CLINICAL RESEARCH STUDY

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Vascular Risk Factors, Cardiovascular Disease, and Restless Legs Syndrome in Women

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ABSTRACT

BACKGROUND: Previous studies evaluating the association of cardiovascular disease and vascular risk factors with restless legs syndrome showed inconsistent results, especially for the potential relation between various vascular risk factors and restless legs syndrome. We therefore aimed to analyze the relationships between vascular risk factors, prevalent cardiovascular disease, and restless legs syndrome.

METHODS: This is a cross-sectional study of 30,262 female health professionals participating in the Women's Health Study (WHS). Restless legs syndrome was defined according to diagnostic criteria of the International Restless Legs Study Group. Information on vascular risk factors (diabetes, hypertension, hypercholesterolemia, body mass index [BMI], alcohol, smoking, exercise, and family history of myocardial infarction) was self-reported. Cardiovascular disease events (coronary revascularization, myocardial infarction, and stroke) were confirmed by medical record review. Prevalent major cardiovascular disease was defined as nonfatal stroke or nonfatal myocardial infarction. Logistic regression models were used to evaluate the association between vascular risk factors, prevalent cardiovascular disease, and restless legs syndrome.

RESULTS: Of the 30,262 participants (mean age: 63.6 years), 3624 (12.0%) reported restless legs syndrome. In multivariable-adjusted models, BMI (odds ratio [OR] for BMI $\geq$ 35 kg/m^2, 1.35; 95% confidence interval [CI], 1.17-1.56), diabetes (OR, 1.19; 95% CI, 1.04-1.35), hypercholesterolemia (OR, 1.17; 95% CI, 1.09-1.26), smoking status (OR for $\geq$ 15 cigarettes/day, 1.41; 95% CI, 1.19-1.66), and exercise (OR for exercise $\geq$ 4 times/week, 0.84; 95% CI, 0.74-0.95) were associated with restless legs syndrome prevalence. We found no association between prevalent cardiovascular disease (major cardiovascular disease, myocardial infarction, and stroke) and restless legs syndrome prevalence. Women who underwent coronary revascularization had a multivariable-adjusted OR of 1.39 (1.10-1.77) for restless legs syndrome.

CONCLUSIONS: In this large cohort of female health professionals, various vascular risk factors are associated with the prevalence of restless legs syndrome. We could not confirm the results of previous reports indicating an association between prevalent cardiovascular disease and restless legs syndrome.

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KEYWORDS: Cardiovascular disease; Cohort study; Restless legs syndrome; Vascular risk factors

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Restless legs syndrome is a neurologic disorder characterized by an urge to move the legs and usually accompanied by unpleasant leg sensations. The symptoms predominantly occur in the evening and at night. Inactivity and rest worsen the symptoms, whereas patients experience relief by movement. The International Restless Legs Syndrome Study

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Group has published minimal diagnostic criteria to facilitate a standardized diagnosis of this disorder that is purely symptom based.[1,2] According to results from population-based studies that have applied the minimal diagnostic criteria, the prevalence of restless legs syndrome ranges from 6% to 12%, women being predominately affected.[3] The mechanisms causing restless legs syndrome are not fully understood. Research involving pharmacologic, endocrinologic, and neuroimaging studies suggest a dysfunction of the dopaminergic system as an important pathophysiologic concept.[4] In addition, studies have shown a genetic predisposition for restless legs syndrome.[5]

CLINICAL SIGNIFICANCE

- Several vascular risk factors, including diabetes, hypercholesterolemia, body mass index, smoking status, and exercise, were associated with the prevalence of restless legs syndrome in this cohort of female health professionals.
- Our data do not suggest a relationship between prevalent cardiovascular disease and restless legs syndrome.

Restless legs syndrome is associated with many comorbidities, and especially the potential relationship between cardiovascular diseases and restless legs syndrome has been evaluated in several studies suggesting an association between the 2 entities.[6-14] An unfavorable vascular risk factor profile among those with restless legs syndrome has been proposed as a potential mechanism linking cardiovascular disease and restless legs syndrome, but cross-sectional studies evaluating the association between various vascular risk factors and restless legs syndrome have shown inconsistent results.[10,12,15-18] Potential explanations for these inconsistent results across studies include differences in study design and populations and varying definitions of restless legs syndrome and the various outcome variables.

We therefore aim to evaluate the association among vascular risk factors, prevalent cardiovascular disease, and restless legs syndrome in a cohort of women using data from the Women's Health Study (WHS).

MATERIALS AND METHODS

Study Population

The WHS was a randomized, placebo-controlled trial designed to test the risks and benefits of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer among apparently healthy women. The design, methods, and results have been described in detail.[19,20] Briefly, a total of 39,876 US female health care professionals aged 45 years or older at study entry (1992-1995) without a history of cardiovascular disease, cancer, or other major illnesses were assigned randomly to receive 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 (Boston, Mass) approved the WHS. Baseline information was self-reported and collected by a mailed questionnaire that asked about several 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.

Assessment of Restless Legs Syndrome

A short questionnaire addressing the 4 minimal diagnostic criteria of the International Restless Legs Study Group[1] has been implemented in the 108-month follow-up questionnaire. Participants were asked to answer the following questions: "Do you have unpleasant leg sensations (eg, crawling, paraesthesias, 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?" For all questions, the response choices were "Yes," "No," or "I don't know." Participants who answered yes to all of the 3 questions were defined as having restless legs syndrome. This questionnaire has been established and validated in previous studies from Germany and Italy.[15,21-23]

Vascular Risk Factor Ascertainment

Participants were asked to report information on cardiovascular disease risk factors at baseline, and information was updated through follow-up. We included the most recent updated information on cardiovascular disease risk factors available with regard to time of restless legs syndrome assessment (108-month follow-up questionnaire). We distinguished the following cardiovascular disease risk factors: history of hypertension (yes/no), history of diabetes (yes/no), history of cholesterol $\geq$ 240 mg/dL (yes/no), alcohol consumption (rarely/never, 1-3 drinks/months, 1-6 drinks/week, $\geq$1 drink/day), exercise (rarely/never, $<$1/week, 1-3 times/week, $\geq$4 times/week), body mass index (BMI) ($<$23, 23-24.9, 25-29.9, 30-34.9, $\geq$35 kg/m^2), smoking status (never, past, current $<$15 cigarettes/day, current $\geq$15 cigarettes/day), and parental history of myocardial infarction before age 60 (yes/no). BMI was calculated on the basis of self-reported height and weight, and we distinguished the following categories: $<$23, 23-24.9, 25-29.9, 30-34.9, $\geq$35 kg/m^2. History of hypertension was defined as blood pressure $\geq$ 140 mm Hg systolic or $\geq$ 90 mm Hg diastolic or receiving antihypertensive treatment.

Assessment of Cardiovascular Disease Events

Participants self-reported cardiovascular events and coronary revascularization. Medical records were obtained for