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Migraine and Restless Legs Syndrome in Women

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Abstract

Background—Few clinic-based studies report an association between migraine and restless legs syndrome (RLS); however, population-based data are unavailable.

Methods—Cohort study among 31,370 women participating in the Women's Health Study. We had detailed self-reported information on migraine, including aura status, and RLS. RLS was ascertained at the 9-year follow-up. We calculated odds ratios (OR) and 95% confidence intervals (CI) for the association between migraine and RLS. We investigated any indication of migraine until RLS ascertainment as well as migraine with and without aura at baseline, prior migraine before baseline, and new reports of migraine during follow-up.

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Conflict of Interest Statement

We present full disclosures for all authors. None of the disclosures for any of the authors represents a conflict of interest with regard to this specific manuscript.

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Results—At baseline or during follow-up 6,857 (21.9%) women reported any migraine. These women had an increased risk for RLS (multivariable-adjusted OR=1.22; 95%CI 1.13–1.32). Further analyses indicated a similar association for migraine with aura (multivariable-adjusted OR=1.27; 95%CI 1.10–1.48) and migraine without aura (multivariable-adjusted OR=1.24; 95%CI 1.09–1.40) as well as for new reports of migraine during follow-up (multivariable-adjusted OR=1.30; 95%CI 1.10–1.54). Prior migraine did not appear to be associated with RLS.

Conclusions—Our data suggest an association between migraine and RLS at the population level. The association is similar for migraine with and without aura and for new reports of migraine during follow-up.

Keywords

migraine; restless legs syndrome; cohort study; association

Introduction

Migraine is a common neurological disorder affecting 10–20% of the population, predominantly women (1). It is characterized by recurrent headache attacks, associated vegetative symptoms, and hypersensitivity of various functional systems of the nervous system (1).

A number of disorders have been firmly associated with migraine including for example cardiovascular disease (CVD), in particular stroke (2), depression (3), and other pain disorders (4, 5). These associations and the clinically heterogeneous picture of migraine suggest that migraine might share pathophysiological pathways with several other disorders or conditions. Studying such comorbidities may therefore provide valuable clinical and biological insights into migraine (6).

Restless legs syndrome (RLS) is a common movement disorder, also predominantly affecting women (7). RLS is characterized by unpleasant leg sensations and an urge to move the legs, typically during rest and at night (8). A common origin for migraine and RLS has been proposed (9) and an association appears plausible based on pathophysiological considerations involving a disturbance of iron and dopamine metabolism (10–12).

The epidemiological evidence supporting an association between migraine and RLS, however, is scarce. Studies without a control group report high frequencies of RLS among patients with migraine (13, 14), but not migraine with aura (15). In addition, case-control studies in clinic-based populations report an increased risk of RLS among migraineurs (16–18). However, population-based studies are unavailable (11).

We therefore sought to investigate the association between migraine including its subtypes and RLS in a large population-based cohort of women participating in the Women's Health Study (WHS).

Subjects and Methods

Study population

The WHS was a randomized trial designed to test the benefits and risks of low-dose aspirin and vitamin E in the primary prevention of CVD and cancer. The design, methods, and results have been described in detail previously (19). Briefly, a total of 39,876 U.S. female health professionals aged ≥45 years at study entry (1992–1995) without a history of CVD, cancer, or other major illnesses were randomly assigned to active aspirin (100 mg on alternate days), active vitamin E (600 IU on alternate days), both active agents, or both

placebos. All participants provided written informed consent and the Institutional Review Board of Brigham and Women's Hospital approved the WHS. Baseline information was self-reported and collected by a mailed questionnaire that asked about many cardiovascular risk factors and lifestyle variables. Twice in the first year and yearly thereafter, participants were sent follow-up questionnaires asking about study outcomes and other information during the study period. All participants are followed observationally since the trial's termination in March 2004. At the 108-month follow-up 33,092 women were still in active follow-up. Of those, 1,722 had missing information on all three RLS questions from the 108-month questionnaire (when RLS was assessed) and were excluded. This left us with 31,370 women for our main analysis.

