ORIGINAL ARTICLE

Periodic Limb Movements and White Matter Hyperintensities in First-Ever Minor Stroke or High-Risk Transient Ischemic Attack

Mark I. Boulos, MD, MSc[1–5]; Brian J. Murray, MD[1–4]; Ryan T. Muir, BHSc[1,2]; Fuqiang Gao, MD[1,2]; Gregory M. Szilagyi, BSc[1]; Menal Huroy, BSc, BEd[1]; Alexander Kiss, PhD[4,6]; Arthur S. Walters, MD[7]; Sandra E. Black, MD[1–5]; Andrew S. Lim, MD, MMSc[1–4]; Richard H. Swartz, MD, PhD[1–5]

[1]*L.C. Campbell Cognitive Neurology Research Unit, Heart and Stroke Foundation Canadian Partnership for Stroke Recovery, Hurvitz Brain Sciences Research Program, Sunnybrook Health Sciences Centre, Toronto, ON, Canada;* [2]*Department of Medicine, Division of Neurology, University of Toronto, Toronto, ON, Canada;* [3]*Sleep Laboratory, Sunnybrook Health Sciences Centre, Toronto, ON, Canada;* [4]*Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, Toronto, ON, Canada;* [5]*Department of Medicine, Division of Neurology, University of Toronto, Toronto, ON, Canada;* [6]*Department of Research Design and Biostatistics, Sunnybrook Health Sciences Centre, Toronto, ON, Canada;* [7]*Department of Neurology, Vanderbilt University School of Medicine, Nashville, TN*

Study Objectives: Emerging evidence suggests that periodic limb movements (PLMs) may contribute to the development of cerebrovascular disease. White matter hyperintensities (WMHs), a widely accepted biomarker for cerebral small vessel disease, are associated with incident stroke and death. We evaluated the association between increased PLM indices and WMH burden in patients presenting with stroke or transient ischemic attack (TIA), while controlling for vascular risk factors and stroke severity.

Methods: Thirty patients presenting within 2 weeks of a first-ever minor stroke or high-risk TIA were prospectively recruited. PLM severity was measured with polysomnography. WMH burden was quantified using the Age Related White Matter Changes (ARWMC) scale based on neuroimaging. Partial Spearman's rank-order correlations and multiple linear regression models tested the association between WMH burden and PLM severity.

Results: Greater WMH burden was correlated with elevated PLM index and stroke volume. Partial Spearman's rank-order correlations demonstrated that the relationship between WMH burden and PLM index persisted despite controlling for vascular risk factors. Multivariate linear regression models revealed that PLM index was a significant predictor of an elevated ARWMC score while controlling for age, stroke volume, stroke severity, hypertension, and apnea-hypopnea index.

Conclusion: The quantity of PLMs was associated with WMH burden in patients with first-ever minor stroke or TIA. PLMs may be a risk factor for or marker of WMH burden, even after considering vascular risk factors and stroke severity. These results invite further investigation of PLMs as a potentially useful target to reduce WMH and stroke burden.

Keywords: white matter hyperintensities, stroke, transient ischemic attack, periodic limb movements of sleep, magnetic resonance imaging, Restless Legs Syndrome.

Statement of Significance

Emerging evidence suggests that periodic limb movements (PLMs) may be linked with the development of vascular events such as stroke. White matter hyperintensities (WMHs) are a well-established neuroimaging marker for incident stroke, dementia and death. Our study demonstrates that elevated PLM indices are associated with a greater quantity of radiographically-detected WMHs, a relationship that persisted even when controlling for age, vascular risk factors, the presence of sleep apnea, and stroke volume. We conclude that PLMs may be a risk factor for or marker of WMH burden. These results invite further investigation of PLMs as a potentially useful target to reduce WMH and stroke burden.

