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Sleep Pattern in Charcot-Marie-Tooth Disease Type 2: Report of Family Case Series

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Objectives: Charcot-Marie-Tooth (CMT) disease is the most prevalent hereditary motor and sensory polyneuropathy, and a condition in which sleep has rarely been studied, particularly in relation to the type 2 (CMT2). Thus, we aimed to characterize the sleep patterns of a family affected by CMT2 disease.

Methods: Sixteen volunteers with CMT2 from the same multigenerational family agreed to participate in the study (refusal rate = 31%). All participants answered sleep questionnaires and came to the sleep laboratory to perform a diagnostic polysomnography (PSG). Clinical manifestation and severity of the disease were also evaluated.

Results: 56% of the sample were male and 44% female, with a mean age of 32 ± 17 years, of normal weight (body mass index 21 ± 3 kg/m^2); 64% presented moderate to severe CMT2. Regarding subjective sleep, 31% had excessive daytime sleepiness and 75% reported poor sleep quality. The PSG results revealed that CMT2 patients had an increase in stage N3 and a reduction in REM sleep, in addition to a high arousal index. Although 81% of the sample were snorers, only 13% had an apnea-hypopnea index (AHI) > 5. However, a positive correlation was found between the severity of disease and the AHI.

Conclusions: Taken together, these data show that CMT2 disease is characterized by important changes in sleep architecture, probably due to sleep fragmentation. Although these alterations may worsen with disease severity, it seems that they are not related to sleep breathing or movement disorders.

Keywords: CMT2, neuropathy, sleep quality, sleep disorder, apnea-hypopnea index.

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Charcot-Marie-Tooth disease (CMT) is a predominantly distal sensory and motor neuropathy, heterogeneously affecting 1 : 2,500 of the population.[1] CMT disease can be divided into 2 main types according to the study of the median nerve conduction: CMT1 and CMT2.[2] CMT1 disease is an inherited demyelinating motor and sensory polyneuropathy commonly associated with significant reduction in the conduction velocity of the median nerve. CMT2 is an inherited axonal motor and sensory polyneuropathy in which nerve conduction velocity is usually normal or slightly reduced. CMT1 is the most common type of CMT, affecting around 70% of the cases. CMT2 is rarer, being observed in 10% to 15% of CMT patients.[3]

The evolution of CMT does not depend on the disease type, and its progression varies even within members of the same family.[4] The clinical presentation includes motor symptoms from the distal segments of the lower limbs, loss of strength, and atrophy of leg and feet muscles. The disease progresses in the distal to proximal direction, affecting the median and proximal segments of the upper and lower limbs.[5] Sensory manifestations may include pain and reduced sensitivity. The tendon reflexes are usually hypoactive. Additional symptoms such as dysphonia, pyramidal signs, deafness, and tremor may also be present in CMT disease.[6,7]

BRIEF SUMMARY

Current Knowledge/Study Rationale: Sleep has been shown to be detrimental for quality of life and may play an important role in the neuropathies. Charcot-Marie-Tooth disease (CMT) is the most common genetic cause of neuropathy, in which sleep has been rarely characterized.

Study Impact: This is the first study which evaluated sleep in a large family affected by CMT2, showing poor sleep quality and fragmented sleep without sleep-breathing or periodic-moviment disorders. This study revealed that Sleep Medicine can contribute to the field of Neuromuscular Medicine, suggesting that improvement of sleep quality may help delay the progression of CMT2.

Importantly, patients with neuromuscular diseases often present symptoms related to sleep problems.[8] In particular, there is some evidence in relation to sleep disordered breathing in CMT disease, but the majority of studies have focused only on CMT1. Dematteis and colleagues[6] showed a high prevalence of obstructive sleep apnea syndrome (OSAS) in a family with CMT1 disease due, at least in part, to the pharyngeal neuropathy that may increase the collapsibility of the upper airway.[9] In addition, a pulmonary impairment has been described in association with dysfunction of the phrenic and laryngeal nerves, diaphragmatic dysfunction, vocal cord paralysis, and abnormalities of the chest in both patients with CTM1 and

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CMT2 disease.[10,11] Of note, a study in diagnosed restless legs syndrome (RLS) patients revealed a high prevalence of CMT2 disease, suggesting a possible cause-consequence relationship.[12] While in CMT1 there is some evidence of sleep apnea predominance, to date there has been no study that has objectively evaluated the sleep pattern of CMT2 patients.