Ascertainment of migraine

Participants were asked on the baseline questionnaire: "Have you ever had migraine headaches?" and "In the past year, have you had migraine headaches?" From this information, we categorized women into "history of migraine at baseline;" "active migraine at baseline," which includes women with self-reported migraine during the past year; and "prior migraine," which includes women who reported ever having had a migraine but none in the year prior to completing the baseline questionnaire. Participants who reported active migraine at baseline were asked further details about their migraine attacks, including attack duration of 4 to 72 hours, unilateral location of pain, pulsating pain quality, aggravation by routine physical activity, sensitivity to light, sensitivity to sound, and nausea or vomiting. In a previous study (20), we have shown good agreement of our classification with the 1988 International Headache Society (IHS) criteria for migraine (21) and we have shown excellent agreement between self-reported migraine and migraine classification based on the revised IHS criteria for migraine from 2004 in the WHS (22). Participants who reported active migraine at baseline were further asked whether they had an "aura or any indication a migraine is coming." Responses were used to classify women who reported active migraine at baseline into "migraine with aura" and "migraine without aura".

During follow-up participants were asked every year: "In the past year, were you newly diagnosed with migraine headaches?" Women giving an affirmative answer to this question up to the 108-month questionnaire (when RLS was assessed) and who did not indicate any migraine history at baseline were categorized as "new reports of migraine". Those categorized as "new reports of migraine" and those with history of migraine at baseline were combined to form the category "any migraine".

Ascertainment of restless legs syndrome

Questions addressing the four minimal diagnostic criteria of the International Restless Legs Study Group (IRLSSG) (23) had been implemented in the 108-month follow-up-questionnaire. Participants were asked the following questions: "Do you have unpleasant leg sensations (like crawling, paresthesias or pain) combined with a motor restlessness and an urge to move?", "Do these symptoms occur only at rest and does moving improve them?", "Are these symptoms worse in the evening or at night compared with the morning?" Participants who answered yes to all of the three questions were defined as having RLS. This set of questions has been established (24–26) and validated (27) in previous studies from Germany and Italy. Comparing the questionnaire based diagnosis of RLS with a physician's diagnosis as a gold standard showed good agreement (unweighted kappa=0.67, $p<0.001$) in the MEMO (Memory and Morbidity in Augsburg Elderly) study (27).

Ascertainment of covariates

Participants in the WHS self-reported personal information, lifestyle factors, and medical conditions. Covariate information from baseline was updated during follow-up and we used

the most recent information with regard to the 108-month questionnaire. Self-reported CVD events were confirmed by medical record review. For this analysis we only used confirmed CVD events up to the 108-month questionnaire. We used the combined endpoint major CVD as a covariate. This was defined as the first occurrence of non-fatal stroke, non-fatal myocardial infarction or death from CVD events.

Statistics

We compared the characteristics of participants with any migraine and without migraine using t-test for continuous variables and chi-square test for categorical variables.

We used logistic regression models to evaluate the association between migraine and RLS and calculated odds ratios (ORs) and their 95% confidence intervals (CIs). We analyzed "any migraine", which includes migraine information from baseline and follow-up. We also investigated "migraine with aura", "migraine without aura", and "prior migraine", which include information from baseline only as well as "new reports of migraine", which includes information from follow-up until the 108-month questionnaire.

We built age-adjusted and multivariable-adjusted models. The multivariable-adjusted model controlled for age (continuous), body mass index (<25, 25–29.9, ≥30 kg/m^2), history of diabetes (yes, no), history of hypertension (yes, no), history of cholesterol ≥240mg/dl (yes, no), alcohol consumption (rarely/never, 1–3 drinks/month, 1–6 drinks/week, ≥1 drinks/day), smoking (never, past, current), exercise (rarely/never, <1/week, 1–3/week, ≥4/week), parental history of myocardial infarction prior to age 60 (yes, no), major CVD events (yes, no), postmenopausal hormone use (never, past, current), menopausal status (premenopausal, postmenopausal, biologically uncertain, unclear), history of depression (yes, no), history of Parkinson's disease (yes, no), number of pregnancies lasting ≥6 months (0, 1–2, 3–4, 5–6), fatigue (yes, no), ethnicity (white, other), and geographic location (northeast, southeast, midwest, west).

We incorporated a missing value indicator if the number of women with missing information on covariates was ≥100. If the number of participants with missing information was <100, we assigned them to the covariate reference category.

All analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC). All p-values were two-tailed and we considered $p<0.05$ as statistically significant.

Results

Of the 31,370 women included for this analysis 6,857 (21.9%) reported any migraine at baseline or during follow-up until the 108-month questionnaire. The characteristics of these women according to migraine are summarized in Table 1. Women with any migraine were younger, had a higher BMI, and were more likely to have a history of hypertension than women without migraine. They were also more likely to have history of elevated cholesterol and parental history of myocardial infarction, and less likely to drink and exercise regularly. Furthermore, migraineurs were more likely to be nonsmokers, to currently use hormones, and to have a biologically uncertain menopausal status. In addition, they more likely reported a history of depression and fatigue than women without migraine.

