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The Impact of Gender on Timeliness of Narcolepsy Diagnosis

Christine Won, M.D., M.S.[1]; Mandana Mahmoudi, M.D.[2]; Li Qin, Ph.D.[1]; Taylor Purvis, B.A.[1]; Aditi Mathur, M.D.[1]; Vahid Mohsenin, M.D., F.A.A.S.M.[1]

[1]Section of Pulmonary, Critical Care and Sleep Medicine, Yale University School of Medicine, New Haven, CT, [2]Yale University School of Public Health and Epidemiology

Study Objectives: To examine the impact of gender in narcoleptic patients on timeliness of diagnosis, symptomology, and health and lifestyle impairment

Methods: This is a cross-sectional study of 109 consecutive patients (68 women) with newly diagnosed narcolepsy with and without cataplexy, from a University sleep disorders center. Consecutive patients were administered an 8-page questionnaire at the time of their diagnosis regarding sleep habits, medications, and medical conditions, lifestyle impairments, as well as details regarding narcolepsy-related symptoms.

Results: Men and women presented with remarkably similar narcolepsy related symptoms, yet women were more likely to be delayed in diagnosis; 85% of men were likely to be diagnosed by 16 years after symptom onset, compared to 28 years in women. More women were likely to remain undiagnosed at any given time point after symptom onset (hazard ratio for diagnosis of men compared to women 1.53; 95% CI 1.01-2.32; p = 0.04). Men and women reported similar degree of subjective sleepiness as measured by the Epworth Sleepiness Scale (mean 16.2 ± 4.5; p = 0.18), though women demonstrated significantly more severe objective sleepiness on multiple sleep latency testing (MSLT) (mean sleep latency in women = 5.4 min (± 4.1), in men 7.4 min (± 3.5); p = 0.03). Despite being more objectively sleepy, women were less likely to report lifestyle impairments in the areas of personal relationships (71% men, 44% women, p = 0.01) and physical activity (36% men, 16% women, p = 0.02), but were also more likely to self-medicate with caffeine (63.4% men, 82.4% women; p = 0.03).

Conclusions: Narcolepsy impacts men and women's health and lifestyle differently, and may cause delays diagnosis for women.

Keywords: Narcolepsy, gender, sex, sleep, hypersomnia, diagnosis, women

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SCIENTIFIC INVESTIGATIONS

Sleep disorders affect women and men differently. This is well described, for example, in sleep disordered breathing, insomnia, and restless leg syndrome. In these common sleep disorders, there are notable sex differences in disease prevalence, manifestation, health effects, and social consequences,[1-9] as well as sex-related discrepancies in diagnosis and health care delivery.[10] There is some evidence from animal models and genetic studies to suggest sex differences in the susceptibility and manifestation of narcolepsy.[11-13] However, sex differences in narcolepsy remain understudied in humans, and there is little scientific information regarding the clinical significance and consequences of the diagnosis of narcolepsy in women. Therefore, this study aimed to compare clinical presentations of narcolepsy in men and women from an academic sleep center, and to identify potential sex differences affecting recognition, diagnosis, and treatment of this disorder. This is the first study dedicated to addressing clinical gender differences in narcolepsy.

BRIEF SUMMARY

Current Knowledge/Study Rationale: There have been descriptions of sex differences in several sleep disorders such as obstructive sleep apnea and restless leg syndrome, however, the impact of sex in narcolepsy has not been previously explored. This study was performed to assess whether narcolepsy clinically presents and affects women differently than men.

Study Impact: This study suggests there are critical differences between men and women in the clinical care and outcomes of patients with narcolepsy. This study supports the necessity for consideration of sex in narcolepsy research.

MATERIAL AND METHODS

Study Population

One-hundred twenty-five consecutive patients with newly diagnosed narcolepsy from 2007 to 2010 were identified from the Yale Center of Sleep Medicine. All patients completed polysomnography (PSG) and multiple sleep latency test (MSLT), and a structured interview by an independent sleep specialist. Patients were administered a standardized 8-page questionnaire within 4 weeks of their narcolepsy diagnosis. Sixteen patients did not complete the questionnaire or had missing data, and were excluded. The study was approved by the Yale Institutional Review Board.