INTRODUCTION

The clinical significance of periodic limb movements (PLMs) in sleep is unclear. PLMs are repetitive stereotyped triple flexion movements involving the great toe, ankle and hip. PLMs are associated with a number of medical conditions including Restless Legs Syndrome (RLS), radiculopathy, Parkinsonism, as well as certain medication exposures.[1] Ischemic stroke has also been reported to give rise to PLMs, however, emerging evidence suggests that PLMs themselves may also contribute to the development of cerebrovascular disease.[2] Recent evidence suggests that long-duration RLS is associated with increased silent cerebral small vessel disease in the absence of vascular risk factors or overt stroke.[3]

PLMs are associated with night-time autonomic hyperactivity, which gives rise to significant nocturnal fluctuations in heart rate[4] and blood pressure (BP),[5,6] and may result in daytime hypertension.[2] PLMs are also associated with increased markers of inflammation[7,8] and may increase the risk of atherosclerotic plaque formation and rupture.[8,9] Although PLMs have been linked with incident cardiovascular disease[10] and mortality,[11] the association with cerebrovascular disease is underexplored, with only one retrospective study supporting a positive association.[12]

White matter hyperintensities (WMHs), which appear hyperintense on T2-weighted magnetic resonance imaging (MRI), are a marker of cerebral small vessel disease and they also predict an increased risk for stroke.[13] Despite their high prevalence and clinical significance, the pathophysiology of WMHs remains largely unknown with traditional vascular risk factors incompletely explaining their occurrence.[14]

We hypothesized that a higher night-time PLM index in patients with and without RLS presenting with first-ever minor stroke or transient ischemic attack (TIA) would be independently associated with a greater quantity of WMHs visualized on neuroimaging, even after controlling for the effects of vascular risk factors and stroke severity.

METHODS

Ethics

This study was approved by the Sunnybrook research ethics board. Written informed consent was provided by all study participants.

Study Population

We consecutively recruited patients presenting within 14 days of symptoms with either a neuroimaging-confirmed minor ischemic stroke (NIH Stroke Scale score[15] ≤3) or high-risk TIA (ie, motor or speech disturbance lasting at least 5 minutes, or any TIA associated with a >50% symptomatic carotid stenosis). Patients also completed polysomnography after recruitment into our study. Patients with a prior stroke seen on neuroimaging (based on a neuroradiologist report and the presence of a chronic appearing infarction on computed tomography (CT) or MRI FLAIR imaging), a life expectancy of less than 12 months at the time of recruitment, cognitive impairment and/or a language barrier restricting the ability to answer questionnaires or participate with polysomnography were excluded.

Clinical Data, Scales and Questionnaires

The following clinical data was obtained: (1) Past medical history, including well-established triggers for PLMs that predated the stroke/TIA (eg, RLS, radiculopathy, myelopathy, Parkinsonism, multiple sclerosis, and medication triggers [ie, selective serotonin reuptake inhibitors, lithium and tricyclic antidepressants]),[1] (2) National Institutes of Health Stroke Scale,[15] (3) Epworth Sleepiness Scale score,[16] and (4) RLS Diagnostic Questionnaire. Questions on the RLS Diagnostic Questionnaire were developed using diagnostic criteria established by the IRLSSG in 2003,[17] and a similar questionnaire has been used in several large studies.[18,19] Patients who endorsed diagnostic criteria for RLS on the RLS Diagnostic Questionnaire were further evaluated in-person by a sleep neurologist, which ensured that RLS mimics (eg, leg cramps, peripheral neuropathy, radiculopathy, positional discomfort, and arthritic pain) were minimized; this also satisfied the recently-added fifth criteria for diagnosing RLS.[20] "Clinically-significant RLS" was defined as RLS symptoms occurring at least 5 to 15 days per month causing at least moderate distress to the patient.[18] A patient was considered to have "mild RLS" if they met diagnostic criteria for RLS but their symptoms did not occur with sufficient frequency and/or severity to be diagnosed with "clinically-significant RLS".

Polysomnography

Level 1, technologist-monitored in-hospital polysomnography (Compumedics Neuroscan, Australia) using standard recording and scoring methods[21] was obtained a median of 51 days (interquartile range [IQR] = 18–109) after the cerebrovascular events. Sleep was manually staged according to criteria from the American Academy of Sleep Medicine (AASM).[21] All studies were interpreted by a diplomate of the American Board of Sleep Medicine and scored by a registered polysomnographic technologist. Limb movements were scored according to the AASM scoring rules,[21] and we used a nasal pressure transducer to exclude upper airway resistance. Limb movements were not scored within 0.5 second of a respiratory event.

Neuroimaging: Quantification of WMHs

MRI and CT were acquired at Sunnybrook Health Sciences Centre a median of 3 days (IQR = 1–8) after the cerebrovascular events. If CT and MRI were performed in the same patient, only MRI data was analyzed. MRI (General Electric Medical Systems) included T2 Fluid Attenuated Inversion Recovery (FLAIR) and Diffusion Weighted Image (DWI) sequences.