The association between any migraine and RLS is summarized in Table 2. Women with any migraine had an age-adjusted OR (95% CI) of 1.35 (1.25–1.46) for RLS. This association was attenuated when adjusting for multiple covariates, but remained statistically significant with an OR of 1.22 (1.13–1.32).

Information on migraine with and without aura as well as prior migraine is only available from baseline, while new reports of migraine were recorded during follow-up. Of the 6,857 women with migraine 1,579 (23.0%) had migraine with aura, 2,418 (35.2%) migraine without aura, and 1,725 (25.2%) prior migraine. Further, 1,135 (16.6%) women gave new reports of migraine.

Table 3 summarizes the association between migraine subtypes and RLS. The associations with RLS were similar for migraine with and without aura as well as new reports of migraine, while the association for prior migraine was weaker. In age-adjusted models all associations were statistically significant. After adjusting for multiple covariates the ORs diminished. In multivariable-adjusted models the ORs for migraine with aura (OR=1.27; 1.10–1.48) and without aura (OR=1.24; 1.09–1.40) as well as new reports of migraine (OR=1.30; 1.10–1.54) remained statistically significant, however, the association for prior migraine became statistically insignificant (OR=1.11; 0.96–1.28).

Discussion

Results from this large population-based study of over 30,000 women indicate that any migraine is associated with a significantly 22% increased odds of RLS. Additional analyses do not suggest that this association is different between women with migraine with aura, migraine without aura, and new reports of migraine during follow-up. In contrast, women reporting prior migraine do not appear to still have a significantly increased risk of RLS, suggesting that this association is limited to women with active migraine.

Previous studies have reported a high percentage of RLS among patients with headache and migraine. In a US study among 50 headache patients (41 with migraine), who presented to an outpatient infusion center, 17 (34%) met criteria for RLS (14). Another study from Taiwan reported an RLS frequency of 11.4% among 772 migraineurs (13). This number needs to be interpreted in conjunction with the lower population prevalence of RLS reported in Asian populations (28) as compared to Western populations (7). However, both studies did not have a control group for direct comparison. A clinic-based case-control study from Japan among 262 migraineurs and 163 controls reported a significantly higher RLS prevalence in migraineurs compared with controls (13.7% vs. 1.8%; $p<0.0001$) (18). However, the authors did not adjust for imbalances between the groups in their analysis. Another clinic-based study from Italy included 200 headache patients (114 with migraine without aura) and 120 sex-and age-matched control subjects. RLS frequency was significantly higher in headache patients than in control subjects (22.4% vs. 8.3%, $p=0.002$) (17). The same group later investigated a group of 63 patients with migraine with aura and found an RLS prevalence of 9.5%, which is similar to headache free individuals (8.3%) in Italy (15). A clinic-based German case-control study among 441 migraine patients and the same number of age- and sex-matched controls found a significantly higher RLS frequency among migraine patients compared with controls (17.3% vs. 5.6%, $p<0.001$) with an OR (95% CI) of 3.5 (2.2–5.8) (16). The difference in effect size between this study and our study (OR=1.22) may be driven by differences in sample size and study design. Altogether our study is in line with the previous reports indicating that migraineurs are more likely to have RLS than non-migraineurs.

However, our study is unique in terms of its large size and prospective design. In addition, we had large numbers of women with migraine subtypes, allowing us to evaluate the associations for these subgroups with RLS. The effect estimates for migraine with and without aura are similar not supporting differential effects as observed for other conditions comorbid with migraine such as ischemic stroke (2). Further, since the effect estimates for women with new reports of migraine were similar to those with migraine at baseline, this

may give some indication that time of migraine onset does not affect risk for RLS. The association between prior migraine and RLS, however, was not statistically significant in multivariable-adjusted models. This may suggest that disease activity is important for the manifestation of comorbid RLS.