Questionnaire

The standardized questionnaire, in addition to other sleep disorder symptoms, sleep history and habits, current medications, and social, psychological, psychiatric, surgical, and

Table 1—Characteristics of narcolepsy patients by gender

	Men	Women	p value
Participants, n (%)	41 (37.6)	68 (62.4)	
Age at diagnosis, years, mean (SD)	28.6 (11.8)	31.4 (10.2)	0.19
Race White, n (%)	20 (48.8)	33 (48.5)	0.98
BMI, mean (SD)	26.3 (4.4)	27.2 (6.5)	0.41
BMI ≥ 30 kg/m^2, n (%)	10 (24.4)	20 (29.9)	0.54
Caffeine, n (%)	26 (63.4)	56 (82.4)	0.03*
Nicotine, n (%)	5 (12.2)	16 (23.5)	0.15
Alcohol, n (%)	12 (29.3)	16 (23.5)	0.51
Over-the-counter stimulants, n (%)	5 (12.2)	13 (19.2)	0.35
Age at onset of symptoms, years, median (25%-75%Q)	15.0 (12.0-23.0)	17.0 (12.5-26.8)	0.67
Current prescribed medications			
Psychiatric, n (%)	19 (46.3)	30 (44.1)	0.82
Stimulants, n (%)	4 (9.8)	5 (7.4)	0.73
Hypnotics, n (%)	1 (2.4)	8 (11.8)	0.15
Symptoms			
Hypersomnia, n (%)	41 (100)	67 (98.5)	0.44
Sleep disruption, n (%)	8 (19.5)	14 (20.6)	0.89
Cataplexy, n (%)	15 (36.6)	38 (55.9)	0.05
Hallucination, n (%)	31 (75.6)	58 (85.3)	0.21
Sleep paralysis, n (%)	20 (48.8)	40 (58.8)	0.31
Initial ESS, mean (SD)	15.5 (4.6)	16.7 (4.4)	0.18
Reported nightly sleep hours, mean (SD)	7.3 (1.6)	7.7 (2.3)	0.36
Initiation insomnia (SOL > 60 min), n (%)	10 (27.0)	14 (21.9)	0.56
Daily naps, n (%)	25 (62.5)	44 (66.7)	0.66
Family history of a sleep disorder, n (%)	10 (24.4)	12 (17.6)	0.40

Data that were normally distributed are reported as means and standard deviations (SD). Data that were not normally distributed are reported as medians and 25%-75% quartiles (Q). BMI, body mass index; ESS, Epworth Sleepiness Scale; SOL, sleep onset latency.

medical conditions, contained detailed questions about sleepiness, the Epworth Sleepiness Scale (ESS), naps, cataplexy, hypnogogic and hypnopompic hallucinations, sleep paralysis, and disrupted nocturnal sleep. The cataplexy section of the questionnaire explored the following conditions: sudden episodes of loss of muscle function in response to emotion, ranging from slight weakness (such as sagging of the jaw and facial muscles, nodding of the head, closure of the eyes, double vision, buckling of the knees, dropping of the arms, weakness of the hands, and loss of speech or slurred speech) to complete body collapse. With regard to hypnogogic or hypnopompic hallucinations, patients were asked whether they have ever experienced vivid dream-like scenes, or tactile, auditory or visual hallucinations upon awakening or falling sleep. For sleep paralysis the questionnaire asked for transient inability to move partially or completely upon awakening from nocturnal sleep or naps.

The questionnaire asked binary questions, followed by open-ended questions regarding the impact of narcolepsy in the following areas: (1) work or school, (2) social activities, (3) personal relationships, and (4) exercise and physical activity. Questionnaire responses were scored and recorded by a single blinded researcher.