The quantity of global WMHs was visually quantified using the Age Related White Matter Change (ARWMC) Scale[22] by a single imaging analyst (RTM). Using this validated rating scale, the degree of WMHs appearing hyper-intense on FLAIR and/or hypo-dense on CT in the bilateral frontal, occipital-parietal, basal ganglia, temporal and infratentorial brain regions were graded on a Likert scale from 0 to 3. With the exception of the basal ganglia sub-score, a score of 1 is given for those WMHs that appear focal; and a score of 2 is given to those WMHs that are beginning to appear confluent; and a score of 3 is given for the presence of fully confluent WMH lesions. For the basal ganglia sub-score, a single observed focal lesion (≥5 mm) is given a score of 1, two or more focal lesions are scored 2, and confluent lesions are scored 3.[22]

Inter-rater reliabilities for the ARWMC ratings were examined using Intraclass Correlation Coefficients (ICC) for absolute agreement with 10 gold standards produced by an experienced research neuroradiologist (FQG). The ICC for single rater RTM was $r^2 = .96$ ($p = .0001$).

Neuroimaging: Quantification of Stroke Volumes

Acute stroke lesions on CT were defined as areas of significant hypodensity (compared with contralateral tissue) that were associated with the acute stroke symptom presentation. Similarly, acute stroke lesions on MRI were defined as areas of hyperintensity on DWI with corresponding hypointensity on the Apparent Diffusion Coefficient (ADC) images compared to contralateral tissue. TIA was diagnosed in the absence of imaging findings of an acute infarction, but a suitable clinical history as determined by a consultant stroke neurologist. All stroke localizations were confirmed by a formal neuroradiologist report.

In order to compute stroke volumes, infarcted tissues were planimetrically traced based on intensity changes compared to contralateral tissue. Acutely infarcted tissues appearing hypodense on CT or hyperintense on MRI DWI were traced using ANALYZE 8.0 (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN).

Statistical Analyses

Frequency counts were computed for categorical variables and compared between groups (PLM index <5, PLM index ≥5) using chi-square tests. Means and SDs were calculated for normally distributed continuous variables and compared between groups using independent samples *t* tests. For non-normally distributed continuous variables and ordinal data, we calculated the median and range and compared group values using the Mann Whitney *U* test.

Multiple linear regression models were constructed to test our hypothesis that PLM index would be independently associated with increased WMH burden as measured by the ARWMC scale. The ARWMC scale was a normally distributed continuous variable in our sample (Shapiro-Wilk statistic = 0.94, $p = .099$). Based on established methodology, our sample size determined the maximum number of predictors entered into each regression model (one predictor for every 10 patients)[23]; therefore, our sample allowed a maximum of three variables per

model (including PLM index). We constructed multiple successive regression models where we entered age with other covariates of interest (ie, stroke volume, presentation with stroke, sex, NIHSS, hypertension, apnea-hypopnea index, clinically significant RLS, antihypertensive medication use, lipid-lowering medication use, prior or current smoking, BMI, and prior spinal surgery). Prior to modeling, all variables were assessed for multicollinearity (tolerance statistic value < 0.4); if multicollinearity was found, only one member of a correlated set of variables was retained in the model. The final model was assessed for any potential violations to linear regression modeling using residual plots.

In order to more fully understand the relationship between PLM index and quantity of WMHs, we also computed bivariate correlation coefficients between ARWMC scores, PLM index and general characteristics, vascular risk factors, and other polysomnography parameters using Pearson's r for normally distributed continuous variables, Spearman's ρ for non-normally distributed continuous variables, and binary linear regression for dichotomous and ordinal variables. Finally, Partial Spearman's rank-order correlations were computed to evaluate the relationship between polysomnography parameters and WMH burden while controlling for vascular risk factors and stroke severity.

Statistical analyses were conducted using P.A.S.W. Statistics 21.0 (SPSS Inc., Chicago, IL). Statistical significance was set at $p < .05$. As the analyses were considered exploratory in nature, no adjustment for multiple testing was carried out.

