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Migraine and Restless Legs Syndrome in Men

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Abstract

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Full Disclosures

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Background—Previous studies suggest an association between migraine and restless legs syndrome (RLS). Population-based data, however, have been limited to women. The aim of this study is to evaluate the association between migraine and RLS in a male cohort.

Methods—Cross-sectional study among 22,926 participants in the Physicians' Health Study. Migraine and RLS information was self-reported. RLS was classified according to four minimal diagnostic criteria. Age-and multivariable-adjusted logistic regression models were calculated.

Results—Of the 22,926 participants (mean age 67.8), 2,816 (12.3%) reported migraine and 1,717 (7.5%) RLS. Migraine was associated with an increased multivariable-adjusted OR (95% CI) of 1.20 (1.04–1.38) for having RLS. The association remained stable after excluding men with potential mimics of RLS and was not modified by age.

Conclusions—Results of our study indicate an association between migraine and RLS in men. The magnitude of effect is similar to what has been reported in women.

Keywords

migraine; restless legs syndrome; cross-sectional study; epidemiology

Introduction

Migraine is a primary headache disorder that has been associated with a variety of comorbidities including other pain conditions, cardiovascular disease and psychiatric disorders (1). A relationship between migraine and restless legs syndrome (RLS) has been hypothesized and plausible shared pathophysiological mechanisms have been proposed (2). RLS is a common movement disorder characterized by an urge to move the legs, mostly accompanied by unpleasant leg sensations. These symptoms typically occur during rest and at night and are temporarily relieved by activity.

Several clinic-based case-control studies suggested an association between migraine and restless legs syndrome (3–6). Data from a large cross-sectional study indicated that women with migraine had a 22% increased odds for having RLS compared to women without migraine (7). However, population-based data on the association between migraine and RLS in men are lacking. We therefore aimed to evaluate the association between migraine and RLS in a large cohort of male physicians.

Methods

Study population

The Physicians' Health Study I (PHS I) was a randomized, double blind, placebo-controlled trial to test the benefits and risks of low dose aspirin (325mg) and beta-carotene (50mg) in the primary prevention of cardiovascular disease (CVD) and cancer among 22,071 apparently healthy male physicians aged 40 to 84 years at baseline in 1982 (8). Baseline information was self-reported and collected by means of a mailed questionnaire that asked about many cardiovascular risk factors and life-style variables. Every six months in the first year and yearly thereafter, follow-up questionnaires were sent to the participants. Since the trials' termination in 1995, participants are continued to be followed either on an observational basis or as part of the Physicians' Health Study II (PHS II).

The PHS II, launched in 1995, is an ongoing randomized, double-blind, placebo-controlled trial to test the effects of vitamin C (500mg), vitamin E (400IU), beta-carotene (50mg), and a daily multivitamin (Centrum Silver) in the prevention of total and prostate cancer, CVD, and age-related eye disease among 14,641 US male physicians aged 55 years and older,

including a total of 7,641 PHS I participants who were willing and eligible to enter the PHS II (9). Baseline information was self-reported and follow-up information was collected annually by mailed questionnaires. For the purpose of this analysis, we pooled data from the PHS I and PHS II, yielding a total of 29,071 participants.

Assessment of migraine

The participating physicians were asked whether they had experienced a migraine since they last filled out the questionnaire on the 6-month and subsequent annual questionnaires. Men were classified as having migraine if they reported migraine during follow-up until the time of RLS assessment. No further information on migraine details and aura status was available, that would have allowed us to classify migraine according to diagnostic criteria of the International Headache Society (IHS). However, results from the Women's Health Study (WHS), a prospective cohort similar in design and data ascertainment to the PHS, showed good agreement of self-reported migraine with IHS diagnostic criteria (10).

Ascertainment of restless legs syndrome

A short questionnaire addressing the four minimal diagnostic criteria of the International Restless Legs Study Group (IRLSSG) was implemented in the 216-month follow-up questionnaire (PHS I) and the 12-month follow-up questionnaire (PHS II), respectively. Participants were asked the following questions: "Do you have unpleasant leg sensations (like crawling, paraesthesis 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 questionnaire has been used and validated in other cohorts (11, 12). Comparing the questionnaire based diagnosis of RLS against a physician's diagnosis as a gold standard showed good agreement (unweighted kappa=0.67, $p<0.001$) in a population-based study (12).

Ascertainment of covariate information

Self-reported baseline information on life-style factors and other covariates was updated during follow-up and we used the most recent information with regard to the date of RLS assessment. Self-reported major cardiovascular events including myocardial infarction, stroke and death due to CVD events were confirmed by medical record review.

Statistics

Of the 25,357 participants in active follow-up at the time RLS was assessed, we excluded 852 men who did not return the questionnaire containing the RLS questions. We additionally excluded 1,579 men with missing information on all three RLS questions, leaving 22,926 participants for this analysis.