Since 2003, we have been studying a multigenerational family in which 66 people have been diagnosed with CMT2 with an autosomal dominant form of transmission.[4] Thus, the current study aimed to subjectively and objectively investigate the sleep patterns of members of this family from Tobias Barreto, a town in Sergipe State, Brazil.

METHODS

Study Protocol

This is an observational family case series study. The family involved in the current study lived in Tobias Barreto, a city located 180 km from Aracaju (capital of Sergipe State, Brazil), with an estimated population of 57,000 inhabitants. Data collection occurred from September 2012 to October 2013. All subjects were informed about the study protocol and signed the informed consent. As well as giving their own consent, those aged younger than 18 years also had authorization from their parents or legally responsible guardian. This study was approved by the ethical committee of Universidade Federal de Sergipe in June 2012.

Subjects

A total of 66 members from 4 generations of the family were diagnosed with CMT2 through clinical and electrophysiological evaluation as described by Neves and Kok.[4] Exclusion criteria were the presence of significant comorbidities (heart failure, chronic obstructive pulmonary disease, and endocrinological diseases); use of medications such as antidepressants, hypnotics and others related to central nervous system or respiratory function; or pregnancy. From the 66 individuals, 36 were randomly selected and invited to participate in the protocol at the premises of the Association of Patients with Charcot-Marie-Tooth in the city of Tobias Barreto. However, due to the distance from Aracaju, low family income, and the possible discomforts associated with the PSG exam, only 25 agreed to participate in the study (refusal rate = 31%). From these, 9 were excluded due to exclusion criteria, resulting in the final number of 16 cases included in the study. Of these, no one was using any medication.

Pyramidal Signs and Severity of CMT2

The presence of pyramidal signs was considered when there were increased tendon reflexes (hyperreflexia) in the lower limbs and/or the presence of Babinski sign, a well-known neurological sign.[4]

The severity of the CMT2 disease was evaluated clinically through the CMT neuropathy score (CMTNS) described by Shy and colleagues.[13] This score is calculated through the responses to questions to the patient during the evaluation of sensory and motor symptoms in the upper and lower limbs; sensory and motor alterations in upper and lower limbs observed during the clinical exam; and alterations in the neural conduction of the sensory and motor nerves assessed by electromyography. Each alteration of a specific domain leads to a given score between 1 and 4, with a global score ranging from 0 to 36. According to Shy et al.,[13] a global score ≤ 10 is considered a mild degree of severity, while > 10 is considered moderate and > 20 severe. Of the 16 patients involved, 2 did not attend the electromyography study, although all the other evaluations were performed. However, they presented a clinical picture compatible with CMT disease.

Questionnaires

At the Association of Patients with Charcot-Marie-Tooth in the city of Tobias Barreto, all patients included in the study answered an identification questionnaire with personal data such as name, birth date, gender, address, and telephone, which were kept confidential. Also, 3 sleep questionnaires validated in Portuguese were self-administered: the Epworth Sleepiness Scale (ESS),[14] the Pittsburgh Sleep Quality Index (PSQI),[15] and the Berlin questionnaire.[16]

Anthropometric Data

The physical evaluation of all patients included weight, height, and body mass index (BMI). These assessments were performed by trained personnel in the city of Tobias Barreto at the Association of Patients with Charcot-Marie-Tooth disease.