An association between migraine and RLS is plausible based on pathophysiological considerations and clinical findings. In both conditions disturbance of the iron and dopamine metabolism have been implicated. While brain iron deposition has been reported in migraine patients with increased iron accumulation being associated with repeated attacks (29), iron deficiency plays a role at least in a subset of patients with RLS (30). Furthermore, dopamine has long been hypothesized to be involved in migraine pathophysiology (10). In particular, yawning, irritability, and mood changes during the premonitory phase as well as nausea and vomiting during the premonitory and headache phases may be ascribed to dopamine. In addition, antiemetics, which possess antidopaminergic properties, can successfully be used in the treatment of migraine attacks (31). Further, it has been shown experimentally in rats that dopamine can modulate neuronal firing in the trigeminocervical complex (32). In RLS the central pathophysiological hypothesis relates to a dysfunction of the dopaminergic system involving A11 neurons descending from the hypothalamus to the spinal cord (12). A “dopaminergic link” between migraine and RLS is further supported by data showing, that migraineurs with RLS report premonitory symptoms significantly more often than migraineurs without RLS (33).

Our study has several strengths, including the prospective design, the large number of participants as well as the large number of women with migraine and with RLS. Further, we had collected detailed information on a large number of personal characteristics, lifestyle features, and medical conditions including physician-verified CVD events. In addition, the homogenous nature of the cohort may reduce confounding.

However, several limitations should be considered. First, migraine was self-reported and women could not be classified according to strict IHS criteria. Thus, misclassification is possible. However, our prevalence of migraine (21.9%) is very similar to other large population-based studies in the U.S. (34) and the Netherlands (35). Moreover, potential misclassification would likely have obscured an association between migraine and RLS. Further, our migraine ascertainment at baseline was in good agreement with the modified 1988 IHS criteria (20), and we have shown excellent agreement between self-reported migraine and the revised IHS criteria from 2004 (22). Second, RLS diagnosis was based on the reply to a set of questions. However, these questions addressed the four minimal diagnostic criteria of the International Restless Legs Study Group (IRLSSG) (23) and they have successfully been used (24–26) and shown to reliable (27) in previous studies from Germany and Italy. Still, language differences should be considered with respect to our study. Third, participants were white female health professionals age ≥45, thus generalizability may be limited. However, women in this age group are preferentially affected by RLS; hence, our population is both relevant and ideal to investigate an association between migraine and RLS. Fourth, the definition of active migraine with and without aura is based on the baseline questionnaire and we have no information on migraine attacks among these women during follow-up. Fifth, information on RLS was only available from one questionnaire obviating analyses of changing time patterns of RLS manifestation. Sixth, aura status was only assessed at baseline; hence, any change in aura status during follow-up might have resulted in misclassification. Finally, information on severity of migraine and RLS was not available to us; hence, we were unable to investigate a potential dose-response effect of the association.

Our study indicates that migraine is associated with RLS in a population-based cohort of women. Further, this association is not influenced by migraine aura status, as is the case for other disorders such as ischemic stroke. Given the high prevalence and burden of both conditions further research at the population level is of great public health importance. Specific unanswered questions pertain to potential gender differences of the migraine-RLS link and whether severity of migraine has an impact on severity of RLS as well as to understanding the underlying pathophysiology linking both conditions.

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Table 1

Characteristics of women according to migraine in the Women's Health Study (n=31,370)