RESULTS

Characteristics of the Study Population

Thirty patients enrolled in our study (mean age 63.7 ± 13.5 years, 57% male, and 53% presented with stroke). Thirty-seven percent of the participants were post-menopausal women: 20% with a PLM index <5 per hour and 53% with a PLM index ≥5 per hour, a difference that approached statistical significance ($\chi^2 = 3.59$, $p = .058$).

Patients with a PLM index ≥5 were more likely to have a greater quantity of WMHs as measured by the ARWMC scale (Table 1). In addition, patients with a PLM index ≥5 had a greater proportion of one or more well-established trigger(s) for PLMs that predated the stroke/TIA compared to patients with a PLM index <5 ($\chi^2 = 8.57$, $p = .003$); however, there were no differences among the groups in the polysomnography parameters examined. Among those with a PLM index ≥5, age ($p = .052$) also approached statistical significance. Patients who had presented with stroke (as opposed to TIA) had a greater quantity of PLMs detected on polysomnography (25.3 ± 29.8 vs. 6.8 ± 8.2; $p = .03$).

Ten patients endorsed diagnostic criteria for RLS (5 with "mild RLS" and 5 with "clinically-significant RLS"); 6 of the 10 patients with RLS noted a prior history of RLS. Among those with or without RLS, there were no statistically significant differences in those with an elevated PLM index ≥5 per hour (Table 1). In addition, there were no statistically significant differences in age among those with and without RLS (RLS: 61.8 ± 8.5 years vs. no RLS: 64.7 ± 15.5; $p = .59$).

Only one patient endorsed consuming a quantity of alcohol that was above the Canadian drinking guidelines; this patient also suffered from a lumbosacral radiculopathy and polysomnography revealed a PLM index of 50.1 movements per hour. Another patient endorsed consuming 1–2 joints of marijuana per week and polysomnography did not reveal the presence of any PLMs; no other patients reported illicit drug use.

Linear Regression Analyses

In all our linear regression models, while sequentially controlling for the impact of age with other covariates of interest, PLM index remained a significant independent predictor of an elevated ARWMC score (Table 2). No other variable emerged as a significant predictor of ARWMC score.

Correlations of ARWMC Scores With General Characteristics, Vascular Risk Factors, and Polysomnography Parameters

Bivariate correlational analyses revealed that the PLM index (ρ = 0.42, $p = .02$) and stroke volume (ρ = 0.38, $p = .04$) were significantly correlated with a greater degree of WMHs as measured by the ARWMC scale, while age ($r = 0.34$, $p = .06$) and presentation with stroke ($R = 0.32$, $p = .09$) approached statistical significance (Table 3). Presentation with stroke (as opposed to TIA) was significantly correlated with an elevated PLM index ($R = 0.39$, $p = .03$). In addition, the presence of *any* prior PLM trigger ($R = 0.4$, $p = .03$) and prior spine surgery ($R = 0.38$, $p = .04$) was significantly correlated with an elevated PLM index (Table 3). Using partial Spearman's rank-order correlations, PLM index remained significantly correlated with WMH burden while controlling for age, gender, BMI, NIHSS, hypertension, hyperlipidemia, diabetes, prior or current smoking history, and coronary artery disease (Table 4).

DISCUSSION

In our sample of patients with or without RLS who presented with a first-ever symptomatic cerebrovascular event, a higher PLM index was associated with a greater degree of WMH burden. This relationship persisted despite controlling for the effects of age, stroke volume, stroke severity, vascular risk factors, medications, and the apnea-hypopnea index. Our study suggests that greater PLMs during sleep may predict a greater burden of WMHs, a well-established marker of cerebral small vessel disease, even after accounting for important covariates. Given the close relationship of PLMs with RLS, this result is also congruent with recent work which demonstrated that an increased duration of RLS was associated with a greater burden of WMHs on neuroimaging.[3]

As our study was cross-sectional in nature, we could not determine the direction of this relationship and several interpretations are plausible. One interpretation of our data is that PLMs may predispose to WMHs. PLMs can develop over time from many different etiologies. In our study, the presence of any prior PLM trigger was associated with an elevated PLM index; prior spine surgery was also significantly correlated with a greater quantity of PLMs (Table 3), however, prior spine surgery was not a significant predictor of WMH burden in our linear regression models, while PLM index was (Table 2). Of note, prior to the cerebrovascular event that enrolled patients in this study, none had a neuroimaging-defined earlier stroke or clinical history of a previous cerebrovascular event that may

Table 1—Characteristics of Study Participants.