Polysomnography

Nocturnal PSG and MSLT were performed after a sleep diary confirmed a patient's regular sleep habits with ≥ 6 h of nocturnal sleep per night during the 2 weeks preceding the evaluation. Patients discontinued any wake-promoting medications 2 weeks before the sleep study. Antidepressants were tapered off 2 weeks prior to the sleep study in subjects who were considered psychiatrically stable and who were willing to come off these medications. For those with obstructive sleep apnea, MSLT was performed after a night on therapeutic positive airway pressure therapy and apnea-hypopnea index (AHI) was < 5 events per hour. PSG and MSLT were standardized, and performed and scored according to American Academy of Sleep Medicine guidelines.[14,15]

Statistical Analysis

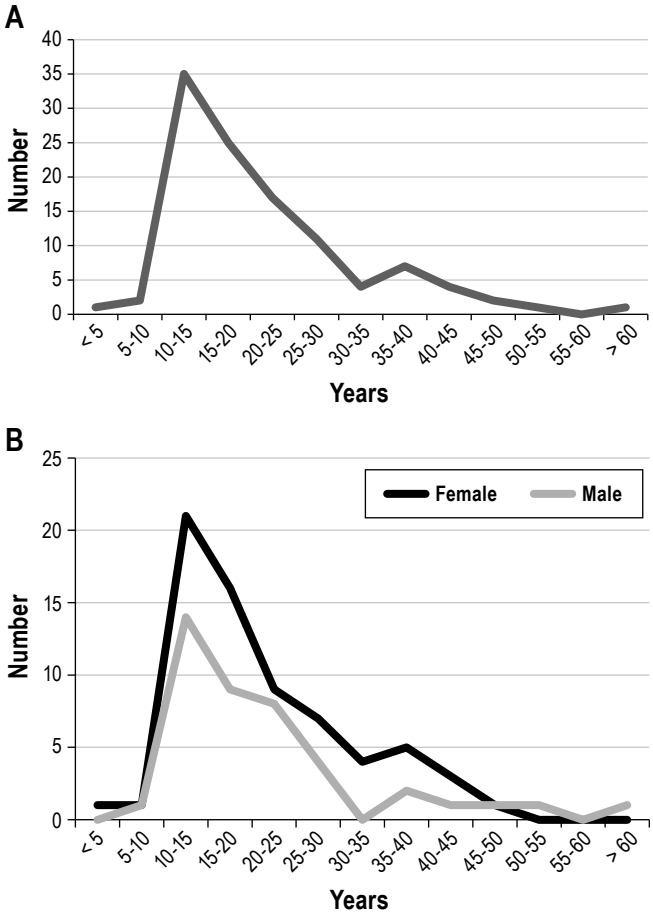
All tests of significance were two-sided. For univariate analysis, continuous variables were reported as means and standard deviations (SD) if they were normally distributed, and student's t-tests were used to do comparisons between two groups. Otherwise they were reported as medians and 25% to 75% quartiles (Q) and were analyzed using nonparametric Wilcoxon method. For categorical variables, frequencies and percentages were reported. Chi-square tests or Fisher exact tests were used to compare differences in proportions of patients as appropriate. Logistic regression was performed to obtain the odds ratios (ORs) of cataplexy with sleep paralysis as the predictor. Association between time to diagnosis and age at symptom onset was assessed by Spearman correlation coefficient. Cox proportional hazards regression survival model were performed by gender with time to diagnosis from symptom onset as the independent variable of interest, and initial ESS, BMI, presence of cataplexy, and age at symptom onset as predictors. Hazard ratio (HRs) and 95% CIs for the incidence of diagnosis were calculated. Cumulative incidence of diagnosis for each gender group was estimated using the Kaplan-Meier method and compared with the log-rank test for patients with age at symptom onset < 15 years old. Analyses were carried out with the use of SAS software (SAS Institute Inc, Cary, NC). P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Patient Characteristics

Among 109 patients with narcolepsy, 68 (62.4%) of participants were women. The patients in this study were predominantly younger (mean [SD] = 30.4 [10.9] years), and their ages ranged between 14 and 62 years. The characteristics of the patients are shown in **Table 1**. Obesity (BMI ≥ 30 kg/m^2) was common, affecting 27.8% of patients, with no gender differences observed. There was a bimodal pattern of age distribution in symptom onset (**Figure 1**). A peak in symptom presentation occurred during the age period of 10-15 years with diminishing

Figure 1—Age of symptom onset



(A) Age of symptom onset of narcolepsy for all subjects. **(B)** Age of symptom onset by gender. In both genders, there was a peak of onset between the ages of 10-15 years, with decreasing frequency with age and a slight increase in onset during the ages of 35-40 years.

