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Original Article

Restless legs syndrome in stroke patients

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ABSTRACT

Background: Restless legs syndrome (RLS) is associated with cerebrovascular risk factors, but its possible association with cerebrovascular disease has yielded conflicting results.
Objective: This was a case–control, in-hospital study to evaluate the association between RLS and acute stroke or transient ischemic attack (TIA).
Methods: We evaluated patients hospitalized with acute stroke/TIA and an age and gender 2:1 frequency-matched control group, for the presence of RLS.
Results: Twenty-two of 149 patients (15%) and 10 of 298 controls (3%) suffered from RLS ($p < 0.0001$). A multivariate logistic regression model employing cerebrovascular risk factors as predictors, that is, hypertension, hyperlipidemia, diabetes, and body mass index (BMI), determined that stroke/TIA was significantly associated with RLS with odds ratio for RLS among patients with stroke/TIA versus controls of 7.60 (95% confidence interval (CI): 2.07–27.87; $p = 0.002$). Another multivariate logistic regression model adjusting for possible RLS risk factors, that is, hypertension, hyperlipidemia, diabetes, BMI, anemia, and reduced renal function, determined that stroke/TIA was significantly associated with RLS with odds ratio of 6.85 (95% CI: 6.85–1.79; $p = 0.005$). Stepwise logistic regression with hypertension, hyperlipidemia, diabetes, BMI, anemia, and reduced renal function as potential predictors revealed that only stroke/TIA predicted RLS with similar odds ratio to the RLS-based multivariate model of 6.54 (95% CI: 2.63–16.27; $p < 0.0001$).
Conclusions: Examining stroke patients while in hospital allowed us to conclude that RLS and acute stroke/TIA are significantly associated. However, the cross-sectional design did not allow for the determination of a causative relationship between the two.

Restless legs syndrome (RLS) is a common sensory-motor disorder of unknown etiology [1]. It is characterized by a desire to move the legs usually accompanied by abnormal leg sensations. Symptoms typically worsen at rest and later on in the day, and they are relieved by movement. Estimates of RLS prevalence in different parts of the world range between 6% and 12% [2], but the persistence of RLS over time is low [3]. RLS has been linked to numerous cerebrovascular risk factors including hypertension, hypercholesterolemia, diabetes, and obesity [4–12], but its association with cerebrovascular disease has been debated. Case reports have suggested the emergence of RLS symptoms within days following stroke [13,14], but given the high prevalence of RLS in the general population, this may be a chance occurrence. A few large longitudinal studies examined the possible association between RLS and cerebrovascular disease, but RLS diagnosis was based on baseline questionnaires without the verification of RLS by a face-to-face interview, thus precluding the elimination of subjects with RLS mimics. Furthermore, RLS status was recorded at baseline, sometimes years before the cerebrovascular event; thus, RLS symptoms may have abated or appeared during the elapsed time.

Our study aimed to examine a possible association between RLS and cerebrovascular disease, by examining patients during hospitalization for acute stroke or transient ischemic attack (TIA), in a matched case–control design.

1. Subjects and methods

1.1. Subjects

1.1.1. Patient selection and determination of stroke diagnosis

We prospectively identified adults hospitalized with a diagnosis of stroke or TIA during weekdays, in the Neurology Department, at the Rambam Health Care Campus in Haifa, Israel, between January and December 2008. Subjects with stroke (International Classification

The study was performed at the Department of Neurology, Rambam Health Care Campus, Haifa, Israel.

Author contributions

Dr. Schlesinger I and Erikh I helped in the study concept and design.
Dr. Schlesinger I, Dr. Nassar M, and Erikh I helped in the acquisition of data.
Dr. Schlesinger I and Dr. Sprecher E carried out analysis and interpretation.
All authors carried out critical revision of the manuscript for important intellectual content.
Dr. Schlesinger I helped in study supervision.

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of Diseases, Ninth Revision (codes 431 and 436) and TIA (code 435) were identified according to their coding on admission.

Controls: Controls were 2:1 frequency-matched to the patient group by gender and age (within 3-year intervals), randomly selected from adults attending their annual checkup at the Rambam Center for Preventive Medicine, Rambam Health Care Campus. Controls had no history of stroke or TIA.

The study was approved by the institutional review board. All patients gave oral consent, while all controls signed written informed consent. The trial was registered at the Clinical Trials.gov, number NCT01967303.

1.1.2. RLS screening

Patients were interviewed by a movement disorders nurse practitioner (I.E.). The interview started with a questionnaire based on the standard questions developed by the International RLS Study Group as previously described as follows: (i) Have you had unpleasant sensations in your legs (such as paresthesias, numbness, and ache) accompanied by a need or urge to move your legs? (ii) Did these sensations occur at rest, and were they improved by movement? (iii) Were these symptoms worse in the evening and at night? (iv) How often did you experience these sensations? Were the sensations less than once a month, two to four times a month, twice a week, two to three times a week, four to five times a week, or six to seven times a week? The questionnaire was translated to Hebrew by two senior neurologists and a professional translator. It was then back-translated to English to ensure the accuracy of the translation. Patients who were screened negative for RLS continued with a face-to-face interview by the nurse, to verify that they did not suffer from RLS. Patients who were screened positive by the questionnaire, and patients whose interview with the nurse was not conclusive, were then interviewed by a senior neurologist with a special interest in RLS (I.S.). If there was a discrepancy between the questionnaire and the interviewer, the final diagnosis was based on the neurologist's assessment.

