Frequencies and Associations of Narcolepsy-Related Symptoms: A Cross-Sectional Study

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Objectives: Narcolepsy is a disabling disease with a delayed diagnosis. At least 3 years before the disorder identification, several comorbidities can be observed in patients with narcolepsy. The early recognition of narcolepsy symptoms may improve long-term prognosis of the patients. Thus, we aimed to investigate the prevalence of the symptoms associated with narcolepsy and its social and psychological association in a sample of Sao Paulo city inhabitants.

Methods: We performed a cross-sectional evaluation with 1,008 individuals from the Sao Paulo Epidemiologic Sleep Study (EPISONO). Excessive daytime sleepiness (EDS) was assessed by the Epworth Sleepiness Scale. Volunteers were also asked about the occurrence of cataplectic-like, hypnagogic or hypnopompic hallucinations, and sleep paralysis symptoms. The participants underwent a full-night polysomnography and completed questionnaires about psychological, demographic, and quality of life parameters.

Results: We observed a prevalence of 39.2% of EDS,

15.0% of cataplectic-like symptom, 9.2% of hypnagogic or hypnopompic hallucinations, and 14.9% of sleep paralysis in Sao Paulo city inhabitants. A frequency of 6.9% was observed when EDS and cataplectic-like symptoms were grouped. The other associations were EDS + hallucinations (4.7%) and EDS + sleep paralysis (7.5%). Symptomatic participants were predominantly women and younger compared with patients without any narcolepsy symptom (n = 451). Narcolepsy symptomatology was also associated with a poor quality of life and symptoms of depression, anxiety, and fatigue.

Conclusions: Narcolepsy-related symptoms are associated with poor quality of life and worse psychological parameters.

Keywords: narcolepsy; symptomatology; epidemiological

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Although narcolepsy may be considered a rare neurological condition, the repercussions of this disorder are substantial. Narcolepsy induces a 1.5-fold increase in the mortality rate compared with healthy individuals.[1] As a consequence, narcoleptic patients have approximately 2-fold increased rates of hospital or other medical services admissions.[2]

Narcolepsy is often associated with a tetrad of symptoms, including, excessive daytime sleepiness (EDS), hypnagogic or hypnopompic hallucinations, sleep paralysis, and cataplexy. EDS is the most frequent symptom observed in narcoleptic patients.[3] In the natural history of EDS, several cardiometabolic and psychiatric conditions are associated with the incidence and persistence of EDS.[4]

Patients with narcolepsy experience the symptoms over a long period until receiving the definitive diagnosis, ranging between 10 and 15 years.[5,6] A possible factor associated with this delay could be the failure to recognize the characteristic clinical features.[7] Indeed, Jennum et al. demonstrated that narcoleptic patients present a wide range of comorbidities at least 3 years before the narcolepsy diagnosis, including a higher frequency of neurological diseases and other sleep disorders.[8] The recognition of the symptoms associated with narcolepsy seems to be an important approach for a better long-term prognosis of the disorder. Thus, we hypothesized that the presence of

BRIEF SUMMARY

Current Knowledge/Study Rationale: Narcoleptic patients present a wide range of comorbidities at least 3 years before the narcolepsy diagnosis. The recognition of the symptoms associated with narcolepsy seems to be an important approach for a better long-term prognosis of the disorder.

Study Impact: We found that symptomatic patients, even without the confirmatory narcolepsy diagnosis, present higher scores of depression and anxiety symptoms, fatigue, and a poor self-perception of life quality. Identification of these symptoms could decrease the delay of narcolepsy diagnosis and improve the patient's prognosis right after the first years of the symptoms onset.

narcolepsy-related symptoms, without a confirmatory diagnosis, could be associated with a poor quality of life and psychological impairments.

In the present study, we aimed to evaluate the prevalence of EDS, cataplectic-like symptoms, hypnagogic and hypnopompic hallucinations, and sleep paralysis in a sample of Sao Paulo city inhabitants. In addition, we purposed to characterize the demographic, psychological, and sleep parameters of individuals who presented EDS, the most prevalent symptom in narcolepsy, in association with another narcolepsy-related symptom.

METHODS

Study Design

We performed an observational cross-sectional analysis with the data obtained from the Sao Paulo Epidemiologic Sleep Study (EPISONO). The complete methodology was described in detail previously.[9] Briefly, the sample was obtained by a probabilistic 3-stage cluster sampling technique.[10] First, the sampling was performed according to the 4 socioeconomic regions of Sao Paulo as classified by the National Institute of Demographics and Statistics (IBGE) census. The next stages consisted of the selection of a given household and the random choose of 1 dweller of each picked house. An initial sample size of 1,056 participants was defined based on previous studies focused on the prevalence of obstructive sleep apnea (OSA), which was the primary objective of the EPISONO study. At that moment, most of the studies reported a prevalence of 2.2% to 4.5% of OSA in the general population.[11–13] For this reason, the power of the study was based on 3% precision. A total of 1,101 volunteers were selected and, from this initial number, 1,042 volunteers (44.9% men; 55.1% women) signed the informed consent form and underwent a full-night polysomnography (PSG). The refusal and response rates were 5.4% and 94.6%, respectively. The study was approved by the University's Institutional Ethics Committee (CEP 0593/06) and was registered with ClinicalTrials.gov (Identifier NCT00596713).

Symptom Tetrad Assessment

Questionnaire

Excessive daytime somnolence: sleepiness was assessed using the Epworth Sleepiness Scale, which consists of an 8-question scale that measures the chance to fall asleep in daily situations.[14] The cut-off for EDS was ≥ 10.