	Study population (*n* = 30)	PLM index <5 per hour (*n* = 15)	PLM index ≥5 per hour (*n* = 15)	*p* (two-tailed)
General characteristics				
Age in years, mean ± SD	63.7 ± 13.5	59.0 ± 14.1	68.5 ± 11.3	.052
Male, %	57	67	47	.27
Postmenopausal female, %	37	20	53	.06
BMI,[a] median (range)	29 (26.8)	30 (24.5)	27.7 (15.3)	.33
Presentation with stroke (as opposed to TIA), %	53	53	53	1.0
NIHSS,[a] median (range)	0 (3)	0 (3)	0 (2)	.60
Days from event to PSG,[a] median (range)	50.5 (224)	36 (224)	70 (187)	.68
Imaging features				
ARWMC scale, mean ± SD	6.0 ± 4.1	4.2 ± 3.8	7.8 ± 3.6	**.012**
Stroke volume[a] in mm^3, median (range)	240 (45 419)	219 (18 622)	530 (45 419)	.63
RLS symptoms				
RLS (mild or clinically-significant), %	33	27	40	.44
Mild RLS, %	17	20	13	.62
Clinically-significant RLS, %	17	7	27	.14
Sleep features				
Presence of any pre-stroke/TIA PLM trigger, %	53	27	80	**.003**
ESS,[a] median (range)	5 (17)	5 (17)	5 (12)	.80
Apnea-Hypopnea Index,[a] median (range)	2.5 (34)	2 (30)	3 (34)	.75
Lowest oxygen saturation in sleep, mean ± SD	87.9 ± 3.9	87.9 ± 4.2	87.9 ± 3.8	.96
Sleep efficiency,[a] median (range)	75.0 (51)	74 (29)	77 (51)	.43
% of total sleep time, mean ± SD				
N1	19.3 ± 10.1	17.3 ± 10.4	21.3 ± 9.8	.29
N2	51.6 ± 11.7	51.8 ± 9.9	51.4 ± 13.6	.94
N3	11.9 ± 9.1	13.0 ± 8.5	10.7 ± 9.9	.51
REM	17.3 ± 8.2	18.0 ± 7.3	16.6 ± 9.3	.65
Medical Co-morbidities				
Prior myocardial infarction, %	7	7	7	1.0
Hypertension, %	53	47	60	.46
Hyperlipidemia, %	40	40	40	1.0
Diabetes, %	10	7	13	.54
Atrial fibrillation, %	3	0	7	.31
Prior smoker, %	17	13	20	.62
Current smoker, %	7	7	7	1.0

p values < .05 are bolded. ARWMC = age-related white matter changes; BMI = body mass index; NIHSS = National Institutes of Health Stroke Scale; PLM = periodic limb movement; PSG = polysomnography; RLS = Restless Legs Syndrome; TIA = transient ischemic attack.
[a]Ordinal or non-normally distributed continuous variables.

have triggered PLMs. One way of interpreting the reported data is that the various pre-existing triggers for PLMs gave rise to PLMs prior to the participants sustaining their index stroke or TIA. Through the different mechanisms postulated to link PLMs with cerebral small vessel disease (detailed below), the PLMs may have contributed to the development of WMHs over the course of years. In addition, presentation with stroke also likely contributed to the presence of PLMs as patients presenting with stroke had a greater mean PLM index compared to those presenting with TIA; moreover, presentation with

Table 2—Linear Regression Models Examining PLM Index as a Predictor of WMH Burden After Controlling for Covariates.

Model covariates	PLM index		
	β	r^2	*p*
Age + Stroke volume	0.40	0.34	.04
Age + Presentation with stroke	0.39	0.34	.04
Age + Sex	0.43	0.34	.02
Age + NIHSS	0.46	0.36	.01
Age + Hypertension	0.45	0.31	.02
Age + Apnea hypopnea index	0.48	0.42	.005
Age + Clinically significant RLS	0.46	0.31	.01
Age + Antihypertensive medication use	0.45	0.32	.02
Age + Lipid-lowering medication use	0.45	0.31	.02
Age + Prior or current smoking	0.41	0.40	.02
Age + BMI	0.46	0.32	.01
Age + Prior spine surgery	0.48	0.31	.02

Dependent variable: Total ARWMC score. ARWMC = age-related white matter changes; BMI = body mass index; NIHSS = National Institutes of Health Stroke Scale; PLM = periodic limb movement; RLS = Restless Legs Syndrome.

stroke was significantly correlated with an elevated PLM index (Table 3). However, presentation with stroke and stroke volume did not emerge as significant predictors of an elevated ARWMC score in our multivariate linear regression models, although the PLM index remained a significant predictor after controlling for these and other covariates of interest (Table 2), suggesting that presentation with stroke did not significantly influence the relationship between PLM index and WMH burden.

