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The Underdiagnosis of Sleep Disorders in Patients with Multiple Sclerosis

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SCIENTIFIC INVESTIGATIONS

Study Objectives: To report at a population level the prevalence of restless legs syndrome, insomnia, and the risk of obstructive sleep apnea in multiple sclerosis patients. Sleep patterns and associations with fatigue and daytime sleepiness were identified.

Methods: A cross-sectional study was performed using a written survey that was mailed to 11,400 individuals from the Northern California Chapter of the National Multiple Sclerosis (MS) Society Database who self-identified as having MS. The survey included individual questions relating to demographics as well as several standard validated questionnaires related to primary sleep disorders, sleepiness, fatigue severity, and sleep patterns.

Results: Among the 11,400 surveys mailed out, 2,810 (24.6%) were returned. Of these, 2,375 (84.5%) met the inclusion criteria. Among the completed surveys, 898 (37.8%) screened positive for obstructive sleep apnea, 746 (31.6%) for moderate to severe insomnia, and 866 (36.8%) for restless legs syndrome. In contrast, only 4%, 11%, and 12% of the cohort reported being diagnosed by a health care provider with obstructive sleep apnea, insomnia, and restless legs syndrome, respectively. Excessive daytime sleepiness was noted in 30% of respondents based on the Epworth Sleepiness Scale. More than 60% of the respondents reported an abnormal level of fatigue based on the Fatigue Severity Scale. Both abnormal fatigue and sleepiness scores were associated with screening positive for obstructive sleep apnea, insomnia, and restless legs syndrome.

Conclusion: A significant percentage of MS subjects in our sample screened positive for one or more sleep disorders. The vast majority of these sleep disorders were undiagnosed. Greater attention to sleep problems in this population is warranted, especially in view of fatigue being the most common and disabling symptom of MS.

Keywords: multiple sclerosis, sleep apnea, restless legs syndrome, insomnia, fatigue, sleep

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Multiple sclerosis (MS) is a central nervous system demyelinating disease affecting approximately 400,000 Americans.[1] It most frequently affects individuals between the ages of 20 to 50 years old. The cause of MS is unknown, but the disease is hypothesized to be autoimmune in origin, in which an unknown environmental trigger in a genetically susceptible host leads to inflammation in the white matter of the brain and spinal cord, resulting in symptoms. Patients often present with a relapsing-remitting pattern of symptoms, depending on the area of central nervous system inflammation, with symptoms such as visual loss, vertigo, weakness, and numbness. Over time, many patients enter into a progressive phase of MS, whereby there is a slow increase in neurological deficits without clear exacerbations, leading to long-term disability.[1]

Primary sleep disorders are noted to occur in MS patients at higher frequency than the general population[2-5] and have been strongly associated with the most common and disabling symptom of the disease: MS fatigue. MS fatigue is estimated to occur in 90% of patients.[6-8] The symptoms of fatigue may be intermittent or permanent. It is often exacerbated by exposure to heat and tends to get worse as the day progresses. MS fatigue is attributed to multifactorial etiologies including nocturia, depression, pain, infection, inflammatory cytokines from an MS exacerbation, and heat exposure.[8-10] It is known that undiagnosed sleep disorders can affect not only fatigue but the overall health and quality of life of the individual with MS.[5,6]

Among primary sleep disorders, sleep disordered breathing, restless legs syndrome, and insomnia have all been reported to be more frequent in MS than the general population. Kaminska et al. looked at the prevalence of obstructive sleep apnea—defined as an apnea-hypopnea index ≥ 15—and noted that it occurred in 36 of 62 MS subjects (58%) and in 15 of 32 controls (47%).[5] After adjusting for confounders, severe fatigue was associated with an obstructive sleep apnea (OSA) diagnosis

BRIEF SUMMARY

Current Knowledge/Study Rationale: Sleep disorders in Multiple Sclerosis patients are reportedly common but the epidemiological data on prevalence is limited to small sample sizes. The rationale for this study was to report on a large population level the prevalence of restless legs syndrome, insomnia, and the risk of obstructive sleep apnea in subjects with Multiple Sclerosis patients using validated screening questionnaires.