Polysomnography

All PSGs were scheduled and performed on Fridays. The analysis was done by trained technicians certified by the Brazilian Association of Sleep and the Sleep Institute (Brazil). The sleep scoring was performed following Rechtschaffen and Kales, which consider the division of the sleep stages in 1, 2, 3, 4, and REM.[17] However, in the current study, we grouped the sleep stages 3 and 4 in only 1 sleep stage (N3), as both of them reflect slow wave sleep. The detection of arousals was done in line with the Task Force of the American Academy of Sleep guidelines, and arousals were scored as abrupt shift in EEG frequency, which could include theta, alpha and/or frequencies > 16 Hz but not spindles, with minimum duration of 3 sec preceded by ≥ 10 sec of sleep.[18] Respiratory events, such as apneas (central, obstructive, or mixed) and hypopneas, were scored in accordance with the recommendations of the American Academy of Sleep Medicine Manual from 2007. Thus, apneas were defined as a reduction in the thermistor airflow ≥ 90% lasting ≥ 10 sec, while hypopneas were defined as a nasal cannula airflow reduction ≥ 30% lasting ≥ 10 sec and associated with 4% oxygen desaturation (recommended rule).[19,20] The classification of the apnea type was based on the respiratory effort signals. If no effort was present, the apnea was scored as central; if the event began as central (without any respiratory effort) but ended with ≥ 1 respiratory effort, the apnea was scored as mixed; and if the event presented respiratory effort throughout its duration, the apnea was scored as obstructive.

The sleep laboratory was located at Aracaju (Sergipe State, Brazil). During the daytime of the PSG day, patients were instructed to avoid the use of stimulants and not to take naps. At 6 pm on day of the PSG, the volunteers were brought by car from their homes in Tobias Barreto to Aracaju. This journey took around 2 hours. After arriving in the sleep laboratory, the patients had dinner and then were prepared for PSG hook-up.

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The acquisition of PSG data was performed using the Poli Icelera BNT 36 (Icelera, Brazil).

The physiological variables registered according to the American Academy of Sleep Medicine were 4 channels for electroencephalogram (EEG) (C3-A2, C4-A1, O1-A2, O2-A1); 2 channels for electrooculogram (EOG); 1 channel for submental muscle electromyogram (EMG) and 1 channel for tibialis anterior muscle EMG; 1 channel for electrocardiogram (ECG); 2 channels for respiratory flow, 1 for thermistor and 1 for nasal cannula; 2 channels for respiratory thoracic and abdominal efforts, using thoracic and abdominal x-trace belts, 1 for thoracic and 1 for abdominal effort; 1 channel for oximetry, and 1 channel for snoring sensor.

Statistical Analysis

Due to the nature of this study as a case series with a small sample, most analysis was descriptive. Analysis of sleep parameters according to the severity of CMT2 disease (mild or moderate to severe) was done using the Mann-Whitney test. Comparison of sleep parameters between CMT2 patients and established normal reference values were performed with one-sample T test; χ^2 was used for analysis of the association between CMT2 severity (low or moderate-to-severe) and sleep quality (good or bad). Spearman correlation test and simple linear regression analysis were used to evaluate the relationship between the CMTNS score and the AHI. The data are presented as mean ± standard deviation (SD). Significance was set at $p \leq 0.05$. All analyses were performed with SPSS 19.0 software (Chicago, IL, USA).

RESULTS

Table 1 shows the clinical data in the sample of CMT2 patients. Of the 16 participants, 9 (56%) were men and 7 (44%) were women, with a mean age of 32 ± 17 years, and normal BMI (21 ± 3 kg/m^2). Regarding the severity of the disease based on the CMTNS score, we found that 64% of the individuals presented moderate to severe CMT2. The presence of pyramidal signs, manifested by hyperreflexia and/or Babinski signal, was observed in 63% of the sample studied. No significant association was found between the presence of pyramidal signs and severity of disease ($p > 0.05$).

The results from sleep questionnaires are represented in **Tables 2** and **3**. The mean ESS score was 7.1 ± 3.8, which is considered normal. However, on closer inspection, we observed that 5 patients (31%) had an ESS score higher than 9, indicating sleepiness. No significant association was found

Table 1—Clinical presentation of patients with CMT2 regarding the frequency of gender, disease severity, and presence of pyramidal signs and mean ± SD of age and BMI.