Closed Questions

All the questions below regarding narcolepsy symptoms were created by a panel of sleep specialists from the Sleep Institute (Sao Paulo, Brazil) and were not validated. Also, confirmatory clinical interview for assessment of narcolepsy features were not performed in the study due to methodological limitations.

Cataplectic-like symptom: the cataplectic-like symptom question covered the occurrence of an event in the last 6 months. The participants were asked if they had "any event of sudden weakness or difficulty in speaking in situations of strong emotion (such as joy, anger, fear, or surprise) without losing consciousness."

Hypnagogic/hypnopompic hallucinations: the question assessing hypnagogic and hypnopompic hallucinations covered the occurrence of an event in the last 6 months, considering only visual hallucinations. The participants were asked if they had ever experienced an event of "viewing strange images immediately before sleep or waking up (such as a hallucination)."

Sleep paralysis: the sleep paralysis question covered the occurrence of events of "feeling paralyzed, unable to move, a few moments before falling asleep or just after awaking" without a time-frame, but including frequency ranging from daily to monthly. Thus, the sample was stratified into patients who had never experienced sleep paralysis and those with a frequency of at least 1 event per month.

Selection Criteria

We stratified the sample into 1 group of participants without narcolepsy symptoms and 3 groups of symptomatic patients. The inclusion and exclusion criteria for each group are described below.

Narcolepsy Symptom Grouping

We excluded participants who reported they "have had seizures or epileptic seizures within the last 7 or the last 30 days" or were using anticonvulsant medication. Patients who showed missing data in the Epworth questionnaire or in the closed questions about the narcolepsy symptoms were also excluded from the analysis. As summarized in **Figure 1**, we grouped the sample according to the presence of EDS and 1 additional narcolepsy-related symptom (cataplectic-like symptom, sleep paralysis, or hypnagogic and hypnopompic hallucinations). Considering the study design, only the association of symptoms with a prevalence of at least 3% was included in the comparison analysis.

- EDS + cataplexy group: patients with Epworth scores ≥ 10 reporting cataplectic-like symptoms in the last 6 months.
- EDS + hallucinations group: patients with Epworth scores ≥ 10 reporting hypnagogic and/or hypnopompic hallucinations in the last 6 months.
- EDS + sleep paralysis group: patients with Epworth scores ≥ 10 reporting at least 1 event of sleep paralysis per month.

Patients without Symptoms

To compare the demographic data and the sleep and psychological parameters, a group of patients without symptoms was selected as a control. As performed in the 3 symptomatic groups, we excluded participants with self-report of epilepsy or using anticonvulsant medication and those who showed missing data in the narcolepsy symptom assessment. In this group, the inclusion criteria for the comparisons consisted of patients without any of the 4 narcolepsy-related symptoms (EDS, cataplectic-like symptom, sleep paralysis, and hypnagogic or hypnopompic hallucinations). From the total amount of participants, 451 participants (44.7%) met the criteria for the group without symptoms.

Psychological Assessments

All questionnaire data were collected by a trained group of 10 psychologists, 3 physical education teachers, and 6 physicians.[9]

Demographic data: we assessed the age, gender, and ethnic classification of all sample. Body mass index (BMI) of each participant was calculated as body weight divided by square of the body height. Socioeconomic classification was obtained according to the Critério de Classificação Econômica Brasil (CCEB).[15]

To evaluate the possible influence of medication use and working period in the polysomnographic and psychological variables, we collected the data about central nervous