Study Impact: Greater than 70% of MS subjects in this large population based survey screened positive for one or more sleep disorders. The vast majority of these sleep disorders are potentially undiagnosed and untreated. Physicians treating patients with Multiple Sclerosis need to be diligent in the screening, evaluation and management of sleep disorders in this population as untreated sleep disorders may impact the fatigue and quality of life of the individual.

in MS patients but not in controls. A large multicenter case-control study on restless legs syndrome in multiple sclerosis known as the Restless Legs Syndrome in Multiple Sclerosis (REMS) study reported the frequency of restless legs syndrome to be 164/861(19%) in MS and 27/649 (4.2%) in control subjects.[11] Stanton et al. looked at the incidence of insomnia in a series of 60 MS patients and noted over a 2-week period that a sleep pattern which demonstrated initial insomnia occurred in 42%, middle insomnia in 53%, and terminal insomnia in 58% of sleep episodes.[10]

The medical literature to date, however, is limited in scope in terms of the array of sleep disorders examined per study, the retrospective design, and often the omission of variables pertaining to sleep patterns. The rationale for this study is to investigate the prevalence of reported primary sleep disorders notably obstructive sleep apnea, restless leg syndrome, and insomnia in the MS population. The important association between MS fatigue and excessive daytime sleepiness will also be examined in a population context as it pertains to these sleep disorders. This study is intended to bring to the attention of the sleep medicine community the extent to which sleep disorders are underdiagnosed and undertreated in this population, suggestive of a missed epidemic.

METHODS

Participants

The study population was recruited from the membership list of the Northern California Chapter of the National MS Society. A total of 11,400 surveys were mailed out, which included all chapter members who self-identified as having MS. Subjects were explicitly informed of the objective of the survey in the instructions part of the survey. Subjects were included if they self-reported an age ≥ 18 years and reported on the survey having a diagnosis of MS confirmed by a physician. Subjects were excluded if a response indicated that they did not carry a diagnosis of MS confirmed by a physician, were deceased, refused to participate, or if the response was received after the designated date.

Procedure

Surveys were mailed out in January 2011 with an accompanying letter explaining the purpose of the study. The survey was administered anonymously. The survey was sent out by a professional printing company arranged by the Northern California Chapter of the National MS Society. Return envelopes were included with postage paid, without return addresses listed.

This process allowed full confidentiality, as researchers were blinded to the names and addresses of participants at times of both distribution and receipt. Four weeks after the initial mailing, a reminder letter was sent to all members of the study population. A study coordinator was available to answer questions by phone or email. Surveys were accepted for 10 weeks from the date of the initial mailing in order to maximize the response rate. The study coordinator manually inputted the returned surveys into a database. Every tenth survey was validated by a second reviewer to ensure accuracy of data entry. The survey and protocol were approved by the National Multiple Sclerosis Society and by the University of California Davis Institutional Review Board (IRB # 224894). Among the 11,400 surveys mailed out, 2,810 (24.6%) were returned. Of these, 2,375 (84.5%) met the inclusion criteria. The remaining 435 surveys were not included because they were received after the cutoff date, they did not meet the eligibility criteria, or the surveys were sent back to the coordinator for reasons such as subject deceased, wrong address, or inability/refusal to complete.

Measures

The survey was 10 pages long and included questions regarding demographics, MS history/duration, medication use, and a detailed sleep history. The survey also included standardized validated questionnaires related to fatigue, sleepiness, restless legs syndrome, sleep disordered breathing, and insomnia. A description of the standardized validated questionnaires follows.

The *STOP-BANG questionnaire* is composed of 8 yes/no questions relating to the risk factors for obstructive sleep apnea. Questions include snoring, daytime tiredness, observed apneas, high blood pressure, body mass index (> 35 kg/m^2), age (≥ 50 years), neck circumference (> 40 cm), and gender (male). A tape measure was included in the survey package, with instructions and anatomical guidelines for measuring neck circumference. A patient was considered at risk for obstructive sleep apnea if they had ≥ 3 positive responses on the survey. This survey was previously studied in the MS population.[12-14]

The *Berlin Questionnaire* is a 3-category questionnaire that determines the risk of obstructive sleep apnea based on a profile of questions similar to the STOP BANG, but measured quantitatively instead of dichotomously. Patients with responses indicating high risk in ≥ 2 categories were predicted to be at high risk of obstructive sleep apnea.[13] Both STOP-BANG and Berlin were used to determine the concordance rate between the surveys, as they are both validated questionnaires to screen for obstructive sleep apnea but have not been used conjointly in the MS population to date.[14]