Variables	N (%) or Mean ± SD
Gender	
Male	7 (44%)
Female	9 (56%)
Disease severity	
Mild	5 (36%)
Moderate to severe	9 (64%)
Pyramidal signs	
Yes	10 (63%)
No	6 (37%)
Age (years)	32 ± 17
BMI (kg/m^2)	21 ± 3

CMT2, Charcot-Marie-Tooth type 2; SD, standard deviation; BMI, body mass index.

Table 2—Subjective data about sleep questionnaires and degree of severity of CMT2 evaluated by CMTNS.

Patients	CMTNS	ESS Score	PSQI	Sleep Quality	Berlin Questionnaire
III-10	26	12	9	Poor	Low risk
III-12	–	10	9	Poor	High risk
III-25	16	12	8	Poor	Low risk
III-32	9	6	7	Poor	Low risk
III-39	10	5	9	Poor	Low risk
III-49	6	10	11	Poor	Low risk
IV-8	16	9	6	Poor	Low risk
IV-13	25	4	5	Good	Low risk
IV-14	23	3	1	Good	Lowr isk
IV-18	11	9	6	Poor	Low risk
IV-32	9	6	9	Poor	Low risk
IV-39	6	6	5	Good	Low risk
IV-44	17	14	9	Poor	Low risk
IV-50	11	2	3	Good	Low risk
IV-52	14	1	7	Poor	Low risk
V-3	–	5	6	Poor	Low risk
Mean ± SD	14.2 ± 6.6	7.1 ± 3.8	6.9 ± 2.6	–	–

CMT2, Charcot-Marie-Tooth type 2; CMTNS, Charcot-Marie-Tooth Neuropathy score; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation.

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Table 3—Subjective data about the 7 domains from the PSQI questionnaire: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction.

Patients	Subjective Sleep Quality	Sleep Latency	Sleep Duration	Habitual Sleep Efficiency	Sleep Disturbances	Use of Sleeping Medication	Daytime Dysfunction
III-10	3	2	2	0	1	0	1
III-12	3	2	2	0	1	1	0
III-25	2	1	2	1	1	0	1
III-32	3	0	2	0	1	0	1
III-39	2	1	2	1	1	1	1
III-49	3	2	2	2	1	0	1
IV-8	1	1	2	0	1	1	0
IV-13	2	1	0	0	1	0	1
IV-14	0	0	0	0	1	0	0
IV-18	2	1	1	1	1	0	0
IV-32	2	3	2	0	1	0	1
IV-39	2	1	1	0	1	0	0
IV-44	2	2	2	0	1	1	1
IV-50	1	0	1	0	1	0	0
IV-52	3	1	1	0	1	0	1
V-3	1	2	0	1	1	0	1
Mean ± SD	2.0 ± 0.9	1.3 ± 0.9	1.4 ± 0.8	0.4 ± 0.6	1.0 ± 0.0	0.3 ± 0.4	0.6 ± 0.5

PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation.

Table 4—Sleep parameters evaluated through polysomnography in the sample of 16 CMT2 patients.

Patients	N1 (%)	N2 (%)	N3 (%)	REM (%)	WASO (%)	PLM Index	Arousal Index	AHI	Mean SpO_2 (%)
III-10	4.4	61.3	29.6	4.7	16.5	0.0	24.0	6.28	85
III-12	2.4	50.5	23.9	23.1	5.0	0.0	10.0	1.38	92
III-25	6.6	47.0	21.7	24.6	4.0	0.0	9.0	0.63	95
III-32	5.2	45.9	32.4	16.2	19.0	0.6	14.0	0.00	95
III-39	2.1	45.9	26.8	25.2	9.8	0.0	13.0	1.19	95
III-49	7.9	50.9	29.6	11.3	9.0	0.9	8.8	6.46	95
IV-8	1.3	58.4	21.9	18.4	22.0	0.0	31.0	2.58	97
IV-13	1.8	52.4	27.6	18.2	4.0	0.0	10.0	0.00	94
IV-14	13.3	58.2	20.3	8.2	21.0	15.9	16.0	1.27	97
IV-18	1.5	50.9	18.9	28.4	6.0	0.0	21.0	0.00	93
IV-32	11.5	52.9	20.1	15.4	19.0	0.0	15.0	0.52	97
IV-39	1.7	54.7	25.2	18.2	2.0	0.0	6.8	0.00	98
IV-44	2.9	45.5	28.8	22.5	28.0	0.1	6.6	0.00	92
IV-50	2.6	62.6	27.1	7.4	11.0	0.0	18.9	0.00	97
IV-52	4.8	41.5	50.7	2.7	20.0	0.0	2.8	0.35	96
V-3	5.6	51.0	39.3	4.1	49.0	15.6	7.2	0.46	96
Mean ± SD	4.7 ± 3.5	51.8 ± 6.0	27.7 ± 8.0	15.5 ± 8.2	15.3 ± 11.9	2.1 ± 5.3	16.3 ± 7.1	1.3 ± 2.1	94.6 ± 3.1