	No Migraine (n=24,513)	Any migraine (n=6,857)	p-value*
Demographic information			
Mean age, yrs (SD)	63.9 (7.1)	62.5 (6.3)	<0.01
Ethnicity White	23,203 (95.4)	6,482 (95.5)	0.83
Geographic location Northeast Southeast Midwest West	4,715 (19.3) 5,568 (22.8) 8,930 (36.5) 5,262 (21.5)	1,344 (19.6) 1,646 (24.0) 2,368 (34.6) 1,491 (21.8)	0.02
Covariates			
BMI, kg/m^2 <25 25–29.9 ≥30	9,976 (41.4) 8,241 (34.2) 5,911 (24.5)	2,646 (39.2) 2,360 (35.0) 1,744 (25.8)	<0.01
History of diabetes	1,841 (7.5)	501 (7.3)	0.57
History of hypertension	11,715 (47.8)	3,508 (51.2)	<0.01
History of cholesterol ≥240mg/dl	13,112 (53.5)	3,974 (58.0)	<0.01
Alcohol consumption Rarely/never 1–3 drinks per month 1–6 drinks per week ≥1 drink/day	10,386 (42.6) 2,746 (11.3) 8,307 (34.1) 2,924 (12.0)	3,121 (45.8) 859 (12.6) 2,208 (32.4) 631 (9.3)	<0.01
Smoking Status Never Past Current	12,242 (50.6) 9,935 (41.1) 2,018 (8.3)	3,579 (53.1) 2,606 (38.6) 559 (8.3)	<0.01
Exercise Rarely/never <1/week 1–3 times/week ≥ 4 times/week	9,386 (38.3) 4,766 (19.5) 7,628 (31.1) 2,725 (11.1)	2,584 (37.7) 1,517 (22.1) 2,093 (30.5) 659 (9.6)	<0.01
Family history of myocardial infarction	4,131 (16.9)	1,298 (19.0)	<0.01
Major CVD	376 (1.5)	117 (1.7)	0.31
Postmenopausal Hormone Use Never Past Current	5,514 (23.4) 5,998 (25.5) 12,011 (51.1)	1,089 (16.6) 1,657 (25.3) 3,815 (58.2)	<0.01
Menopausal Status Premenopausal Postmenopausal Biologically uncertain Unclear	417 (1.7) 22,012 (91.5) 1,397 (5.8) 235 (0.99)	110 (1.7) 5,917 (88.5) 589 (8.8) 69 (1.03)	<0.01
Number of pregnancies 0 1–2 3–4 5–6	3,077 (12.6) 9,202 (37.7) 9,386 (38.4) 2,759 (11.3)	782 (11.4) 2,661 (38.9) 2,718 (39.8) 677 (9.9)	<0.01
History of depression	2,863 (11.7)	1,237 (18.0)	<0.01
History of Parkinson's disease	934 (3.9)	281 (4.2)	0.25
Iron supplementation use	107 (0.4)	31 (0.5)	0.86

	No Migraine (n=24,513)	Any migraine (n=6,857)	p-value*
Fatigue	8,644 (35.4)	3,063 (44.9)	<0.01

Values are number of people (%) unless denoted otherwise.

* p-value from t-test for continuous variables and chi-square test for categorical variables.

Table 2

Age- and multivariable-adjusted odds ratios for restless legs syndrome according to migraine in the Women's Health Study (n=31,370)

Migraine	Women with RLS % (n)	Age-adjusted Model		Multivariable-adjusted Model*	
		OR (95% CI)	p-value	OR (95% CI)	p-value
No migraine (n=24,513)	11.2 (2,749)	Ref	-----	Ref	-----
Any migraine (n=6,857)	14.5 (996)	1.35 (1.25–1.46)	<0.0001	1.22 (1.13–1.32)	<0.0001

RLS, restless legs syndrome; OR, odds ratio; CI, confidence interval.

*adjusted for: age, BMI, history of diabetes, history of hypertension, history of elevated cholesterol, alcohol consumption, smoking, physical activity, parental history of myocardial infarction prior to age 60, major CVD, postmenopausal hormone use, menopausal status, history of depression, history of Parkinson's disease, number of pregnancies lasting ≥6 months, iron supplementation use, fatigue, ethnicity, and geographic location.

Table 3

Age- and multivariable-adjusted odds ratios for restless legs syndrome according to migraine subtypes at baseline in the Women's Health Study (n=31,370)

Migraine subtype	Women with RLS % (n)	Age-adjusted Model		Multivariable-adjusted Model*	
		OR (95% CI)	p-value	OR (95% CI)	p-value
No migraine (n=24,434)†	11.2 (2,738)	Ref	-----	Ref	-----
Migraine with aura (n=1,579)	15.1 (239)	1.42 (1.23–1.63)	<0.0001	1.27 (1.10–1.48)	0.001
Migraine without aura (n=2,418)	14.5 (351)	1.35 (1.20–1.52)	<0.0001	1.24 (1.09–1.40)	<0.001
Prior migraine (n=1,725)	13.4 (232)	1.23 (1.07–1.42)	0.005	1.11 (0.96–1.28)	0.17
New reports of migraine (n=1,135)	15.3 (174)	1.44 (1.22–1.70)	<0.0001	1.30 (1.10–1.54)	0.003

RLS, restless legs syndrome; OR, odds ratio; CI, confidence interval.

*adjusted for: age, BMI, history of diabetes, history of hypertension, history of elevated cholesterol, alcohol consumption, smoking, physical activity, parental history of myocardial infarction prior to age 60, major CVD, postmenopausal hormone use, menopausal status, history of depression, history of Parkinson's disease, number of pregnancies lasting ≥6 months, iron supplementation use, fatigue, ethnicity, and geographic location.

†79 women with missing information on migraine at baseline were included in the model as a separate "dummy" category.