The *Epworth Sleepiness Scale* is used to measure daytime sleepiness by assessing the patient's likelihood of falling asleep under 8 common scenarios. Likelihood is scored between 0 (never) and 3 (high chance), with a total score out of 24. A score > 10 is indicative of excessive daytime sleepiness.[15]

The *Fatigue Severity Scale* rates the severity of fatigue symptoms in MS patients, applying a Likert scale (1-strongly disagree to 7-strongly agree) to 9 questions relating to the patient's experiences in the past week. Patients with a score of 36/64 or higher are found to be suffering from fatigue.[6]

The *Insomnia Severity Index* includes 7 questions that relate to the timing of individuals' potential insomnia and the extent to which insomnia affects their quality of life. Each question is graded on a scale of 0 through 4. A cumulative score ≥ 15 indicates clinically significant insomnia.[16]

The *Restless Legs Syndrome questionnaire* is structured based upon the 4 diagnostic criteria developed by the International Restless Legs Syndrome Study Group (IRLSSG). Patients met the criteria for RLS by answering yes to all 4 criteria.[17]

Statistical Analysis

Two-sided Fisher exact test was used to study the association between 2 dichotomous variables. Fisher exact test was

Table 1—Demographics of study participants.

Variable	Frequency
Age	
Mean age in years (SD)	54.7 (12.4)
Gender, n (%)	
Female	1,917 (81.0)
Male	450 (19.0)
Race, n (%)	
Caucasian	2,058 (88.3)
African American	101 (4.3)
Asian	25 (1.1)
Hispanic	87 (3.7)
Native Hawaiian or Pacific Islander	6 (0.3)
American Indian or Alaskan Native	15 (0.6)
Prefer Not to Answer	39 (1.6)
BMI, n (%)	
Underweight: < 18.5 kg/m^2	88 (3.8)
Normal: > 18.5 and ≤ 24.9 kg/m^2	1,005 (42.8)
Overweight: ≥ 25 and ≤ 29.9 kg/m^2	732 (31.2)
Obese: ≥ 30 kg/m^2	521 (22.2)
Severely Obese: ≥ 35 kg/m^2	204 (8.7)
MS Disease Duration	
Mean age in years since diagnosis (SD)	16.3 (10.8)

BMI, body mass index; MS, multiple sclerosis, SD, standard deviation.

Table 2—Sleep characteristics of study participants.

Self-reported Sleep History	Frequency
Sleep Duration on Weekdays, n (%)	
< 6 hours	557 (23.9)
6 to < 7 hours	829 (35.3)
7 to 8 hours	657 (28.1)
> 8 hours	292 (12.5)
Sleep Duration on Weekends, n (%)	
< 6 hours	449 (19.1)
6 to < 7 hours	715 (30.4)
7 to 8 hours	697 (29.6)
> 8 hours	494 (21.0)
Subjects reporting sleep latency > 30 minutes, n (%)	1,199 (51.6)
Mean number of reported awakenings per night (SD)	2.7 (8.8)
Have you or your healthcare provider ever discussed issues related to your sleep? n (%)	
Yes	1,060 (45.4)
No	1,274 (54.6)
Have you ever been prescribed a medication to help you fall or stay asleep? n (%)	
Yes	251 (10.6)
No	2,128 (89.5)
Have you ever undergone a polysomnogram? n (%)	
Yes	261 (11.1)
No	2,090 (88.9)
Have you ever been treated with positive airway pressure? n (%)	
Yes	142 (6.1)
No	2,195 (93.9)
Has your healthcare provider ever diagnosed you with…? n (%)	
Obstructive sleep apnea	101 (4.3)
Insomnia	253 (10.6)
Restless legs syndrome	287 (12.1)