Baseline characteristics of participants according to migraine status were compared using t-tests for continuous and chi-square tests for categorical variables.

Age-and multivariable-adjusted logistic regression models were calculated with migraine as independent and RLS status as dependent variable. The multivariable models were adjusted for age, race, region, body mass index (BMI), alcohol consumption, smoking status, exercise, diabetes, history of hypertension, hypercholesterolemia, family history of myocardial infarction, confirmed major CVD events, depression, Parkinson's disease, and iron-supplementation use. Excluding men who reported history of diabetes did not alter the results.

Effect modification was tested for age (<60, 60–70, 70–80, ≥80 years) by contrasting models with and without an interaction term indicator variable using the likelihood ratio test.

In sensitivity analyses, we excluded 4,652 men with potential secondary causes for RLS including men with a history of polyneuropathy, kidney disease, liver disease, liver cirrhosis, rheumatoid arthritis, intermittent claudication and men who underwent peripheral artery disease surgery.

A missing value indicator was incorporated in the models for covariates if the number of men with missing information was ≥100. If the number of men with missing values was <100, we assigned these participants to the category indicating no event.

For all analyses, we used SAS (version 9.1.3, SAS Institute Inc. Cary, NC). All p values were 2-tailed and $p<0.05$ was considered statistically significant.

Results

The mean age of the cohort at the time of RLS assessment was 67.8 (standard deviation 8.9) years. Of the 22,926 participants, 2,816 (12.3%) men reported migraine until the time of RLS assessment and 1,717 (7.5%) were classified as having RLS. Migraineurs were younger (mean age 67.3 years) compared with men without migraine (mean age 67.8 years). They were more likely to be white, never smokers and to have a history of depression compared with men without migraine (appendix table).

Migraine was associated with an increased odds for having RLS in age-adjusted models (OR: 1.22; 95%CI: 1.06–1.41) which did not attenuate after adjustment for potential confounders (Table 1).

The association was not modified by age (p for interaction: 0.26) and remained stable in sensitivity analyses excluding men with potential secondary causes of RLS (OR: 1.23; 95% CI: 1.04–1.45).

Discussion

In this large cohort of male physicians, migraine was associated with a 20% increased odds for having RLS. The association was not modified by age and remained robust after excluding men with potential mimics for RLS.

Our findings are in line with results of several clinic-based case-control studies which reported a higher frequency of RLS among migraineurs compared to controls (3, 5, 6). Population-based data on the association between migraine and RLS are sparse to date. In a recently published cross-sectional study among 31,370 participants of the WHS, any history of migraine was associated with a multivariable-adjusted OR of 1.22 (95% CI: 1.13–1.32) for RLS (7). The odds for having RLS did not differ according to migraine aura status. In our study, no information on migraine aura status was available. The magnitude of the observed multivariable-adjusted effect estimate for any migraine history in the WHS is similar to our finding suggesting no gender difference.

Several plausible mechanisms involving the dopaminergic system and iron-metabolism have been proposed to link these two disorders (2). Furthermore, studies have identified a genetic predisposition for both diseases and a joint origin on chromosome 14q21 has been proposed recently (13). However, further studies are warranted to better understand underlying genetic and shared pathophysiological mechanisms linking migraine with RLS.

This study has several strengths including the large sample size, the definition of RLS according to the IRLSSG criteria and the information on a variety of covariates allowing us to adjust the association. The following limitation should be considered when interpreting our results. First, migraine and RLS information was self-reported. However, results from the WHS, a study similar in design, showed good agreement with IHS criteria (10) and the RLS questionnaire has been validated in previous reports (11, 12), although this was done based in questions in German. Second, we used self-reported information to adjust the models and to exclude participants with potential RLS mimics in our sensitivity analysis. However, PHS participants are all physicians and previous reports indicate that health professionals accurately report information. Third, the design of our study is cross-sectional and does not allow us to determine a causality and time sequence of the association. Fourth, our cohort consists of predominately white middle-aged male physicians which may limit the generalizability of our results to other cohorts.

In summary, results of this large cross-sectional study indicate an association between migraine and RLS in men. Future research should focus on identifying biological mechanism linking these two disorders.