Figure 1—Flowchart of the study protocol and the frequencies of the narcolepsy associated symptoms in the sample.
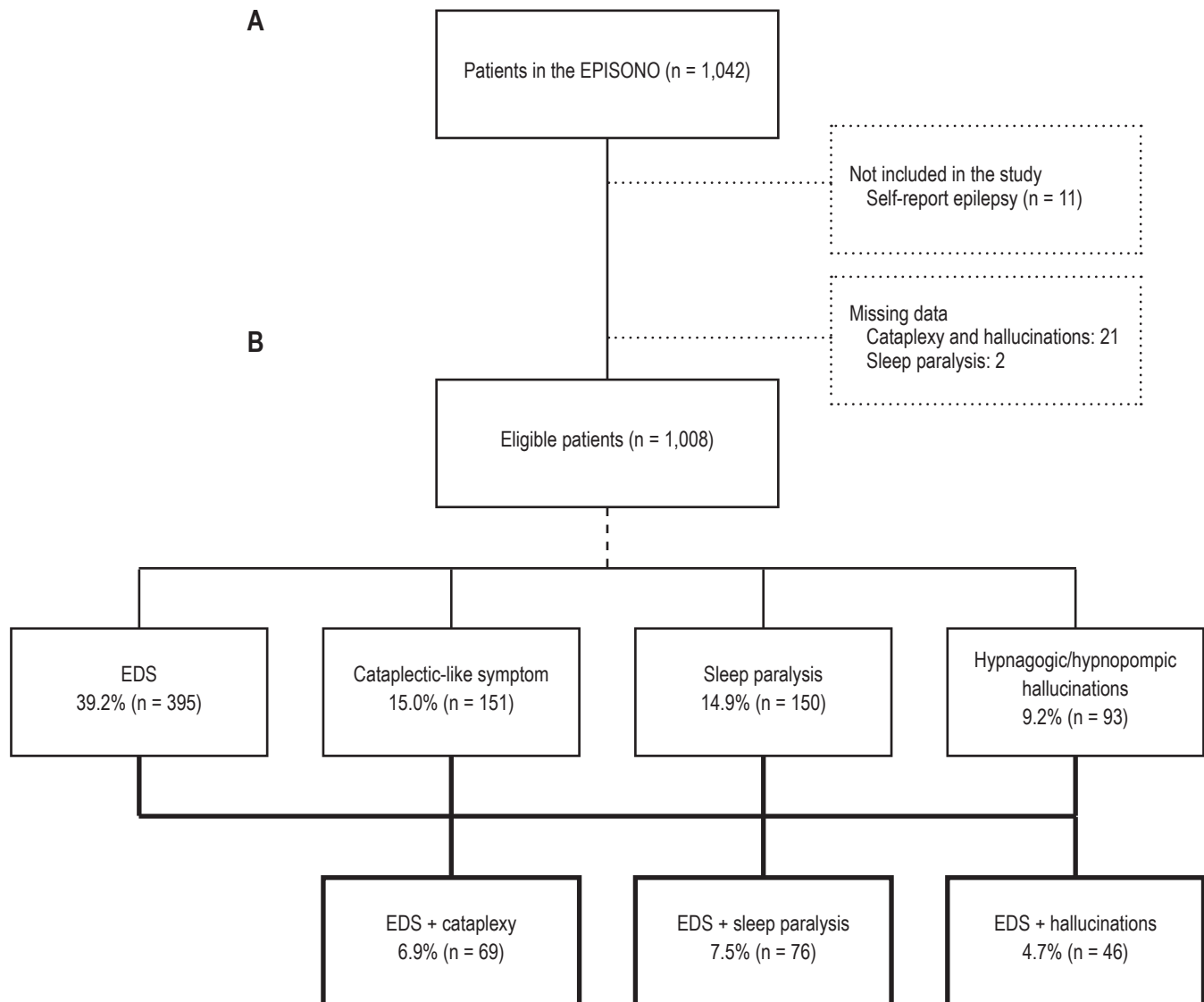
(A) flowchart; **(B)** frequencies of the narcolepsy associated symptoms in the sample.

system-acting medications (CNS-acting medication) and the proportion of shift-workers by UNIFESP Sleep Questionnaire.[16] CNS-acting medication comprised antidepressants, benzodiazepines, and amphetamines.

Quality of life: patients filled the Portuguese version of the abbreviated World Health Organisation Quality of Life assessment (WHOQOL-BREF).[17] This instrument comprises 26 questions distributed into 4 different domains associated with quality of life: physical health, psychological health, social relationships, and environment. The mean scores in each domain range from 0 to 100, according to the WHOQOL transformation table. Higher scores correspond to a better quality of life.

Psychological assessment: anxiety and depressive symptoms were evaluated by the Portuguese version[18] of Beck Anxiety Inventory (BAI)[19] and the Beck Depression Inventory (BDI),[20] respectively. The final scores were classified as: < 11 (no anxiety or depression) and ≥ 11 (anxiety and depression).

Sleep quality and fatigue: to assess the perception of sleep quality and fatigue, the participants completed the Pittsburgh Sleep Quality Index (PSQI)[21] and the Chalder Fatigue Scale,[22] respectively. Cut-offs for PSQI were ≤ 5 (good sleepers) and > 5 (poor sleepers) and for fatigue were ≤ 4 (no fatigue) and > 4 (fatigue).

Polysomnography

Data from PSG were evaluated to compare the sleep parameters between the symptomatic and asymptomatic patients, and to control other possible sleep disorders from the analyses. The PSG procedures and criteria for sleep scoring have been previously described.[9] To evaluate the possible association of the narcolepsy-related symptoms with the presence of other sleep disorders, we stratified the groups by apnea-hypopnea index (AHI) > 15 events/h and periodic limb movement index (PLMI) > 5 events/h.

Table 1—Sociodemographic characteristics of the study population.

	Without Sx (n = 451)	EDS + Cataplexy (n = 69)	Without Sx (n = 451)	EDS + Hall (n = 46)	Without Sx (n = 451)	EDS + Sleep Paralysis (n = 76)
Age (years)	44.0 ± 0.7	38.0 ± 1.8*	44.0 ± 0.7	38.0 ± 2.2*	44.0 ± 0.7	35.1 ± 1.7*
Gender (%)						
Female	51.4	66.7*	51.4	67.4*	51.4	67.1*
Male	48.6	33.3*	48.6	32.6*	48.6	32.9*
BMI (kg/m²)	26.9 ± 0.3	27.1 ± 0.7	26.9 ± 0.3	26.4 ± 0.8	26.9 ± 0.3	26.4 ± 0.6
Ethnicity (%)						
Caucasian	59.0	59.4	59.0	50.0	59.0	59.2
Afro-Brazilian	10.6	14.5	10.6	23.9*	10.6	11.8
Mulatto	13.1	15.9	13.1	10.9	13.1	13.2
Asian	3.3	1.5	3.3	0.0	3.3	3.9
Native	2.9	2.9	2.9	10.9*	2.9	2.6
Unknown/Other	11.1	5.8	11.1	4.3	11.1	9.2
Socioeconomic status (%)						
High	14.0	8.7	14.0	4.3	14.0	10.5
Mid	37.5	30.4	37.5	34.8	37.5	38.2
Low	48.6	60.9	48.6	60.9	48.6	51.3
Education level (%)						
High	57.8	56.5	57.8	56.5	57.8	67.1
Elementary and middle	34.8	31.9	34.8	32.6	34.8	27.6
Illiterate	7.4	11.6	7.4	10.9	7.4	5.3
CNS-acting medication (%)	18.0	13.3	18.0	20.0	18.0	12.0
Shift-worker (%)	3.4	0.0	3.4	2.6	3.4	1.6
AHI > 15 events/h	40.8	34.8	40.8	37.0	40.8	34.2
PLMI > 5 events/h	6.0	0.0*	6.0	0.0	6.0	2.6

