA). Pedroso, Braga-Neto, Felício, Aquion, et al., (2011); Pedroso, Braga-Neto, Felício, Dutra, et al., (2011); Pedroso, Braga-Neto, et al., 2013 showed that the frequency of RLS was 23% in SCA1, 18% in SCA2, 56.7% in SCA3 and 23.8% in SCA 6. In the same study, the frequency of RBD was 80% in SCA2 and 45.9% in SCA3, and SOA was detected in 22.6% of SCA3 patients. Sleep disorders have not been described in SCA10. In this study, we therefore sought to investigate sleep disorders in SCA10 patients.

2 | METHODS

2.1 | Subjects and clinical protocols

Twenty-three patients, from six families, with a confirmed molecular diagnosis of SCA10 followed at the Ataxia Outpatient Clinic of the Neurology Service, Hospital de Clinicas, Federal University of Paraná, were recruited from July 2013 to July 2014. The study was approved by the Ethics Committee of the Hospital de Clinicas, Federal University of Paraná (HC-UFPR), Curitiba, Brazil. All patients included in the study signed a voluntary written informed consent form. SCA10 patients with respiratory diseases or cognitive or behavioural alterations were not included because these disorders would not allow performance of polysomnography.

A control group with 23 apparently healthy individuals matched for age, gender and body mass index (BMI) was also recruited at the same institution. The control subjects had no family members with ataxia and no sleep complaints or chronic pulmonary, neurological, psychiatric or cardiovascular disease and no history of drug abuse or use of hypnotic medications.

All study subjects were assessed using a standardised protocol in which demographic and clinical variables and data on general and neurological examinations were collected. On the day of the PSG, patients were assessed by neurologic examination, and any history of abnormal behaviours during sleep was obtained from the patients, their bed partners and their caregivers. Ataxia severity was rated using the validated Brazilian version of the Scale for the Assessment and Rating of Ataxia (SARA) (Schmitz-Hü et al., 2006). In addition, patients with SCA10 were assessed using the Epworth Sleepiness Scale (ESS). Patients with Epworth scores > 10 were considered to have excessive daytime sleepiness (EDS) (Johns, 1991). Finally, patients were asked about sleep problems, the characteristics of their dreams and the presence of symptoms of RBD (Postuma, 2014).

2.2 | Polysomnography (PSG)

All patients and controls agreed to undergo polysomnography (PSG) for one full night. PSG was performed with a digital Brain Wave II electroencephalogram (EEG) polygraph (Neurovirtual, São Paulo, SP, Brazil). A standard montage was used, including F3, F4, C3, C4, O1, O2, A1 and A2 electrodes, vertical and horizontal electro-oculography (EOG) and electromyography (EMG) of the mental, submental and both tibialis anterior muscles. Respiration was monitored by measuring nasal airflow, thoracic and abdominal respiratory effort and oxyhaemoglobin saturation. Patients were monitored with a video camera and observed continuously by experienced technicians. Sleep was scored according to the criteria in the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events (AASM, 2007). Sleep onset latency, REM sleep latency, sleep efficiency and arousals were defined according to the AASM criteria (American Academy of Sleep Medicine, 2007). An average value of up to 10 arousals/hr is considered normal. Respiratory events were defined as the sum of apneas and hypopneas (American Academy of Sleep Medicine, 2007). Apnea was defined as a decrease in nasal and oral air flow of more than 90% for 10 s or longer, and hypopnea as a decrease in nasal and oral air flow of more than 30% with a decrease in oxyhaemoglobin saturation of more than 4% for 10 s or longer (American Academy of Sleep Medicine, 2007).

The respiratory disturbance index (RDI) was defined as the number of respiratory disturbances per hour of sleep, in accordance with the criteria proposed by the AASM. Patients with an RDI > 5 were considered to have a respiratory disorder: (i) grade I respiratory disturbance was defined as an RDI of 6 to 15; (ii) grade II as an RDI of 16 to 30; and (iii) grade III as an RDI of more than 30 [15]. Periodic limb movements (PLMS) were recorded and scored according to standard criteria (American Academy of Sleep Medicine, 2007). REM sleep was scored according to the AASM criteria (American Academy of Sleep Medicine, 2007); that is, when eye movements are slow, muscle activity is decreased and there are more delta waves. According to these criteria for scoring REM sleep (tonic and phasic), REM density and RBD, REM sleep should be scored even in the presence of persisting tonic and phasic muscle activity in the chin, and/or extremity EMG used if other signs of REM sleep are present (e.g. rapid eye movements and typical mixed-frequency, low-voltage activity with sawtooth waves in the EEG). AAMS criteria were used to assess RLS and sleep respiratory disorders (American Academy of Sleep Medicine, 2007).