chosen over the ordinary χ^2 test by our statistician. The Fisher exact test, by accounting for small sample sizes, imposes more stringent criteria for rejection of the null hypothesis than the ordinary χ^2 test. The Fisher exact test was chosen by the statistician not because the overall sample size was small but it was determined to be the appropriate test when at least one cell in the rXc table contains ≤ 5 instances. The STOP-BANG was dichotomized to be positive if there were ≥ 3 positive answers to the 8 questions. The Berlin was dichotomized to be positive if there were ≥ 2 positive categories. The Epworth sleepiness scale (ESS) was dichotomized to be positive if the total ESS score was > 10. The fatigue severity scale (FSS) was dichotomized to be positive if the total FSS score was ≥ 36. The Restless Legs Syndrome (RLS) was dichotomized to be positive if all answers to the 4 questions were positive. A p-value < 0.05 was considered statistically significant. All analyses were carried out with SAS v9.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Demographic data are displayed in **Table 1**. Our study population was highly female (81%) and Caucasian (88.3%), with few African Americans (4.3%) or Hispanics (3.7%), which is consistent with the reported epidemiology of the disease in North America.[1] More than half of the participants (53.4%) were overweight or obese. These statistics in MS are slightly lower than the general population of California.[18] The mean age for the entire cohort was 54.7 ± 12.4 years, with a mean duration of illness of 16.3 ± 10.8 years.

Participants' sleep history is reported in **Table 2**. Close to a quarter of the subjects report a sleep restriction (< 6 hours per night) both during the week (23.9%) and on weekends (19.1%). More than half of subjects (51.6%) noted taking > 30 min to fall asleep at night, and subjects reported a mean of 2.7 awakenings per night. About 10.6% of respondents reported taking a medication to help them fall asleep or stay asleep. Only 11.1% of respondents had undergone polysomnogram, and 6.1% reported using positive airway pressure.

Table 3 reports on sleep survey results as it pertains to the screening questionnaires. Among the completed surveys, 898 (37.8%) screened positive for obstructive sleep apnea, 746 (31.6%) for moderate to severe insomnia, and 866 (36.8%) for restless legs syndrome. Among responders, 30.2% reported an abnormal level of daytime sleepiness based on the Epworth Sleepiness Scale (ESS). The association between respondents with excessive daytime sleepiness and those with excessive fatigue was statistically significant ($p < 0.001$), suggesting that individuals experiencing excessive daytime sleepiness also experience excessive fatigue. In addition, ESS and FSS positive scores were each significantly associated with both STOP BANG positive outcome and Berlin positive outcome ($p < 0.001$).

A binary logistic regression was also performed to determine if sleepiness and fatigue confer more risk for OSA symptoms. The odds ratio of STOP BANG positive to having an ESS > 10 compared to having an ESS ≤ 10 was 1.788, with a

Table 3—Summary of outcomes for screening questionnaires.

Screening Questionnaire	Frequency
Epworth Sleepiness Scale Score	
Median (range)	8 (0-24)
Score > 10, n (%)	712 (30.2)
Fatigue Severity Scale	
Median (range)	45 (6-63)
Score ≥ 36, n (%)	1,555 (66.3)
Obstructive sleep apnea	
STOP-BANG positive, n (%)	898 (37.8)
Berlin score positive, n (%)	887 (37.3)
Insomnia	
Insomnia Severity Index moderate, n (%)	576 (24.4)
Insomnia Severity Index severe, n (%)	170 (7.2)
Restless legs syndrome	
All 4 criteria present, n (%)	866 (36.8)

95% confidence interval (1.494, 2.141); p-value < 0.001. The odds ratio of STOP BANG positive to having an FSS ≥ 36 compared to having an FSS score < 36 was 1.850, with a 95% confidence interval is (1.538, 2.226); p-value < 0.001. This implies an important association between complaints of excessive daytime sleepiness and/or fatigue and risk of obstructive sleep apnea.

Moderate insomnia was reported in 24.4% of the respondents based on the Insomnia Severity Index, and 7.2% reported severe insomnia. ESS and FSS positive scores were each statistically significantly associated with the individual's likelihood of screening positive for insomnia (p < 0.001).

Using the Restless Leg Syndrome (RLS) questionnaire, 36.8% of our respondents met all 4 major criteria for RLS. Likelihood of RLS was significantly associated with each ESS (p = 0.006) and FSS positive scores (p < 0.001). Among the cohort, 40.1% screened positive for one sleep disorder, 24.2% screened positive for 2 sleep disorders, and 5.7% screened positive for all 3 sleep disorders (**Table 4**). It is noteworthy that 70% of subjects screened positive based on the validated questionnaires for at least one sleep disorder.