Data are presented as mean ± SEM and percentage. *p < 0.05 compared with patients without symptoms. EDS, excessive daytime sleepiness; BMI, body mass index; CNS, central nervous system; AHI, apnea-hypopnea index; PLMI, periodic limb movements index; Sx, symptoms; Hall, hallucinations.

Statistical Analysis

Qualitative variables were analyzed using χ^2 test. To evaluate the effect of narcolepsy-related symptoms on the psychological and demographic parameters, the general linear model (ANCOVA) was performed. In the comparison between EDS + cataplexy group and patients without symptoms, the adjusted confounding factors were age, gender, and PLMI > 5 events/h. For the comparisons with EDS + hallucinations group, the adjusted confounding factors were age, gender, and ethnicity. For EDS + sleep paralysis group, the analyses were only controlled for age and gender. The data were represented as adjusted mean ± standard error of the mean (SEM) or percentage. Statistical significance was considered at a level of p < 0.05.

RESULTS

As shown in **Figure 1A**, 11 participants who reported having epilepsy were excluded from the analyses. Twenty-one patients did not correctly complete the cataplectic-like symptom and hallucinations questions. In the sleep paralysis question, there were 2 missing values.

Of the 1,008 individuals initially selected in the study, 39.2% (n = 395) had EDS. Sleep paralysis, cataplectic-like symptom, and hypnagogic or hypnopompic hallucinations were reported

by 14.9% (n = 150), 15.0% (n = 151), and 9.2% (n = 93) of participants, respectively. When participants were grouped according to the presence of EDS and 1 more associated narcolepsy symptom, a frequency of 6.9% (n = 69) was observed for EDS + cataplexy (**Figure 1B**). The other associations were EDS + hallucinations (4.7%) and EDS + sleep paralysis (7.5%). When the 4 symptoms were grouped, a frequency of only 1.5% was observed. Regarding the design of the present study, this prevalence was not considered statistically precise. Thus, the grouping of 4 symptoms (narcolepsy tetrad) was not used in the analyses.

The 3 symptomatic groups (EDS + cataplexy, EDS + hallucinations, and EDS + sleep paralysis) showed similar demographic profiles when compared with the patients without symptoms (**Table 1**). On average, the 3 symptomatic groups were 6–9 years younger than the group without symptoms. A significant association with female gender was also observed. Approximately 67% of the participants with EDS + cataplexy ($\chi^2 = 6.6$; df = 1; p < 0.05), EDS + hallucinations ($\chi^2 = 4.3$; df = 1; p < 0.05), and EDS + sleep paralysis ($\chi^2 = 6.4$; df = 1; p < 0.05) were women. No significant effect of the narcolepsy symptoms was observed on the BMI, indicated by similar values between the symptomatic groups and patients without symptoms. The group EDS + hallucinations showed a significant association with a higher proportion of Afro-Brazilian

Table 2—Polysomnographic variables among the participants with and without narcolepsy symptoms.

	Without Sx (n = 451)	EDS + Cataplexy (n = 69)	Without Sx (n = 451)	EDS + Hall (n = 46)	Without Sx (n = 451)	EDS + Sleep Paralysis (n = 76)
Total sleep time (min)	335.7 ± 3.5	357.7 ± 9.2*	335.5 ± 3.6	357.1 ± 11.3	336.4 ± 3.6	358.3 ± 8.9*
Sleep latency (min)	19.2 ± 1.2	13.1 ± 3.1	19.2 ± 1.2	14.4 ± 3.8	19.1 ± 1.2	13.1 ± 2.9
REM sleep latency (min)	105.2 ± 2.6	100.4 ± 6.6	105.4 ± 2.7	86.9 ± 8.9	105.5 ± 2.6	92.6 ± 6.5
REM sleep latency < 15 min (%)	1.1	0.0	1.1	0.0	1.1	0.0
Sleep efficiency (%)	80.3 ± 0.6	84.7 ± 1.5*	80.2 ± 0.6	84.4 ± 1.9*	80.4 ± 0.6	83.8 ± 1.5*
Arousal index (events/h)	14.7 ± 0.5	15.3 ± 1.2	14.9 ± 0.5	14.0 ± 1.4	14.6 ± 0.5	14.9 ± 1.1
% N1	4.8 ± 0.2	4.1 ± 0.4	4.8 ± 0.2	4.0 ± 0.5	4.8 ± 0.2	4.1 ± 0.4
% N2	55.1 ± 0.4	53.7 ± 1.2	55.2 ± 0.4	54.8 ± 1.4	55.1 ± 0.4	53.8 ± 1.1
% N3	21.8 ± 0.4	22.4 ± 1.0	21.8 ± 0.4	19.8 ± 1.2	21.8 ± 0.4	21.4 ± 1.0
% REM	18.3 ± 0.3	19.9 ± 0.8	18.3 ± 0.3	21.4 ± 1.0*	18.3 ± 0.3	20.8 ± 0.8*

Data are presented as adjusted mean ± SEM and percentage. In the comparison between EDS + cataplexy group and patients without symptoms, the confounding factors were age, gender, and PLMI > 5 events/h. For the comparisons with EDS + hallucinations group the confounding factors were age, gender, and ethnicity. For EDS + sleep paralysis group, the analysis were controlled for age and gender. *$p < 0.05$ compared with patients without symptoms. EDS, excessive daytime sleepiness; Sx, symptoms; Hall, hallucinations.

and native self-declared ethnicities compared with patients without symptoms ($\chi^2 = 17.6$; df = 5; $p < 0.05$). The frequency of socioeconomic status, education level, CNS-acting medication use, and shift-workers were similar between the groups.