Table 2—Comorbid disorders

	Men (N = 41) N (%)	Women (N = 68) N (%)	p value
Sleep disorders			
OSA	10 (24.4)	12 (17.6)	0.40
UARS	7 (17.0)	5 (7.5)	0.13
RLS	0 (0.0)	0 (0.0)	NA
PLMD	0 (0.0)	0 (0.0)	NA
RBD	0 (0.0)	2 (2.9)	0.53
Bruxism	0 (0.0)	0 (0.0)	NA
Parasomnias	6 (14.6)	15 (22.1)	0.34
Cardiovascular disorders	7 (17.1)	11 (16.2)	0.90
Psychiatric disorders			
Anxiety	13 (31.7)	22 (32.4)	0.94
Depression	21 (51.2)	40 (58.8)	0.44
ADHD	8 (19.5)	2 (2.9)	0.006*
Neurologic disorders	6 (14.6)	29 (42.6)	0.002*
Endocrine disorders	2 (4.9)	7 (10.3)	0.25
Fibromyalgia or chronic pain syndromes	1 (2.4)	7 (10.3)	0.09
Autoimmune disorders	0 (0.0)	7 (10.3)	0.03*

OSA, obstructive sleep apnea (AHI ≥ 5); UARS, upper airways resistance syndrome (respiratory disturbance index ≥ 10); RLS, restless leg syndrome; PLMD, periodic limb movement disorder (periodic limb movement index > 15); RBD, REM behavior disorder; ADHD, attention deficit hyperactivity disorder.

frequency with increasing age and a second slight increase in presentation between the ages of 35-40 years. We did not observe a gender difference in the bimodal character of age at which symptoms presented. Twenty-four percent of men and 22% of women (p = 0.78) associated the onset of hypersomnia with a discreet event. The most common events described by women included head trauma (n = 5), infection (e.g., Lyme disease, mononucleosis, viral infection) (n = 4), and childbirth (n = 2). The most common preceding event reported by men was infection (e.g., Lyme disease, mononucleosis, encephalitis) (n = 5).

There was a high prevalence of self-reported anxiety (32.1%) and depression (56.0%) in both men and women, and greater than 40% of men and women were taking psychiatric medications at the time of diagnosis. As shown in **Table 2**, the prevalence of attention deficit hyperactive disorder ([ADHD]; in men, 19.5%, in women, 2.9%; p = 0.006) and autoimmune disorders (in men, 0%, in women, 10.3%; p = 0.03) differed in similar gender trends as those observed in the general population.[16] Autoimmune disorders included 4 women with rheumatoid arthritis, 2 women with lupus and/or antiphospholipid syndrome, and one woman with Hashimoto thyroiditis. Neurologic conditions were reported more frequently in women (men, 14.6% vs. women, 42.6%; p = 0.002), with the most common condition being headaches or migraines (82%). The prevalence of cardiovascular disease was similar for both men and women (17%), and consisted mostly of hypertension (67%). Other cardiovascular diagnoses included arrhythmias (reported by 3 men) and a patent foramen ovale reported by one woman.

Objective sleepiness as measured by mean sleep latency on MSLT was more severe in women (women 5.7 [4.1]; men 7.4 [3.5] min; p = 0.03) despite significantly longer total sleep time and sleep efficiency, and fewer respiratory events during the preceding night's sleep (**Table 3**). The mean sleep latency was not affected by cataplexy status: 5.7 (4.6) min in women with cataplexy *vs* 5.8 (3.3) min in women without cataplexy, (p = 0.9), compared to 6.6 (3.2) min in men with cataplexy *vs*. 7.8 (3.6) min in men without cataplexy, (p = 0.3).

There were 17 women and 11 men diagnosed with narcolepsy despite lack of initial MSLT findings of mean sleep latency (MSL) < 8 min and ≥ 2 SOREMPs. For 7 of these women and 9 of these men, narcolepsy was diagnosed despite negative MSLT findings, based on a history of clear-cut cataplexy. For 14 women and 8 men diagnosed with narcolepsy (there was overlap with the cataplectic group mentioned above), the lack of ≥ 2 SOREMPs on their initial MSLT was attributed to active selective serotonin reuptake inhibitor or other antidepressant use at the time of the study.