A sensitivity analysis was conducted post hoc to deal with the nonresponse rate using the "best-case scenario" and "worst case scenario" approach, as described by Cochran et al.[19] The best case scenario confidence interval was the interval under the assumption that all the non-responders would have been positive for the specific sleep syndrome (OSA, insomnia, RLS) on the survey. In a "worst-case scenario" the analysis would calculate the confidence interval under the assumption that none of the non-responders would have screened negative for the sleep syndrome. If we used those people responding to the survey, the observed proportion of screened positive for obstructive sleep apnea was 37.8% and the 95% CI was (35.8%, 39.7%). The observed proportion of moderate to severe insomnia was 31.6% and the 95% CI was (29.8%, 33.5%). The observed proportion of restless legs syndrome was 36.8% and the 95% CI was (34.9%, 38.8%).

If we used 11,400 people as denominator and assumed that those people who did not respond screened positive for obstructive sleep apnea, the observed proportion of screened positive for obstructive sleep apnea is 87.0% and the 95% CI is (86.4%, 87.6%). If we used 11,400 people as denominator and assumed that those people who did not respond had moderate to severe insomnia, the observed proportion of moderate to severe insomnia is 85.9% and the 95% CI is (85.2%, 86.5%). If we used 11,400 people as denominator and assumed that those people who did not respond had positive screening for restless legs syndrome, the observed proportion of restless legs syndrome is 87.0% and the 95% CI is (86.3%, 87.6%). If we used 11,400 people as denominator and assumed that those people who did not respond did not screen positive for obstructive sleep apnea, the observed proportion of screened positive for obstructive sleep apnea is 7.9% and the 95% CI is (7.4%, 8.4%). If we used 11,400 people as denominator and assumed that those people who did not respond did not screen positive for moderate to severe insomnia, the observed proportion of moderate to severe insomnia is 6.5% and the 95% CI is (6.1%, 7.0%). If we used 11,400 people as denominator and assumed that those people who did not respond do not have restless legs syndrome, the observed proportion of restless legs syndrome is 7.6% and the 95% CI is (7.1%, 8.1%).

Table 4—Frequency of subjects screening for 1, 2, or 3 sleep disorders.

	Frequency, n (%)	Cumulative Percent for Group
Subjects having no sleep disorder on screening	714 (30)	30
Subjects having 1 sleep disorder on screening	955 (40.1)	70.2
Subjects having 2 sleep disorders on screening	575 (24.2)	94.3
Subjects having 3 sleep disorders on screening	135 (5.7)	100

DISCUSSION

This survey demonstrates there is a significant burden of sleep disorders that are likely undiagnosed and unrecognized in the MS population. Among our cohort, 70% of subjects screened positive for at least one sleep disorder based on the questionnaires, yet only a small fraction of the subjects reported being diagnosed by a physician with the respective sleep problem. Approximately 37.8% of our surveyed population screened at risk for obstructive sleep apnea by questionnaire; by contrast, 4.25% reported having been diagnosed by a physician with obstructive sleep apnea. Insomnia was noted to be present based on screening in 31.6% of subjects, yet only 10.6% reported being diagnosed by a physician with insomnia. Subjects met the restless legs syndrome criteria in 36.8% of our surveyed population based on the questionnaire, but only 12.1% reported being diagnosed with RLS by a health care provider.

Although the screening questionnaires are not independently sufficient to make a clinical diagnosis, the discrepancy between the percentage screening at risk and the percentage reporting

being diagnosed by a medical provider is striking. In addition, the percentage screening positive on questionnaires in the MS survey is much higher than the prevalence of what is reported in the general population—5% and 5.5% for obstructive sleep apnea and restless leg syndrome, respectively.[20,21] Nearly 31.6% of the subjects screened positive for insomnia in our study—this is in keeping with the 20% to 40% prevalence of insomnia noted in the general population.[22]