A significant association between a lower frequency of patients with PLMI > 5 events/h and the group EDS + cataplexy ($\chi^2 = 4.4$; df = 1; $p < 0.05$) was observed. To evaluate a possible association between the narcolepsy symptoms and OSA, we stratified the sample by AHI > 15 events/h. We observed no significant differences in the frequency of apneic patients between the 3 symptomatic groups (EDS + cataplexy, EDS + hallucinations, and EDS + sleep paralysis) and patients without symptoms.

Sleep parameters obtained from the PSG exam are presented in **Table 2**. The 3 symptomatic groups (EDS + cataplexy, EDS + hallucinations, and EDS + sleep paralysis) showed higher sleep efficiencies compared with patients without symptoms. However, the mean values of sleep efficiency of all groups were lower than normal range ($\geq 85\%$). A significant effect of the groups EDS + cataplexy ($F_{1,518} = 5.0$; $p < 0.05$) and EDS + sleep paralysis ($F_{1,530} = 5.2$; $p < 0.05$) were observed in the total sleep time. Patients with EDS + cataplexy and EDS + sleep paralysis showed longer total sleep time in the PSG compared with the group without symptoms. The percentage of REM sleep was also significantly higher in the EDS + hallucinations ($F_{1,500} = 9.0$; $p < 0.05$) and EDS + sleep paralysis ($F_{1,530} = 8.8$; $p < 0.05$) compared with the group without symptoms.

Narcolepsy symptoms were associated with a poor subjective sleep quality and psychiatric symptoms (**Table 3**). A higher frequency of poor sleepers was observed in the groups EDS + cataplexy ($\chi^2 = 16.4$; df = 1; $p < 0.05$) and EDS + hallucinations ($\chi^2 = 20.3$; df = 1; $p < 0.05$). Only 30.4% and 21.7% of the participants from EDS + cataplexy and EDS + hallucinations groups were classified as good sleepers. We observed a fatigue frequency of 75.4% in the EDS + cataplexy ($\chi^2 = 60.0$; df = 1; $p < 0.05$), 65.9% in EDS + hallucinations

(χ^2 2 8.7; df = 1; $p < 0.05$), and 58.9% in EDS + sleep paralysis ($\chi^2 = 29.7$; df = 1; $p < 0.05$) groups compared with 26.9% in patients without symptoms. Approximately 72%, 70%, and 55% of the participants from EDS + cataplexy ($\chi^2 = 44.8$; df = 1; $p < 0.05$), EDS + hallucinations ($\chi^2 = 26.4$; df = 1; $p < 0.05$), and EDS + sleep paralysis ($\chi^2 = 18.5$; df = 1; $p < 0.05$) groups were classified with depressive symptoms, respectively. The symptomatic groups also showed a significant association with anxiety symptoms in the BAI. Anxiety symptoms were observed in 75.8%, 69.2%, and 43.1% of the individuals with EDS + cataplexy ($\chi^2 = 87.1$; df = 1; $p < 0.05$), EDS + hallucinations ($\chi^2 = 48.7$; df = 1; $p < 0.05$), and EDS + sleep paralysis ($\chi^2 = 19.3$; df = 1; $p < 0.05$) groups, respectively. In the group without symptoms, only 19.5% of the participants showed anxiety symptoms. To exclude a possible effect of psychological symptoms on the sleep parameters, we reanalyzed the data including also the results of BDI and BAI as continuous covariates (data not shown). As the only alteration in the results was in the percentage of REM sleep of the EDS + hallucinations group that was no longer different from the patients without symptoms, we elected to keep our data without this control.

All the 3 symptomatic groups (EDS + cataplexy, EDS + hallucinations, and EDS + sleep paralysis) also showed poor quality of life in the physical health and psychological domains of WHOQOL-BREF, corroborating the findings of BAI and BDI. Only the EDS + hallucinations group showed a significant effect on the 4 domains of WHOQOL-BREF, presenting lower scores compared with the group without symptoms.

DISCUSSION

We investigated the frequencies of associated symptoms of narcolepsy in a sample of Sao Paulo city inhabitants. Symptomatic participants were predominantly women and younger compared with patients without symptoms. The presence of EDS in addition to cataplectic-like symptom, hallucinations,

Table 3—Association of quality of life and psychological parameters with narcolepsy symptoms.