PLMs may be linked with small vessel disease of the brain through multiple pathophysiological mechanisms (Figure 1). PLMs are associated with significant night-time fluctuations in heart rate[4] and BP.[5,6] Given the vulnerability of the subcortical white matter to ischemia, abnormal diurnal BP decreases could lead to WMHs.[24] Furthermore, nocturnal autonomic dysfunction could deregulate daytime BP, giving rise to daytime hypertension.[2] Consistent with this, PLMs have been found to be prevalent in patients with essential hypertension,[25] a risk factor for WMHs.[14] In addition, BP oscillations themselves may also warrant special attention.[26] Variability of blood flow is thought to induce shear stress, platelet activation, leading to a potentially hypercoagulable state[27]; moreover, experimental models have shown that pulsatile blood flow may promote inflammation, oxidative stress and increase the risk of atherosclerotic plaque formation and rupture.[9,28] Not surprisingly, variability in BP has also been demonstrated to be associated with silent cerebral damage in multiple studies.[29,30] Furthermore, patients with elevated PLM indices have been found to have increased markers of inflammation and oxidative stress.[7,8] Finally, another postulated mechanism is the link of PLMs with hypoxia. PLMs have been demonstrated to be associated with cerebral hemodynamic fluctuations,[31] which have been interpreted to represent transient cerebral hypoxia.[3] Peripheral hypoxia has also been shown to be linked with the presence and severity of RLS symptoms.[32]

Elevated PLM indices have been demonstrated to be associated with incident cardiovascular events[10,11] and structural changes of the left ventricle of the heart,[11,33] however, whether PLMs are similarly linked with silent or overt cerebrovascular disease remains uncertain. A single retrospective study has suggested an association between a history of stroke and elevated PLM indices,[12] but a prospective study did not demonstrate that elevated PLMs indices were associated with incident stroke (although a link with cardiovascular events was found).[10] To our knowledge, this is the first study to reveal a possible association between nocturnal PLMs and the degree of WMHs in patients with first-ever stroke/TIA. PLMs during sleep could be related to cerebral small vessel disease, of which WMHs are an important surrogate, though future validation in prospective studies is needed.

Another possible explanation for our results is that WMHs may contribute to the development of PLMs. The pathways implicated in the generation of PLMs are still being determined via animal models.[34] Whether the small vessel disease pathology that gives rise to WMHs is actually sufficient to cause PLMs is unknown. In further analyses, we did not find that WMHs aggregated in any particular brain region in patients with greater PLM indices, however, a yet-undetermined multifocal network may be implicated in the generation of PLMs, and WMHs may have aggregated in several nodes of such a network. Alternatively, the presence of WMHs may make pathways important in the pathogenesis of PLMs vulnerable to ischemic insult and thus exacerbate the PLM index in the setting of acute stroke/TIA. If this explanation was correct, the presence of PLMs would be a surrogate marker for increased vascular burden, as defined by a greater quantity of WMHs on neuroimaging.

PLMs are known to increase in prevalence with advanced age,[1] and in our patients with a PLM index ≥5 per hour compared to those with a PLM index <5 per hour, age approached statistical significance ($p = .052$). To control for the potentially important impact of age in our analyses, we included age as a covariate in our linear regression models and partial Spearman rank-order correlations, and the PLM index still remained significantly associated with WMH burden (Tables 2 and 4).

We did not find an association of respiratory-related polysomnography parameters (ie, apnea-hypopnea index or lowest oxygenation in sleep) with WMHs. This is consistent with the present literature that has not firmly established a link between OSA or nocturnal hypoxia and cerebral WMHs.[35,36] Of note, several studies reporting a positive association did not control for the effect of vascular risk factors, particularly hypertension, as we do in the present study. Prior studies that explored the relationship between respiratory-related sleep parameters and WMHs did not report on PLMs, and many used portable polysomnography devices that did not measure limb movements in sleep; thus, an association of WMHs with PLMs may not have been detected.