A reduced total sleep time was noted in the MS subjects. It is generally recommended that adults sleep 7 to 8 hours per night, and in general, a sleep latency less than 30 minutes is within normal limits.[23-25] However, the survey noted that close to 59.4% of subjects report sleeping < 7 hours per night and more than 50.6% report having a sleep latency greater than 30 minutes. Of note, 30% report excessive daytime sleepiness based on the ESS, and 62.3% report excessive fatigue based on the FSS. In the general population, according to the National Sleep Foundation 2005 Sleep Poll, 40% of subjects sleep less than 7 hours per night during the week.[26] Groeger et al. looked at sleep duration in a random sample of 2000 British adults and noted 47% of the adults sleep less than 7 hours per night.[27] By comparing our data to both the American and British surveys of the general population, it may suggest that inadequate sleep duration—sleeping less than the recommended 7 to 8 hours in this survey—sleep is a greater issue in the MS population than in the general population.[26,27]

The sleep disorder frequency, sleep patterns, and complaints of excessive daytime sleepiness suggest that sleep problems may be a hidden epidemic in the MS population, separate from MS fatigue.

This is the largest survey of sleep disorders in the MS population to date; however, we acknowledge several limitations of the study. It is important to take into consideration whether there was selection and non-response bias in our survey. We reached out to all 11,400 members of the Northern California Chapter of the National Multiple Sclerosis Society listed on the database as having MS. We received 2,810 (24.6%) responses. We believe the responders in this survey are representative of the Northern California MS population, for several reasons. Firstly, a prior survey in this same population relating to symptoms in MS showed a response rate similar to our survey. Goodin et al. mailed a survey on MS symptoms randomly to 493 individuals registered with the Northern California Chapter of the National Multiple Sclerosis Society and reported a response rate of 34%.[7] Secondly, the independent variables in our survey such as age, gender, disease duration, and race of the respondents were similar to what is known about the epidemiology of MS and is in keeping with the demographics of other surveys reported in the Northern California MS population.[28] Even the dependent variables from our survey, including the percentage of respondents with abnormal fatigue, excessive daytime sleepiness, RLS, and STOP-BANG positive, are similar to other smaller surveys reported on the MS population.[5,7,11,28] The issue of response bias can also be raised, as subjects diagnosed by physicians with sleep problems may have been more likely to agree to participate in the survey, as survey instructions were explicit in describing our goal to examine sleep problems. It is, however, important to note that only a small percentage of subjects were aware of meeting criteria for a primary sleep disorder, and most remained unaware and undiagnosed.

The non-response rate is a limitation of our study, but one should also consider the absolute number of responders in our study in addition to the response rate. The nonresponse bias can affect our study estimates in either direction. For example, more seriously affected patients may have chosen not to respond. Our worst-case scenario analysis demonstrates that even if all survey non-responders would have screened negative for obstructive sleep apnea, insomnia, and restless legs syndrome, the incidence of obstructive sleep apnea and restless legs syndrome would be higher than the prevalence in the general population. According to the best-case scenario analysis, if the bias was in the opposite direction, then our estimate may be too low.

We acknowledge several other limitations in this study. Although all questionnaires have been validated, a clinician did not separately interview or examine the subjects to confirm the diagnosis, nor was polysomnography included as part of the study to validate the findings of obstructive sleep apnea. Polysomnography is considered the gold standard diagnostic screening test for OSA and is required to confirm a clinical diagnosis. Although the STOP-BANG and Berlin questionnaire have good sensitivity in identifying OSA, a positive result on the questionnaire does not equate with a clinical diagnosis of obstructive sleep apnea. In the survey, we determined there were 142 subjects who reported using CPAP. We did not exclude these subjects from the analysis to simplify the analysis in view of the small numbers. In addition, without compliance data, we were unable to determine if the subjects were compliant with CPAP therapy. Although the numbers of CPAP users were small, this may be a limitation by underestimating the incidence of subjects reporting symptoms of OSA, as CPAP therapy might reduce the number reporting OSA symptoms. The study defined subjects who self-reported RLS based on the 4 major symptoms of RLS per the International Restless Legs Syndrome Study Group (IRLSSG). It is important to note that many MS patients present with lower limb symptoms such as spasms, tremors, and paresthesias, which may mimic RLS, potentially causing false positive responses. No healthy control group was surveyed, as our a priori objective was to explore symptomatology only in MS subjects. The study was limited by the reliance questionnaires without a follow-up clinical examination or polysomnography. It is important for the reader to understand a positive result on the questionnaire would not necessarily translate to a positive clinical diagnosis, which is a limitation of this study and other survey studies.