CMT2, Charcot-Marie-Tooth type 2; REM, rapid eye movement; WASO, wake after sleep onset; PLM, periodic limb movement; AHI, apnea-hypopnea index; SpO_2, oxygen saturation; SD, standard deviation.

between sleepiness (ESS ≤ 9 or ESS > 9) and the severity of disease. In relation to the PSQI questionnaire, 12 (75%) patients had poor sleep quality. This may have been explained mainly due to changes in the PSQI domains of subjective sleep quality, sleep duration, and sleep latency. Eighty-one percent of patients complained about difficulty in initiating or maintaining sleep. However, most of them did not complain about sleep efficiency, daytime dysfunction, use of sleeping medication, or sleep disturbances. In the overall sleep quality domain, 75% of patients reported fairly bad or very bad sleep quality. No statistical significant association was found between sleepiness and severity of CMT2 disease. Regarding the Berlin questionnaire, of the 16 patients evaluated, only one was classified with a high risk for sleep disordered breathing.

The sleep parameters evaluated objectively by the PSG are represented in **Table 4**. We can observe that sleep efficiency was within a normal range, although half the patients had some reduction (normal > 85% of sleep efficiency). The sleep stages

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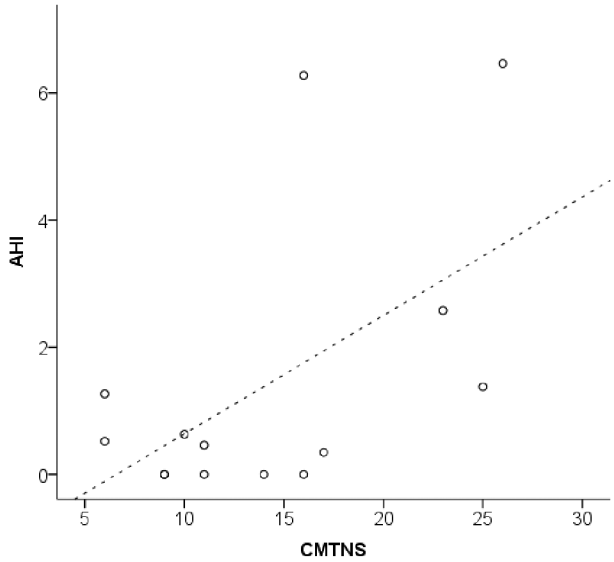
were also affected, as an increase of N3 stage (normal: 15% to 20% of N3) was observed in association with a decrease in REM sleep (normal: 20% to 25% of REM). No significant changes were observed in N1 (normal: up to 5% of N1) and N2 (normal: 45% to 55% of N2) stages. Nevertheless, 5 patients (31%) presented higher values of N1. Fourteen patients (87%) had increased quantity of N3 stage, while 11 patients (69%) had a decreased quantity of REM sleep. No important changes were observed in sleep latency or REM sleep latency. Wake after sleep onset (WASO) was significantly increased in CMT2 patients in relation to the normal range (normal < 3% of WASO). Fifteen patients (94%) had an increase of WASO. Mean arousal index was also affected by the disease (normal: up to 10/h), with 8 (50%) of the patients with increased arousal index. No important changes were observed in the PLM index (normal: up to 15/h of PLM index). Only 2 patients had increased PLM index. There was no patient with bruxism detected by PSG.