2.3 | Statistical analysis

The Shapiro-Wilk and Shapiro-Francia normality tests were used to check if continuous variables were normally distributed. Differences
in the means of normally distributed variables were tested by the t test, whereas the Wilcoxon-Mann-Whitney non-parametric test was used to compare medians of non-normally distributed continuous variables. Binomial variables were tested by the chi-squared test or Fisher’s exact test. Pearson’s correlation coefficient was used to determine the correlations. A p-value of <.05 was considered statistically significant.

3 | RESULTS

Of the 23 SCA10 patients, 52.17% were male and 47.83% female, with a mean age of 47.3 ± 11.6 years for ataxic patients. The demographic and clinical characteristics of the SCA10 patients and controls are shown in Table 1.

Total sleep time was 343 minutes (19–475) for SCA10 patients and 365 minutes (322–386) for controls. The median for sleep efficiency was below normal for both groups. The median for arousal index was above normal for both groups, and there was a statistical difference between them (Table 2).

Although three SCA10 patients had a history of clinical RBD, no vigorous movements were observed on the EMG and no sounds mimicking speech were recorded during the single full-night PSG study. However, other REM sleep changes were significant in the SCA10 group compared with controls. Patients with SCA10 had longer REM sleep onset latencies and more REM arousals. There was also a statistically significant difference in the number of REM arousals between controls and SCA10 patients. The mean REM-sleep percentage was 14.1 ± 5.6 for SCA10 patients and 16.2 ± 5.8 for controls (p = .22) (Table 2).

Eleven of the 23 SCA10 patients exhibited respiratory disturbances during sleep (RDI > 5, Table 2). Sleep-disordered breathing was 9.3 (6.1–16.4) for SCA10 patients and 3.2 (2.6–4.6) for controls (p = .0002) (Table 2). Mean RDI (>5/hr) and prevalence of respiratory disturbance were significantly higher in SCA10 patients than in controls. Nine SCA10 patients with RDI had above-normal BMI. None of the 23 patients had RLS or PLMS.

When the significant sleep disturbances in patients with SCA10 in relation to the controls were correlated with severity parameters of SCA10, it was observed that there was a direct correlation of REM sleep onset with the age of onset of symptoms (r = .459, p = .0021 [95% CI = −.03199 to .03619], r = .1458, p = .03619, r = .3313 [95% CI = .04437 to .61823]).

There was no correlation between RDI and BMI (r = .1458, p = .0021 [95% CI = −.08518 to .12778], p = .2534) in patients with...
SCA10. There was no correlation among CAG expansions and polysomnographic parameters.

4 | DISCUSSION

This is the first study about sleep disorders in SCA10 patients. Our findings indicated that patients with SCA10 have longer REM sleep onset latencies, more REM arousals and a greater frequency of respiratory disturbances than healthy controls. They did not appear to have a great impact on quality of sleep in these patients. In other SCAs, such as SCA1, SCA2, SCA3 and SCA6, the most frequent sleep disorders include RBD, RLS, insomnia, excessive daytime sleepiness, excessive fragmentary myoclonus and sleep apnea, all of which can be considered important modifiers of quality of life (Boesch, Frauscher, Brandauer, Wenning, Högl, et al., 2006; Boesch, Frauscher, Brandauer, Wenning, Poewe, et al., 2006; Chi, Shiao, Ku, & Soong, 2013; Friedman, Fernandez, & Sudarsky, 2003; Pedroso, Braga-Neto, Felício, Aquino, et al., 2011; Pedroso, Braga-Neto, Felício, Dutra, et al., 2011b; Pedroso, França, et al., 2013; Raggi, Bella, Pennisi, Neri, & Ferri, 2013; Syed, Rye, & Singh, 2003; Velázquez-Pérez et al., 2011). In our study with SCA10 patients, however, these sleep disorders were not detected.

We found predominantly changes in REM sleep; however, there were no patients with RBD. Previous studies have shown REM atonia to increase significantly in SCA3 patients with RBD (Friedman et al., 2003; Pedroso, França, et al., 2013; Syed et al., 2003). Other SCA3 series showed a reduction in REM sleep percentage and an increase in REM sleep latency and REM sleep arousals even in the absence of RBD (Boesch, Frauscher, Brandauer, Wenning, Högl, et al., 2006; Pedroso, Braga-Neto, et al., 2013; Pedroso, França, et al., 2013; Raggi et al., 2013). SCA3 patients also have non-rapid eye movement (NREM)-related parasomnias (Silva et al., 2016).