Gender differences were not apparent in the subgroups of narcoleptics with and without cataplexy, with two notable exceptions. Those with cataplexy were more overweight than their non-cataplectic counterparts (BMI 28.0 [6.7] kg/m^2 *vs* 25.7 [4.7] kg/m^2, respectively; p = 0.04), and those with cataplexy

Table 3—Polysomnographic features

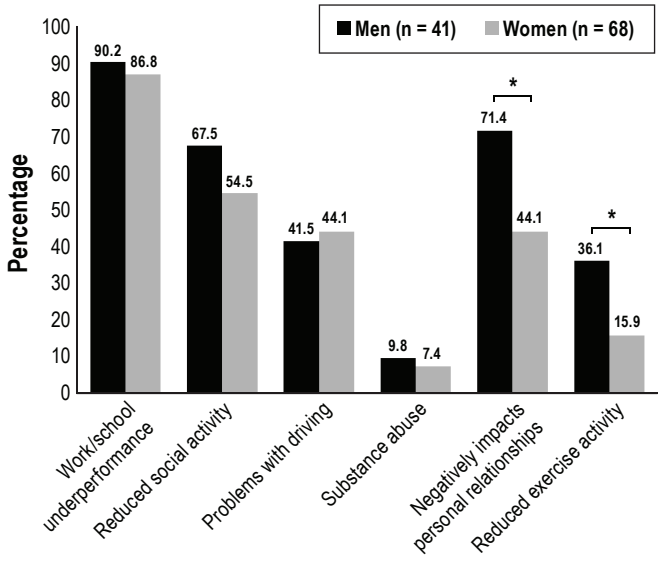
	Men (N = 41)	Women (N = 68)	p value
Multiple sleep latency test			
Mean latency (min), mean (SD)	7.4 (3.5)	5.7 (4.1)	0.03*
2 or more SOREMPs, n (%)	30 (73.2)	51 (78.4)	0.05
Polysomnography			
Total sleep time (min), mean (SD)	381.2 (60.9)	411.5 (51.7)	0.007*
REM onset (min), mean (SD)	71.9 (40.1)	80.1 (32.5)	0.26
Sleep onset (min), median (25%-75%Q)	8.5 (3.5-24.0)	8.0 (3.7-13.5)	0.35
Sleep efficiency (% TST/SPT), median (25%-75%Q)	89.0 (83.0-94.0)	94.0 (89.0-96.0)	0.002*
AHI, median (25%-75%Q)	1.0 (0.3-1.7)	0.4 (0.0-1.0)	0.01*
PLMI, median (25%-75%Q)	0.0 (0.0-0.6)	0.0 (0.0-0.0)	0.08

Data that were normally distributed are reported as means and standard deviations (SD). Data that were not normally distributed are reported as medians and 25%-75% quartiles (Q). SOREMP, sleep onset REM period; TST, total sleep time; SPT, sleep period time; AHI, apnea-hypopnea index; PLMI, periodic limb movement index.

Table 4—Results of multivariable Cox proportional hazard model for time to narcolepsy diagnosis from symptom onset for all patients

Covariate	Hazard Ratio (95% CI)	p value
Gender Male	1.53 (1.01, 2.32)	0.04*
Onset Age, year	1.06 (1.04, 1.08)	< 0.0001*
BMI	1.05 (1.01, 1.09)	0.02*
Presence of Cataplexy	0.70 (0.47, 1.04)	0.08

Figure 2—Lifestyle impairments attributed to narcolepsy



Values represent percentages of men or women who attribute the listed impairments directly to symptoms of narcolepsy. *p-value < 0.05

were more likely to use nicotine than those without cataplexy (32.1% vs 7.1%; p = 0.001). ESS were similar in those with and without cataplexy (16.0 [5.0] *vs.* 16.5 [4.0]; p = 0.5).

Time to Diagnosis

Multivariable Cox proportional hazards model showed men were diagnosed earlier than women, and more women remained undiagnosed at any given time point after symptom onset (male hazards ratio [HR] 1.53; 95% CI 1.01-2.32; p = 0.04). Among men, 85% were likely to be diagnosed by 16 years after symptom onset, compared to 28 years in women. Patients achieved a sooner diagnosis if their symptoms started at an older age (HR 1.06; 95% CI 1.04-1.08; p < 0.0001). Patients with greater BMI also experienced sooner time to diagnosis (HR 1.05; 95% CI 1.01-1.09; p = 0.02). The presence of cataplexy did not impact timing of diagnosis (HR 0.70; 95% CI 0.47-1.04; p = 0.08; **Table 4**).