Regarding the respiratory parameters, we observed a high frequency of snoring (81%), with no predilection to gender. However, the mean AHI was within the normal range (normal: up to 5/h of AHI). Only 2 (13%) had an AHI > 5, indicating the presence of sleep disordered breathing. According to PSG data, no significant changes were observed in the mean oxygen saturation (SpO_2) in relation to the normal range (normal: above 92% SpO_2). Only one patient had significant desaturation. Respiratory related arousal effort (RERA) was found only in one patient.

We observed a significant negative correlation of N1 (%, $R = -0.50$, $p < 0.05$) and N3 (%, $R = -0.60$, $p < 0.05$) with REM (%). Also, a positive correlation was observed between sleep efficiency and the REM sleep (%, $R = 0.54$, $p < 0.05$). In addition, we found a positive correlation of the arousal index with stage N1 ($R = 0.79$, $p < 0.0001$) and the number of PLMs ($R = 0.54$, $p < 0.05$).

Interestingly, we observed a positive correlation between the CMTNS and the AHI ($R = 0.65$, $p < 0.05$, $N = 14$), indicating a direct relationship between the degree of severity of CMT2 disease and the AHI. **Figure 1** illustrates the simple linear regression model showing that the variations in the CMTNS can explain, at least in part, 31% of the alterations observed in the AHI from the sample of CMT2 patients studied. However, no significant correlation was observed between CMTNS and arousal index or WASO (%).

Figure 1—Correlation between CMTNS and AHI in CMT2 patients (N = 14).



CMTNS, Charcot-Marie-Tooth neuropathy score; AHI, apnea-hypopnea index; CMT2, Charcot-Marie-Tooth type 2.

DISCUSSION

The current study is the first to describe the sleep pattern of CMT2 patients from the biggest multigenerational family in Brazil with autosomal dominant transmission. Sixteen patients with CMT2 were subjected to sleep questionnaires and PSG. The ESS showed that 31% had daytime sleepiness, probably associated with fatigue. Boentert et al. evaluated by telephone the prevalence of daytime sleepiness and fatigue, finding that CMT1 group reported more fatigue and daytime sleepiness.[21] Regarding the subjective quality of sleep, we observed that most patients had a poor quality of sleep, mainly due to difficulties in beginning or maintaining sleep, suggesting possible insomnia. Conversely, Phillips et al. did not show evidence of hypersomnia assessed by ESS in 13 patients with CMT, but found 38% had insomnia due to leg cramps.[22]

The Berlin questionnaire application showed low risk for sleep disordered breathing, which was then confirmed by PSG, as most patients presented AHI < 5. Although only 2 patients had sleep disordered breathing, snoring was prevalent (81%) in the CMT2 patients. Snoring is usually more frequent in men than women, linked to obesity, and with a general prevalence between 3.6% to 35%.[23–26] However, in our sample, the presence of snoring evaluated through PSG was higher than in general population, and was independent of gender and BMI. The snoring is commonly observed in patients with sleep apnea in association with a reduction of the upper airway.[27] The progressive character of OSA over the years suggests a continuous spectrum of severity, ranging from isolated presence of snoring to severe OSA.[28] However, how the transition of habitual snoring to OSA occurs it is not yet clear. Although we did not observe an increase of sleep apneas during sleep in the CMT2 patients, the linear regression analysis showed a relationship between the severity of the disease and the AHI. Greater scores in the CMTNS, which indicated higher commitment of the proximal segments, could well affect muscle tone in breathing-related muscles, explaining at least in part this correlation. Studies in CMT1 patients also found a correlation between the severity of CMT1 neuropathy and the severity of OSAS.[9,29] It is possible that the degree of severity of the patients with CMT2 was not severe enough to contribute to increased respiratory events, but was limited to snoring and possible flow limitation. However, this assumption would need a further longitudinal prospective study to confirm if indeed the progression of CMT2 disease would be followed by a greater increase in AHI.