Boesch, Frauscher, Brandauer, Wenning, Högl, et al., (2006) studied five patients with SCA6 and found no alterations in REM sleep, but observed PLMS in four cases and RLS in two patients. Velázquez-Pérez et al. (2011) assessed sleep disorders in 32 SCA2 patients and they found REM muscular tonus increased in 30% of the patients. Tuin et al. (2006) reported the sleep of eight patients with SCA2 and reported a decrease in the proportion of REM sleep. Boesch, Frauscher, Brandauer, Wenning, Poewe, et al., (2006) performed a polysomnographic study of five patients with SCA2 and in four cases observed absence of muscle atony during REM sleep. Other sleep disorders observed in patients with SCA2 were RBD, RLS and PLMS (Pedroso, Braga-Neto, Felício, Aquino, et al., 2011; Pedroso, Braga-Neto, Felício, Dutra, et al., 2011). Changes in sleep architecture and sleep abnormalities in SCA2 constitute an important marker of the disease.

In the present study, REM sleep disorders were related to a shorter disease time and lower ataxia severity, and also to a later age at onset. This is a pattern of REM sleep similar to that found in Parkinson’s disease, but different from SCA2 in which RBD is associated with a greater disease severity (Raggi et al., 2013; Velázquez-Pérez et al., 2011). SCA3 patients presented with poor sleep efficiency and REM sleep abnormalities as the disease progressed (Chi et al., 2013). Fragmented sleep in patients with other neurodegenerative diseases, such as Parkinson’s disease, SCA2 and SCA3, may share similar pathomechanisms (Chi et al., 2013; Dang & Cunnington, 2010; Raggi et al., 2013). In Parkinson’s disease, the reduction in REM sleep duration is caused by degeneration of the dopaminergic nigrostriatal pathway with compensatory activation of monoaminergic neurons in the brain stem (Velázquez-Pérez et al., 2011). Reduced concentrations of the dopamine transporter in the nigrostriatal pathway have also been reported in SCA2 and SCA3 (Velázquez-Pérez et al., 2011). Patients with RBD also experience pathological changes in basal ganglia anatomy, with neuroimaging studies showing reduced striatal dopaminergic activity (Pedroso et al., 2016). However, sleep disorders in neurodegenerative diseases may be associated with more diffuse structural damage in the central nervous system, more specifically to sleep–wake-generating cells and their networking (Raggi et al., 2013; Silva et al., 2016).

The brainstem circuits known to be associated with RBD pathogenesis come from breakdown of the circuits responsible for REM sleep atonia (subcoeruleus complex, gigantocellular reticular nucleus, dorsal raphe nucleus and pedunculopontine nucleus) (Pedroso et al., 2016). The progressive loss of pons neurons could also influence REM sleep as a result of the degeneration of part of the group of REM neurons that participate in the cholinergic system and present maximal tonus during REM sleep, promoting cortical and limbic activation (Siegel, 2004). The cerebellum participates in the REM sleep atonia, the phasic activity of the lateral rectus muscles of the eyes, and the delta wave inhibition leading to REM sleep desynchronisation and wakefulness (Gadea-Ciria & Fuentes, 1976). Therefore, cerebellar atrophy would contribute to the reduction in the quantity of REM sleep, and to the absence of atony during REM sleep (DeRossi & Hoque, 2014).

In our study, the frequency of respiratory disturbances in the SCA10 patients was higher than in the controls. There was no correlation between BMI and sleep obstructive apnea. Rueda et al. (2016), in a study of 12 patients with SCA6, found a higher incidence of sleep-disordered breathing in patients than in controls. Pedroso, Braga-Neto, Felício, Aquino, et al. (2011); Pedroso, Braga-Neto, Felício, Dutra, et al. (2011) showed 22.6% of SCA3 patients and no cases in SCA1, SCA2 and SCA6. Speculative pathophysiological mechanisms in SCA3 and sleep obstructive apnea may include dystonia or denervation of the laryngeal muscles, which isAbsent in SCA10 (Pedroso et al., 2016).

This clinical and polysomnographic study shows that our SCA10 patients had sleep disorders related to shorter disease duration and lower severity of ataxia, in a pattern similar to that of other neurodegenerative diseases. However, a longitudinal study with more patients is required to follow the changes in clinical manifestations and PSG as the disease evolves and study the possible relationship between the SCA mechanism and the mechanism of sleep disorders in SCA10 patients.
AUTHOR CONTRIBUTIONS

EL planned the project, collected data and wrote the manuscript. CHFC wrote, corrected and reviewed the manuscript. AZ wrote and reviewed the manuscript. ACC planned, organised and supervised the project and reviewed the manuscript. SR supervised the project and reviewed the manuscript. RPM supervised the project and reviewed the manuscript. TA supervised the project and reviewed the manuscript. HAGT planned, organised and supervised the project, and corrected/reviewed the manuscript.

CONFLICT OF INTEREST

No conflicts of interest declared.

ORCID

Carlos H. F. Camargo http://orcid.org/0000-0002-3533-0347

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