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References

1. Diener HC, Kuper M, Kurth T. Migraine-associated risks and comorbidity. J Neurol. 2008; 255:1290–1301. [PubMed: 18958572]
2. Cannon PR, Larner AJ. Migraine and restless legs syndrome: is there an association? J Headache Pain. 2011; 12:405–409. [PubMed: 21660429]
3. d'Onofrio F, Bussone G, Cologno D, Petretta V, Buzzi MG, Tedeschi G, et al. Restless legs syndrome and primary headaches: a clinical study. Neurol Sci. 2008; 29(Suppl 1):S169–S172. [PubMed: 18545926]
4. Seidel S, Bock A, Schlegel W, Kilic A, Wagner G, Gelbmann G, et al. Increased RLS prevalence in children and adolescents with migraine: A case-control study. Cephalalgia. 2012; 32:693–699. [PubMed: 22659118]
5. Rhode AM, Hosing VG, Happe S, Biehl K, Young P, Evers S. Comorbidity of migraine and restless legs syndrome--a case-control study. Cephalalgia. 2007; 27:1255–1260. [PubMed: 17888079]
6. Suzuki S, Suzuki K, Miyamoto M, Miyamoto T, Watanabe Y, Takashima R, Hirata K. Evaluation of contributing factors to restless legs syndrome in migraine patients. J Neurol. 2011; 258:2026–2035. [PubMed: 21538231]
7. Schurks M, Winter AC, Berger K, Buring JE, Kurth T. Migraine and restless legs syndrome in women. Cephalalgia. 2012; 32:382–389. [PubMed: 22395798]
8. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. N Engl J Med. 1989; 321:129–135. [PubMed: 2664509]
9. Christen WG, Gaziano JM, Hennekens CH. Design of Physicians' Health Study II--a randomized trial of beta-carotene, vitamins E and C, multivitamins, in prevention of cancer, cardiovascular

disease, and eye disease, and review of results of completed trials. Ann Epidemiol. 2000; 10:125–134. [PubMed: 10691066]

10. Schurks M, Buring JE, Kurth T. Agreement of self-reported migraine with ICHD-II criteria in the Women's Health Study. Cephalalgia. 2009; 29:1086–1090. [PubMed: 19735535]
11. Berger K, Luedemann J, Trenkwalder C, John U, Kessler C. Sex and the risk of restless legs syndrome in the general population. Arch Intern Med. 2004; 164:196–202. [PubMed: 14744844]
12. Berger K, von Eckardstein A, Trenkwalder C, Rothdach A, Junker R, Weiland SK. Iron metabolism and the risk of restless legs syndrome in an elderly general population--the MEMO-Study. J Neurol. 2002; 249:1195–1199. [PubMed: 12242538]
13. Sabayan B, Bagheri M, Borhani Haghighi A. Possible joint origin of restless leg syndrome (RLS) and migraine. Med Hypotheses. 2007; 69:64–66. [PubMed: 17258401]

Appendix

Appendix Table

Characteristics of participants according to migraine status (n=22,926)

	No Migraine (n=20,110)	Any migraine (n=2,816)	p-value*
Demographic information			
Mean age, yrs (SD)	67.8 (9.1)	67.3 (8.2)	<0.01
Ethnicity			<0.01
White	18,221 (91.1)	2,606 (93.0)	
Covariates			
BMI, kg/m^2			0.54
<25	8,437 (42.0)	1,206 (43.0)	
25–29.9	9,291 (46.3)	1,268 (45.2)	
≥30	2,357 (11.7)	334 (11.9)	
History of diabetes	1,777 (8.8)	206 (7.3)	<0.01
History of hypertension	10,562 (52.5)	1,517 (53.9)	0.18
History of cholesterol ≥240mg/dl	10,560 (52.5)	1,481 (52.6)	0.94
Alcohol consumption			0.04
Rarely/never	3,706 (18.5)	511 (18.2)	
1–3 drinks per month	2,430 (12.1)	349 (12.4)	
1–6 drinks per week	7,303 (36.4)	1,086 (38.7)	
≥1 drink/day	6,647 (33.1)	863 (30.7)	
Smoking Status			0.02
Never	10,607 (52.8)	1,506 (53.5)	
Past	8,922 (44.4)	1,254 (44.6)	
Current	574 (2.9)	55 (2.0)	
Exercise			0.66
Rarely/never	7,171 (35.8)	1,001 (35.6)	

	No Migraine (n=20,110)	Any migraine (n=2,816)	p-value*
≤1/week	474 (2.4)	77 (2.7)	
2–4 times/week	8,770 (43.8)	1,234 (43.9)	
5–7 times/week	3,630 (18.1)	500 (17.8)	
Family history of myocardial infarction	2,334 (11.6)	350 (12.4)	0.20
Major CVD	1,061 (5.3)	173 (6.1)	0.06
History of depression	2,014 (10.2)	386 (13.9)	<0.01
Iron supplementation use	379 (2.2)	69 (2.9)	0.02
History of Parkinson's disease	285 (1.4)	35 (1.2)	0.46

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

Table 1

Age- and multivariable-adjusted odds ratios for restless legs syndrome according to migraine in the Physicians' Health Study (n=22, 926)

Migraine	Men with RLS % (n)	Age-adjusted Model	Multivariable-adjusted Model*
		OR (95% CI)	OR (95% CI)
No migraine (n=20,110)	7.3 (1,427)	1.00	1.00
Any migraine (n=2,816)	8.7 (245)	1.22 (1.06–1.41)	1.20 (1.04–1.38)

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, history of depression, history of Parkinson's disease, iron supplementation use, ethnicity, and geographic location.