	Without Sx (n = 451)	EDS + Cataplexy (n = 69)	Without Sx (n = 451)	EDS + Hall (n = 46)	Without Sx (n = 451)	EDS + Sleep Paralysis (n = 76)
PSQI score						
Good sleepers	56.6	30.4*	56.6	21.7*	56.6	48.6
Poor sleepers	43.4	69.6*	43.4	78.3*	43.4	51.4
Chalder Fatigue Scale						
No fatigue	73.1	24.6*	73.1	34.1*	73.1	41.1*
Fatigue	26.9	75.4*	26.9	65.9*	26.9	58.9*
BDI score						
No depression	71.0	28.1*	71.0	29.7*	71.0	45.1*
Depression	29.0	71.9*	29.0	70.3*	29.0	54.9*
BAI score						
No anxiety	80.5	24.2*	80.5	30.8*	80.5	56.9*
Anxiety	19.5	75.8*	19.5	69.2*	19.5	43.1*
WHOQOL-BREF						
Physical health	72.5 ± 0.7	57.9 ± 1.8*	72.5 ± 0.7	60.3 ± 2.2*	72.6 ± 0.7	62.5 ± 1.7*
Psychological	67.9 ± 0.6	57.9 ± 1.6*	67.9 ± 0.6	60.6 ± 2.0*	67.9 ± 0.6	62.8 ± 1.5*
Social relationships	69.5 ± 0.9	57.8 ± 2.2*	69.5 ± 0.8	63.3 ± 2.7*	69.5 ± 0.8	65.5 ± 2.0
Environment	53.1 ± 1.0	48.8 ± 2.5	53.2 ± 1.0	44.9 ± 3.1*	53.1 ± 1.0	53.6 ± 2.4

Data are represented as adjusted mean ± SEM and percentage. In the comparison between EDS + cataplexy group and patients without symptoms, the confounding factors were age, gender, and PLMI > 5 events/h. For the comparisons with EDS + hallucinations group the confounding factors were age, gender, and ethnicity. For EDS + sleep paralysis group, the analysis were controlled for age and gender. *$p < 0.05$ compared with patients without symptoms. EDS, excessive daytime sleepiness; PSQI, Pittsburgh Sleep Quality Scale; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; Sx, symptoms; Hall, hallucinations.

or sleep paralysis was associated with poor quality of life and worse psychological parameters.

EDS is the most prevalent symptom of narcolepsy and can be observed in up to 91% of the patients.[3] In 40% of narcolepsy cases, EDS onset preceded cataplexy, and in 54% it was concomitant with cataplexy.[23] Cataplexy may occur in 60% to 90% of the narcoleptic patients and hypnagogic or hypnopompic hallucinations in 30% to 60%.[24,25] The occurrence of 2 or 3 symptoms is present in approximately 30% of narcoleptic patients.[24] On the other hand, the complete symptom tetrad is observed in only 10% to 15% of narcolepsy cases.[25]

In the general population of Sao Paulo city, we observed a prevalence of 39.2% of EDS, 15.0% of cataplectic-like symptom, 9.2% of hypnagogic or hypnopompic hallucinations, and 14.9% of sleep paralysis. The frequency of cataplectic-like symptom in the present study was within the range of 7.6% to 29.3% previously reported in different ethnic populations.[26–29] A study of five European countries by Ohayon et al.[30] has investigated the prevalence of the narcolepsy tetrad in a general population. In the whole sample, daytime sleepiness, cataplexy, hypnagogic or hypnopompic hallucinations, and sleep paralysis were reported by 15%, 1.2%, 24%, and 6.2% of the participants, respectively. Some factors may explain these discrepancies in the symptom proportion between our results and the study of Ohayon et al.[30] Firstly, we assessed EDS using only the Epworth Sleepiness Scale. Although this is the most widely used instrument for the evaluation of sleepiness, EDS comprises other clinical features in narcolepsy, such as the irresistible sleep attack and the relief of sleepiness provided by naps.[31] Thus, a broad investigation of sleepiness could decrease

the proportion of participants with EDS in our study. Secondly, in the study of Ohayon et al., narcolepsy symptoms differed considerably among the countries. For example, in Portugal, a lower frequency of 10.4% of hypnagogic or hypnopompic hallucinations was reported, corroborating the prevalence of 9.2% in our study.

The association between gender and narcolepsy is controversial. Some reports have suggested a higher frequency of narcolepsy in women,[32] while others have indicated a 73% greater prevalence of the disease in men.[33] In addition, gender seems to affect the interval between the symptom onset and diagnosis. Won et al.[34] demonstrated that men are diagnosed on average 12 years earlier than women. The authors suggested that a possible factor involved in this delayed diagnosis is that women may be less forthcoming about their symptoms. However, our findings contradict this hypothesis, showing that women have higher frequency of reported narcolepsy-related symptoms. Thus, women seem to have a better perception of the symptoms associated with narcolepsy that could favor the early diagnosis of the disorder.

Indeed, it is not simply the patient's perception which affects the disease diagnosis, but also the difficulty that health professionals have in recognizing symptoms related to narcolepsy, that leads to delayed diagnosis.[35] EDS and hallucinations are features commonly observed in other sleep, neurological, and psychiatric disorders.[36] Although cataplexy is a phenomenon present only in narcolepsy, the variety of phenotypes can make it very difficult to diagnose.[37] The severity of cataplexy ranges from partial muscle weakness to complete body paralysis with different frequencies, triggered by a variety of emotional

conditions.[37] In cases of narcolepsy without cataplexy, the diagnosis can be even more challenging due to the nonspecific nature of the symptoms.[38]