Impact on Lifestyle

The majority of men and women (90%) reported having trouble at work and/or school due to narcolepsy, and specifically due to excessive sleepiness (**Figure 2**). More men reported their narcolepsy-related symptoms negatively affected their personal relationships, with the main reason being excessive sleepiness and not cataplexy or other REM-intrusive symptoms. More men were also likely to reduce their physical activity and exercise due to symptoms associated with narcolepsy. Up to a third of both men and women reported having to reduce their social activities due to excessive sleepiness. Patients generally reported oversleeping or feeling too tired to engage in social activities, and 2 patients reported cutting back on social activity because of concerns about driving. Seven patients ascribed drug abuse to sleep problems, with 4 patients abusing stimulants such as amphetamines and cocaine, and the remaining 3 using alcohol to assist with sleep. More than 40% of narcoleptic men and women reported at least one incident of falling asleep while driving.

DISCUSSION

Gender differences in the presentation and manifestation of common sleep disorders are well recognized. However, aside from few animal and genetic data, there is a paucity of data regarding potential gender differences in the clinical presentation and manifestation of narcolepsy. Given the relevance of sex hormones and/or gender roles on other sleep disorders such as sleep disordered breathing and restless leg syndrome, the potential for gender differences in narcolepsy—a disease commonly emergent during adolescence and young adulthood[17,18]—necessitates further investigation.

It has been reported that a diagnosis of narcolepsy is commonly delayed on the order of 10 years[19,20], and it is important to understand the impact of gender on these delays since narcolepsy may be associated with significant morbidity. Patients in this study were also delayed in their diagnosis by a median of 8 years (25% to 75%Q 2-15 years) from the time of symptom onset. Gender seemed to impact the timeliness of diagnosis with women being more likely to be delayed despite women reporting more occurrences of cataplexy and having greater objective sleepiness on MSLT. This held true even after considering age of symptom presentation, presence of cataplexy, and ESS.

Interestingly, we observed a bimodal pattern of age distribution in symptom onset, similar to that that has been described in previous studies.[21,22] We observed a peak in symptom presentation during the age period of 10-15 years with diminishing frequency with age and a second slight increase in presentation between the ages of 35 and 40 years. We did not observe a gender difference in the bimodal character of age at which symptoms presented, and therefore could not explain its contribution to the observed gender difference in time to diagnosis.

We were able to ascertain occupational history and found at the time of diagnosis, three women were homemakers, 17 were students (ranging from undergraduate to graduate or professional students), and the remainder were employed. Examples of female occupations include teachers, research assistants, waitresses, secretaries, nurses, and financial consultants. Two men did not work due to retirement and disability, 19 were students, and the remainder were employed. Men also varied widely in their occupations, and examples include teachers, auto mechanics, bankers, and engineers. There were significantly more male students compared to female students (46% vs 25%, respectively, $p = 0.02$). However, student status was not found to contribute to gender differences in the delay to diagnosis. Our cohort may represent a greater proportion of adult students compared to those seen at other sleep centers, and likely reflects the association of this sleep center to a large university.

Narcolepsy is a relatively rare disorder and presents with nonspecific complaint of daytime sleepiness, and therefore requires a high index of suspicion for the diagnosis. The diagnosis is often readily made by sleep specialists, and we assume a delay in referral to a sleep specialist likely contributes to the delay in diagnosis. This delay in referral may reflect either delay in recognition by the referring provider or delay in seeking medical help by the patient. When looking at referral patterns, 53% of women and 58% of men were referred to the sleep center by their primary care providers. The next most common referring provider was a neurologist ($n = 13$) then a psychiatrist ($n = 8$) for women, and a neurologist ($n = 6$) and an ENT ($n = 4$) for men. Geriatricians, pediatricians, endocrinologists, rheumatologists, and pulmonologists referred fewer than 3 patients each of men or women. We did not observe differences in time to diagnosis between the referring provider specialties; however, there were small numbers in each group.