Dematteis and colleagues described the prevalence of OSAS in 82% of CMT1 patients, with a predominance of

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obstructive events, and an increase with age and male gender.[6] Later, Dziewas et al.[9] corroborated this study, also showing a higher frequency of OSAS in CMT1 patients (42%) compared to a control group, possibly due to a pharyngeal neuropathy. In the general population, the prevalence of OSAS is 2% to 32.9%.[25,30,31] Indeed, most studies of sleep apnea in CMT have focused on the type 1 of this disease. The few studies describing sleep in CMT2 through questionnaires reveal a high prevalence of RLS and PLM disorder during sleep, mainly because of the central role of the axonal atrophy in CMT2 disease.[12,32–34] However, in the current study we did not find any evidence of movement-related sleep disorders. Only 2 (13%) patients presented a PLM index greater than 15/h against 40% found by Gemignani and colleagues.[32] Also, the absence of sleep bruxism in the PSG corroborates a previous study in this same family, in which the subjective complaint of clenching teeth associated with orofacial pain was not observed.[35]

In the sleep architecture, our study showed no important changes in sleep latency, although most patients reported difficulty in initiating sleep in the PSQI questionnaire. However, there was an increase of WASO (%) and arousals, suggesting a fragmented sleep pattern, contributing to the lower sleep efficiency (< 85%) found in 50% of the patients. Also, we found a decrease in REM sleep—characterized by cortical desynchronization—in association with an increase in N3, the sleep stage characterized by slow wave sleep and cortical synchronization. The underlying mechanisms for the increase of arousals and WASO are unknown, as they were related to neither sleep disordered breathing nor PLM. Although we did not evaluate pain in the current study, most of the patients with severe CMT2 reported feeling pain in the feet during walking, but not during sleep or the PSG exam. As sleep and pain present a bidirectional relationship (i.e., pain may impair sleep quality, while sleep deprivation may lead to hyperalgesia), this may partially explain our findings on sleep pattern.[36,37] Sleep fragmentation might contribute to frequent interruptions of REM sleep stages, leading to its decrease, followed by compensation with an increase in N3 sleep stage. Further study of cortical arousals and electrophysiological precipitants would be necessary to elucidate the possible causes of this finding in CMT2 patients.

Usually, REM sleep occurs for 20% to 25% of the total sleep time. Although there have been no previous studies about sleep pattern in CMT patients, a study on diabetic neuropathy found an increase in light sleep stages (N1 and N2) and a reduction in deeper sleep stages (N3) and REM, in association with snoring and an increased respiratory disturbance index.[38]

The presence of pyramidal signs indicates the commitment of the central nervous system. Although it is not frequent in CMT patients, in this study we found 63% of individuals presented pyramidal signs. These patients did not differ in any of the parameters evaluated compared to those without pyramidal signs, suggesting this may not influence the sleep pattern.

This study has some limitations. First, the PSG was evaluated without an adaptation night, due to financial and logistic difficulties. However, it is known that some alterations in sleep architecture may occur because of unfamiliar sleep environment bias and first-night effect.[39,40] Also, we have to consider that they were transported around 180 km to the sleep laboratory in Aracaju city. Second, the absence of a control group with family members not affected by CMT2 did not allow us to compare the results obtained in the CMT2 group regarding the sleep pattern. Third, the use of the Rechtschaffen & Kales criteria is a limitation of the study, as our results could have differed if we had used the American Academy of Sleep criteria. Fourth, although the current study included the largest CMT2 family described in the literature, it would be desirable to include other families in future approaches to reduce sample bias and increase analysis power.

In summary, we found in a large family with CMT2 disease a high prevalence of snoring unrelated to sleep disordered breathing and poor sleep quality due to fragmentation, leading to reduction of REM sleep. As sleep plays an important role in the body's homeostasis, promoting physical and mental health, future studies focusing on the early detection and treatment of sleep problems in CMT2 patients are necessary to understand if improvement in sleep quality may help to avoid or delay the progression of the disease, leading to a lower neuropsychological impact and a better quality of life.

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