A full-night PSG followed by the multiple sleep latency test (MSLT) is mandatory for the narcolepsy diagnosis.[39] However, these exams are expensive and need many resources, which may hinder their implementation in large-scale health services. In addition, the MSLT has been reported to have low sensitivity and specificity for EDS diagnosis,[40] and a high false-positive and false-negative rate.[41] Therefore, the assessment of the symptoms associated with narcolepsy may be a more effective initial way to increase diagnostic coverage. Indeed, structured interviews for sleep disorders present good agreement with PSG and MSLT, having an accuracy of 80% for narcolepsy with cataplexy.[42]

Patients with narcolepsy often experience more difficulties at their workplace than at home, especially because of their incapacity to remain awake during daytime.[24] Consequently, these individuals show lower employment rates and income levels than healthy patients.[43] Narcolepsy is also associated with poor quality of life[44] and psychiatric disorders.[45] In a case-control study, Droogleever et al.[46] found that 53% of narcoleptic patients report anxiety or panic attacks, which were mainly related to frightening episodes during hypnagogic hallucinations. To our knowledge, we performed the first study that investigated the association of psychological and narcolepsy-related symptoms in the general population. We found that symptomatic patients, even without the confirmatory narcolepsy diagnosis, present higher scores of depression and anxiety symptoms, fatigue, and a poor perception of their quality of life. In this sense, the development of therapeutic approaches aiming to increase awareness about the importance of early recognition of associated symptoms of narcolepsy is necessary. Identification of these symptoms could decrease delay in narcolepsy diagnosis and improve quality of life of patients following symptom onset.

Study limitations include lack of a definitive narcolepsy diagnosis by MSLT after the full-night PSG. Thus, the prevalence of the associated symptoms of narcolepsy could have been overestimated by the presence of non-narcoleptic patients in the group. Regarding the study design, the results of the present study did not establish a causal relationship between narcolepsy-related symptoms and the psychological parameters. In addition, the questionnaire used for assessing cataplectic-like symptom, hallucinations, and sleep paralysis symptoms were not validated. The evaluation of cataplectic-like symptom may also not represent a genuine cataplexy event in narcolepsy. Thus, further studies should be performed to elucidate this relationship and to evaluate the accuracy and effectiveness of the early recognition of the narcolepsy-related symptoms in the patients' life.

ABBREVIATIONS

AHI, apnea-hypopnea index
BAI, Beck Anxiety Inventory
BDI, Beck Depression Inventory
BMI, body mass index
CCEB, Critério de Classificação Econômica Brasil

CNS-acting medication, central nervous system acting medication
EDS, excessive daytime sleepiness
EPISONO, Sao Paulo Epidemiologic Sleep Study
Hall, hallucinations
IBGE, National Institute of Demographics and Statistics
MSLT, multiple sleep latency test
OSA, obstructive sleep apnea
PLMI, periodic limb movement index
PSG, polysomnography
PSQI, Pittsburgh Sleep Quality Index
SEM, standard error of the mean
Sx, symptoms
WHOQOL-BREF, abbreviated World Health Organisation Quality of Life assessment

REFERENCES

1. Ohayon MM, Black J, Lai C, Eller M, Guinta D, Bhattacharyya A. Increased mortality in narcolepsy. Sleep 2014;37:439–44.
2. Black J, Reaven NL, Funk SE, et al. The Burden of Narcolepsy Disease (BOND) study: health-care utilization and cost findings. Sleep Med 2014;15:522–9.
3. Carter LP, Acebo C, Kim A. Patients' journeys to a narcolepsy diagnosis: a physician survey and retrospective chart review. Postgrad Med 2014;126:216–24.
4. Fernandez-Mendoza J, Vgontzas AN, Kritikou I, Calhoun SL, Liao D, Bixler EO. Natural history of excessive daytime sleepiness: role of obesity, weight loss, depression, and sleep propensity. Sleep 2015;38:351–60.
5. Flygare J, Parthasarathy S. Narcolepsy: let the patient's voice awaken us! Am J Med 2015;128:10–3.
6. Morrish E, King MA, Smith IE, Shneerson JM. Factors associated with a delay in the diagnosis of narcolepsy. Sleep Med 2004;5:37–41.
7. Thorpy MJ, Krieger AC. Delayed diagnosis of narcolepsy: characterization and impact. Sleep Med 2014;15:502–7.
8. Jennum P, Ibsen R, Knudsen S, Kjellberg J. Comorbidity and mortality of narcolepsy: a controlled retro- and prospective national study. Sleep 2013;36:835–40.
9. Santos-Silva R, Tufik S, Conway SG, Taddei JA, Bittencourt LR. Sao Paulo Epidemiologic Sleep Study: rationale, design, sampling, and procedures. Sleep Med 2009;10:679–85.
10. Kish I. Survey sampling. New York: John Wiley & Sons Inc., 1965.
11. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230–5.
12. Marin JM, Gascon JM, Carrizo S, Gispert J. Prevalence of sleep apnoea syndrome in the Spanish adult population. Int J Epidemiol 1997;26:381–6.
13. Kim J, In K, Kim J, et al. Prevalence of sleep-disordered breathing in middle-aged Korean men and women. Am J Respir Crit Care Med 2004;170:1108–13.
14. Bertolazi AN, Fagondes SC, Hoff LS, Pedro VD, Menna Barreto SS, Johns MW. Portuguese-language version of the Epworth sleepiness scale: validation for use in Brazil. J Bras Pneumol 2009;35:877–83.
15. Associação Brasileira de Empresas de Pesquisa – ABEP. Critério de Classificação Econômica Brasil (CCEB), 2003.
16. Braz S, Neumann BRB, Tufik S. Evaluation of sleep disorders: elaboration and validation of a questionnaire. Revista ABP-APL 1987;9:9–14.
17. Fleck MP, Louzada S, Xavier M, et al. Aplicação da versão em português do instrumento abreviado de avaliação da qualidade de vida WHOQOL-BREF. Rev Saude Public 2000;34:178–83.
18. Gorenstein C, Andrade L. Validation of a Portuguese version of the Beck Depression Inventory and the State-Trait Anxiety Inventory in Brazilian subjects. Braz J Med Biol Res 1996;29:453–7.
19. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988;56:893–7.
20. Beck AT, Guth D, Steer RA, Ball R. Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. Behav Res Ther 1997;35:785–91.
21. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213.