We suggest one possible reason for the gender difference in time to diagnosis may be that women are less forthcoming with their symptoms, opting to self-medicate, or because they are less affected in their daily lives than men. Although men and women had similar ESS scores and similar narcolepsy related symptoms, men were more likely to report problems with personal relationships and more likely to experience a negative impact on their physical activity. Interestingly, greater impairments were reported by men even while women had more severe findings on MSLT. It is possible that women are delayed in their diagnosis due to underestimating their subjective sleepiness on the Epworth Sleepiness Scale and/or underestimating their degree of impairments. Alternatively, women may cope with narcolepsy symptoms differently allowing for different lifestyle implications. For example, women demonstrated more self-medicating behavior with greater proportion of women reporting use of daily caffeinated beverages. We ascertained daily caffeine use by asking subjects on average the number of cups of caffeinated coffee consumed per day, number of caffeinated sodas consumed per day, and number of power drinks consumed per day. We analyzed the percentage of subjects reporting daily caffeine use rather than comparing amount of caffeine intake because we assumed the former was more indicative of self-medicating behavior while the amount of caffeine per day is more reflective of caffeine response. Our study also showed greater percentage of women using over-the-counter stimulants and nicotine; however, these were not statistically significant. It should be noted that in both men and women, the vast majority reported impairments in work/school, social, and intimate relationships, confirming narcolepsy is a debilitating disease for the majority of patients. These discrepancies may not be specific to narcolepsy per se, and may represent a general pattern of gender effect on chronic disease. It is important to understand these implications in narcolepsy, however, because current treatments are directed at symptom management and improving quality of life. Understanding the impact of narcolepsy on lifestyle allows us to interpret treatment efficacy and affect important outcomes such as depression and obesity.

Obesity predicted a sooner narcolepsy diagnosis, and it may have been that obese individuals were more likely to be referred to sleep specialists for concerns of the more commonly recognized sleep disorder, sleep apnea, and in this process were diagnosed with narcolepsy. Patients whose symptoms started in childhood (age < 15 years old) were more likely to be delayed in their diagnosis ($\rho = -0.61$, $p < 0.001$); gender differences were apparent in this group as well. The median time for women with childhood onset symptoms ($n = 23$) was 15 years (13-23; 25% to 75%Q) compared to men ($n = 15$) who had a median time of 11 years (9-13; 25% to 75%Q; $p = 0.04$). Those with childhood narcolepsy were also more likely to have acquired psychiatric diagnoses ($p = 0.045$), suggesting that children with narcolepsy may have been more likely to be misdiagnosed with a psychiatric disorder, or that they are at greater risk for psychiatric comorbidities. It should be noted that these patients were from an adult sleep clinic, and therefore reflect adult patients who escaped diagnosis as children and are distinct from children with narcolepsy who are diagnosed accurately during childhood.

There were remarkably very little differences in the clinical presentation of men and women with narcolepsy, with the exception of a trend toward greater cataplexy in women. We suspect because of the elusive nature of cataplexy, the observed difference reflects a complex gender-influenced interaction between the patient's ability to recognize and communicate cataplexy symptoms, and the clinician's ability to diagnose cataplexy.

Epidemiologic studies on narcolepsy have not consistently found a gender difference, and prevalence and incidence rates in both men and women differ by ethnicities and with changing narcolepsy definitions.[23-26] Hypocretin deficiency, which is tightly associated with cataplexy,[27-31] has not been described to be influenced by gender, although studies addressing this specific question have not been rigorously performed. The possibility of a true gender difference, however, should not be discounted. For example, greater rates of HLA DQB1 genotype has been described in Mexican women compared to men,[32] suggesting greater susceptibility for cataplexy in women in this specific ethnic group.