Patients underwent the same diagnostic procedure, and they were all interviewed face to face by the senior neurologist (I.S.).

1.2. Medical information

Information regarding medical history, use of medications, and body mass index (BMI) calculation was gathered from the medical records for all participants. Laboratory results consisted of blood samples that were drawn in the morning after a 12-h fast, and they included a complete blood count, chemistry, and kidney function tests (Hitachi 911, Tokyo, Japan). Medical records of each patient were reviewed to confirm the diagnosis of stroke/TIA.

1.3. Cerebrovascular risk factors

We defined subjects as suffering from diabetes mellitus, hypercholesterolemia, or hypertension when subjects reported that their physician had diagnosed the disorder and was treating them for it or when fasting glucose was ≥126 mg/dl, cholesterol was >230 mg/dl, or blood pressure was above 140/90 mm Hg. Reduced renal function was defined as serum creatinine ≥1.3 mg/dl and anemia as hemoglobin <13.5 g/dl in men and <11.5 g/dl in women.

1.4. Outcome measures and analysis

The primary outcome measure was the prevalence of RLS in patients with acute stroke/TIA versus controls. Prospective power analyses suggested that a 1:2 case–control study would require at least 120 stroke cases and 240 controls to achieve statistical significance at power 0.8 in the worst case. In order to ensure that this sample size would be reached, we interviewed all potential patients within a period of one year.

Preliminary analyses involved simple statistics and univariate comparisons between the stroke/TIA patients and control subjects on a number of demographic and clinical parameters. Two-tailed *t*-tests, median tests, or Fisher exact tests were employed for comparisons as appropriate.

In order to simultaneously control for potentially correlated statistical predictors, the relationship of RLS with prevalent cerebrovascular risk factors was also examined by multivariate logistic regression analysis using 1:2 case:control stratification. We performed two multivariate logistic regression analyses. The first regression model used the known cerebrovascular risk factors that included hypertension, hyperlipidemia, diabetes, and BMI. The second regression model used possible RLS risk factors that included hypertension, hyperlipidemia, diabetes, BMI, anemia, and reduced renal function. This was followed by stepwise logistic regression analysis (using stepwise selection with default options) starting from the same basic model to develop the most efficient predictive model for RLS. For all analyses, p-values <0.05 were considered to be significant. JMP and SAS (both SAS Institute, Cary, NC, USA) were used for univariate analyses and logistic regression analysis (specifically SAS PROC LOGISTIC), respectively.

2. Results

Of the patients with stroke/TIA who were hospitalized during the study period, 426 were screened by the study team. In 19 patients, the diagnosis was changed during the hospitalization. One hundred and sixty-five patients were excluded because their medical condition precluded an interview (coma, dementia, aphasia, etc.). None refused to participate. Among the remaining 261, one patient was admitted three times and 28 patients were admitted twice; only the first hospitalization was included in the analysis. Patients were then matched by age and gender to those attending the Preventive Medicine Department. As subjects in the Preventive Medicine Department are mostly referred for their annual checkup from their workplace, the pool of subjects is mostly below the age of 67 (the official Israeli retirement age) with few elderly subjects. This limited the matching of older patients and excluded all patients above the age of 84. Thus, another 84 patients were randomly excluded for lack of matched controls. Therefore, the total number of subjects participating in the study was 447 (149 patients with stroke/TIA and 298 controls). Among the stroke/TIA group, 30 suffered from TIA, 110 from ischemic stroke, and nine from hemorrhagic stroke. Demographic characteristics are presented in Table 1. The mean age of the study sample was 59.5 years (standard deviation (SD) 9.4, range 32–83); 74% (330/447)

Table 1
Characteristics of the stroke/TIA subjects and controls.

	Controls	Stroke/TIA	*p*
	N = 298	*N* = 149	
RLS, No. (%)	10 (3%)	22 (15%)	<0.0001
Age, years (mean ± SD)	59.4 ± 9.4	59.5 ± 9.4	CCM
Gender, male %	220 (74%)	110 (74%)	CCM
Hypertension, No. (%)	106 (36%)	114 (77%)	<0.0001
Hyperlipidemia, No. (%)	108 (36%)	100 (67%)	<0.0001
Diabetes, No. (%)	57 (19%)	70 (47%)	<0.0001
BMI, kg/m^2, median (range)	27 (18–42)	27 (19–44)	0.73
Anemia, No. (%)	17 (6%)	27 (18%)	<0.0001
Reduced renal function, No. (%)	28 (9%)	27 (18%)	0.01

Abbreviations: TIA, transient ischemic attack; RLS, restless legs syndrome; CCM, Case–control matched; BMI, body mass index.
Statistical tests employed for group comparisons were *t*-tests, median tests, or Fisher exact tests for these summary statistics as appropriate.