22. Chalder T, Berelowitz G, Pawlikowska T, et al. Development of a fatigue scale. J Psychosom Res 1993;37:147–53.

23. Sturzenegger C, Bassetti CL. The clinical spectrum of narcolepsy with cataplexy: a reappraisal. J Sleep Res 2004;13:395–406.

24. Frauscher B, Ehrmann L, Mitterling T, et al. Delayed diagnosis, range of severity, and multiple sleep comorbidities: a clinical and polysomnographic analysis of 100 patients of the Innsbruck narcolepsy cohort. J Clin Sleep Med 2013;9:805–12.

25. Drakatos P, Leschziner GD. Update on hypersomnias of central origin. Curr Opin Pulm Med 2014;20:572–80.

26. Honda Y. Census of narcolepsy, cataplexy and sleep life among teenagers in Fujisawa city. Sleep Res 1979;8:191.

27. Billiard M, Alperovitch A, Perot C, Jammes A. Excessive daytime somnolence in young men: prevalence and contributing factors. Sleep 1987;10:297–305.

28. Hublin C, Kaprio J, Partinen M, et al. The prevalence of narcolepsy: an epidemiological study of the Finnish Twin Cohort. Ann Neurol 1994;35:709–16.

29. Wing YK, Li RH, Lam CW, Ho CK, Fong SY, Leung T. The prevalence of narcolepsy among Chinese in Hong Kong. Ann Neurol 2002;51:578–84.

30. Ohayon MM, Priest RG, Zulley J, Smirne S, Paiva T. Prevalence of narcolepsy symptomatology and diagnosis in the European general population. Neurology 2002;58:1826–33.

31. Alóe F, Alves RC, Araújo JF, et al. Brazilian guidelines for the diagnosis of narcolepsy. Ver Bras Psiquiatr 2010;32:294–304.

32. Longstreth WT Jr, Ton TG, Koepsell T, Gersuk VH, Hendrickson A, Velde S. Prevalence of narcolepsy in King County, Washington, USA. Sleep Med 2009;10:422–6.

33. Wu H, Zhuang J, Stone WS, et al. Symptoms and occurrences of narcolepsy: a retrospective study of 162 patients during a 10-year period in eastern China. Sleep Med 2014;15:607–13.

34. Won C, Mahmoudi M, Qin L, Purvis T, Mathur A, Mohsenin V. The impact of gender on timeliness of narcolepsy diagnosis. J Clin Sleep Med 2014;10:89–95.

35. Ueki Y, Hayashida K, Komada Y, et al. Factors Associated with Duration Before Receiving Definitive Diagnosis of Narcolepsy among Japanese Patients Affected with the Disorder. Int J Behav Med 2014;21:966–70.

36. Teeple RC, Caplan JP, Stern TA. Visual hallucinations: differential diagnosis and treatment. Prim Care Companion J Clin Psychiatry 2009;11:26–32.

37. Dauvilliers Y, Siegel JM, Lopez R, Torontali ZA, Peever JH. Cataplexy--clinical aspects, pathophysiology and management strategy. Nat Rev Neurol 2014;10:386–95.

38. Baumann CR, Mignot E, Lammers GJ, et al. Challenges in diagnosing narcolepsy without cataplexy: a consensus statement. Sleep 2014;37:1035–42.

39. American Academy of Sleep Medicine. International classification of sleep disorders, 3rd ed. Westchester, IL: American Academy of Sleep Medicine, 2014.

40. Johns MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the Epworth Sleepiness Scale: failure of the MSLT as a gold standard. J Sleep Res 2000;9:5–11.

41. Leschziner G. Narcolepsy: a clinical review. Pract Neurol 2014;14:323–31.

42. Merikangas KR, Zhang J, Emsellem H, et al. The structured diagnostic interview for sleep patterns and disorders: rationale and initial evaluation. Sleep Med 2014;15:530–5.

43. Jennum P, Ibsen R, Petersen ER, Knudsen S, Kjellberg J. Health, social, and economic consequences of narcolepsy: a controlled national study evaluating the societal effect on patients and their partners. Sleep Med 2012;13:1086–93.

44. Rovere H, Rossini S, Reimão R. Quality of life in patients with narcolepsy: a WHOQOL-bref study. Arq Neuropsiquiatr 2008;66:163–7.

45. Zimerman L, Högl B, Delazera M, et al. Subjective deficits of attention, cognition and depression in patients with narcolepsy. Sleep Med 2015;16:45–51.

46. Droogleever Fortuyn HA, Mulders PC, Renier WO, Buitelaar JK, Overeem S. Narcolepsy and psychiatry: an evolving association of increasing interest. Sleep Med 2011;12:714–9.

SUBMISSION & CORRESPONDENCE INFORMATION

DISCLOSURE STATEMENT