The lack of a gender difference in the prevalence of cardiovascular disease and obstructive sleep apnea (defined as AHI ≥ 5)—diseases otherwise typified by male predominance—were unexpected, and raised the question of whether narcolepsy could be a risk factor for these diseases in women. We found an overall high prevalence of OSA in narcolepsy (> 20%) akin to that described by Sansa et al. (28% for AHI ≥ 10).[33] While obesity was predictive of OSA in women with narcolepsy, women were not more likely to be obese than men. This suggests perhaps being female is not protective for OSA in patients with narcolepsy. Hypocretin-deficient mouse models such as the preprohypocretin knockout and orexin/ataxin-3 transgenic mice have shown greater levels of serum leptin and greater leptin resistance in female than male mice.[13] Leptin is known to be a ventilatory stimulant whose levels are elevated in OSA and decrease with CPAP use,[34-38] and thus leptin has been hypothesized to be partially pathogenic in OSA.

Being female was also not protective of cardiovascular disease in this predominantly premenopausal sample of narcoleptics. In this group of patients, the occurrence of cardiovascular disease was independent of OSA status. Cardiovascular risk factors such as obesity and insulin resistance have been described in narcolepsy.[42-44] Metabolic derangements are hypothesized to arise from perturbations in feeding and energy expenditure as well as sleep fragmentation, and hypocretin and leptin have been shown to directly impact cardiovascular function.[45] It has been suggested that estrogen provides women cardiovascular protection through a hypocretin-mediated pathway,[46,47] and our findings are supportive of the hypothesis that hypocretin-deficiency may reduce a woman's protective advantage against cardiovascular disease.[48]

Limitations of the Study

There were 17 women and 11 men diagnosed with narcolepsy despite lack of initial MSLT findings of MSL < 8 minutes and 2 or more SOREMPs. These patients were diagnosed with narcolepsy based on highly suggestive clinical features such as cataplexy, and their MSLTs interpreted within their clinical context. For 14 women and 8 men, the lack of 2 or more SOREMPs on initial MSLT was attributed to REM suppressing medication use at the time of the study. Our MSLT positivity findings are consistent with the Aldrich study,[49] in which they describe 2 or more SOREMPs occurring in approximately 80% of narcoleptic subjects during an initial diagnostic MSLT. They also reported 93% of those with cataplexy and 97% of narcoleptics without cataplexy had MSL < 8 minutes, a finding similar to our cohort. They concluded that while the MSLT is highly sensitive and specific for narcolepsy when narcolepsy is clinically suspected, exclusive reliance on MSLT for the diagnosis of narcolepsy may lead to misdiagnosis or non-diagnosis. It is recommended if there is a high clinical suspicion for narcolepsy without cataplexy that MSLT be repeated when initial results are non-diagnostic. Unfortunately in many of our cases it was felt unsafe or patients refused to be discontinued off confounding medications for a repeat MSLT. Because we do not have repeat MSLT data, we concede it is possible that up to 27% of our study group may represent alternative diagnoses such as idiopathic hypersomnia. However, there were no clinical or demographic differences between those that did and did not meet strict International Classification of Sleep Disorders 2nd edition criteria for narcolepsy.

The results of this study represent a cohort of patients from a single academic adult sleep center, and thus its application to narcoleptics from other centers is limited. Hypocretin levels were not measured thus the role of hypocretin deficiency was speculative. While hypocretin deficiency is ubiquitous in cataplexy, its role in narcolepsy without cataplexy is heterogeneous and unpredictable.[50,51] Sixteen patients otherwise qualifying for the study were not included in the analysis due to pertinent missing data. Thirteen of these 16 patients were women. While selection bias may have affected results, we were reassured by similar demographic and polysomnographic findings in this excluded group. Finally, since many of the symptoms and disease history depended on self-reporting, we are not able to exclude gender-influenced recall bias.

CONCLUSION

This is the first study dedicated to addressing gender differences in the clinical presentation of narcolepsy, and to investigate the impact of the diagnosis in women. There are many studies to suggest gender impacts disease differently across a spectrum of common sleep conditions. Likewise, we have shown that men and women with narcolepsy despite similar symptom severity and profile have important differences in health care, health risks, and lifestyle impairments. This study substantiates the need for further research on the influence of gender on narcolepsy, and emphasizes the importance of thoughtfulness to gender in future research on narcolepsy.

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Address correspondence to: Christine Won, M.D., M.S., PO Box 208057, 300 College St., New Haven, CT 06520-8057; Tel: (203) 785-4163; Fax: (203) 785-3634; E-mail: christine.won@yale.edu

DISCLOSURE STATEMENT

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