The lack of a control group may also be a limitation of this study although our study was not designed to compare the incidence of sleep disorders in the MS population to healthy controls subjects. Prior papers on OSA, insomnia, and RLS also examined the underdiagnosis of sleep disorders and similarly noted the underdiagnosis of sleep disorders is also large in the general population.[20-22] Although it is clear that there is an underdiagnosis of sleep problems, we cannot determine from our research if this underdiagnosis is specific to the MS population, as no control group was obtained.

A final limitation is that the survey was conducted in Northern California, and may not be considered generalizable to

patients in other geographic locations, as the demographic characteristics may differ from region to region.

All three sleep disorders considered in this study have been shown to have independent, long- term health consequences and affect quality of life. OSA is now recognized as an independent risk factor for myocardial infarction, hypertension, diabetes, stroke, pulmonary hypertension, heart failure, and cardiac rhythm disturbances.[29,30] In addition, OSA has been linked to cognitive deficits, motor vehicle accidents, and depression; and RLS has been shown to be an independent risk factor for cardiovascular disease.[31] The diagnosis of insomnia has been also been associated with an increased risk of mood disorders and cardiovascular disease.[32]

Compared to the general population, the MS population appears to have a higher frequency of symptoms suggestive of RLS, OSA, and sleep restriction, but a comparable level of insomnia.[20-22] Not only are these symptoms more frequent, they remain undiagnosed and untreated. They are likely not only impacting the quality of life, but they may have an effect on both the physical and mental health status of the MS population.

Fatigue is known to be frequent and disabling in the MS population. We noted that 62.3% of the respondents' surveys screened positive for abnormal levels of fatigue (scoring ≥ 36 on the FSS). The fatigue of MS is multifactorial in origin, and sleep problems should be placed in the differential diagnosis of an MS patient complaining of fatigue. A strong association was demonstrated in our study between an abnormal level of fatigue and sleep disorders including RLS, insomnia, and OSA. FSS scores ≥ 36 were statistically significantly associated with both screening positive for OSA on the STOP BANG outcome and BERLIN screening test ($p < 0.001$). Although not implying causation, the important association between complaints of fatigue and risk of obstructive sleep apnea merits further attention. Chervin et al. reported that most OSA patients (without MS) report their symptoms as lack of energy, tiredness, or fatigue rather than sleepiness.[33] It is of interest to note that in our survey, there was an association between MS patients who are at risk of OSA and reported high levels of fatigue. This may suggest that OSA should be considered more routinely in the differential of MS patients presenting with fatigue.

As both OSA and multiple sclerosis affect the immune system and alter the cytokine profile of patients, further studies are needed to look at this important association given the impact of cytokines on fatigue and sleep.[34] OSA subjects (without MS) show a pro-inflammatory cytokine profile with elevations of interleukin-6, IFN-γ, and tumor necrosis factor-α (TNF-α) compared to BMI-matched controls without OSA.[34] These cytokines are believed to arise out of oxidative stress and are known to be pro-inflammatory in nature. TNF- α and IFN-γ are also known to be somnogenic, thus causing fatigue and sleepiness if administered to healthy subjects. TNF-α and IL-6 cytokines decrease when subjects receive CPAP. Of importance, MS is known to be also associated with a similar pro-inflammatory TH-1 cytokine profile, with patients showing elevations of L-6, IFN-γ, and TNF-α, well as other TH-1 cytokines.[34] Although research is ongoing, one may hypothesize that the cytokine profile in MS and fatigue may also be related to undiagnosed OSA syndrome, given the high frequency of OSA noted in these MS patients. Researchers are also currently looking at screening for OSA in MS patients complaining of fatigue and using CPAP as a therapeutic modality to treat MS fatigue in view of these findings.

In conclusion, a large percentage of MS subjects in our sample are sleep deprived and screened positive for one or more sleep disorders. The vast majority of these sleep disorders are potentially undiagnosed and untreated. Fatigue is the most common and disabling symptom of MS and is often attributed to the primary diagnosis of MS. However, these findings contribute to a growing body of evidence suggesting that there may be a comorbid sleep diagnosis requiring independent evaluation and management. Our next steps will include trying to determine a clinically useful predictive model for identifying risk of sleep disorders in this population with a therapeutic arm.

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