We did not find an association between a diagnosis of RLS and WHMs, consistent with one prior study,[37] but we were likely under-powered to observe a significant relationship. Recent evidence suggests that it may be the duration of RLS

Table 3—Unadjusted Correlation Coefficients of WMH Burden (as Measured by the ARWMC Scale) and PLM Index With General Patient Characteristics, Vascular Risk Factors, and Polysomnography Parameters.

***n* = 30**	**Correlation with ARWMC scale**	**Correlation with PLM index**
General characteristics		
Age[a]	0.34 (0.06)	0.30 (0.10)
Sex	0.24 (0.21)	0.19 (0.33)
BMI[b]	−0.16 (0.41)	−0.14 (0.46)
Presentation with stroke (as opposed to TIA)	0.32 (0.09)	**0.39 (0.03)**
Stroke volume[b]	**0.38 (0.04)**	0.27 (0.15)
NIHSS	0.27 (0.14)	0.06 (0.76)
Clinically Significant RLS	0.09 (0.64)	0.11 (0.55)
MRI use (as opposed to CT)	0.07 (0.73)	0.13 (0.51)
Time from event to polysomnography[b]	0.01 (0.97)	0.18 (0.36)
Vascular risk factors		
Prior myocardial infarction	0.17 (0.38)	0.25 (0.18)
Hypertension	0.18 (0.33)	0.31 (0.10)
Hyperlipidemia	0.03 (0.86)	0.01 (0.97)
Diabetes	0.22 (0.24)	0.29 (0.12)
Prior or current smoker	0.22 (0.25)	0.04 (0.82)
Medications		
Antihypertensive	0.17 (0.37)	0.19 (0.32)
Lipid-lowering	0.17 (0.38)	0.27 (0.15)
Diabetic control	0.23 (0.22)	0.36 (0.053)
Polysomnography parameters		
PLM index[b]	**0.42 (0.02)**	—
Apnea hypopnea index[b]	−0.05 (0.79)	0.17 (0.37)
Lowest oxygen saturation[a]	0.03 (0.87)	−0.11 (0.58)
Sleep efficiency[b]	−0.06 (0.76)	−0.02 (0.92)
Arousal index[b]	0.22 (0.25)	0.29 (0.12)
Well-established PLM triggers that predated stroke/TIA		
Any PLM trigger that predated stroke/TIA	0.27 (0.15)	**0.40 (0.03)**
Iron deficiency	0.09 (0.63)	0.01 (0.98)
Medications (SSRI, SNRI, TCA, or Lithium)	0.02 (0.91)	0.19 (0.32)
RLS prior to stroke/TIA	0.02 (0.92)	0.19 (0.33)
REM sleep disorder with parkinsonism	0.28 (0.14)	0.33 (0.07)
Radiculopathy or myelopathy	0.02 (0.91)	0.23 (0.23)
Prior spine surgery	0.13 (0.48)	**0.38 (0.04)**
Prior diagnosis of multiple sclerosis	0.23 (0.22)	0.08 (0.67)

Significant ($p < .05$) variables are bolded. ARWMC = age related white matter changes; BMI = body mass index; CT = computed tomography; NIHSS = National Institutes of Health Stroke Scale; ESS = Epworth Sleepiness Scale; PLM = periodic limb movement; RLS = Restless Legs Syndrome; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; TIA = transient ischemic attack; TCA = tricyclic antidepressant; WMH = white matter hyperintensities.

[a]Pearson's *r* (normally distributed continuous variables).

[b]Spearman's ρ (non-normally distributed continuous variables)

All other values are binary linear regression R (dichotomous or ordinal variables); *p* values are in parentheses.

that confers the increased risk of cerebral small vessel disease.[3] Moreover, RLS has been fairly convincingly demonstrated to be associated with cardiovascular disease in multiple cross-sectional studies,[38] and a single prospective study demonstrated that women with RLS for at least 3 years had an elevated risk of incident cardiovascular events.[39] Evaluation of patients with more severe and/or chronic forms of RLS may reveal significant associations with covert and overt cerebrovascular events.

There was an approximate 2-month delay between patient recruitment and polysomnography, however, we do not think that this delay significantly impacted our results since WMHs are known to evolve over the course of years.[14] Furthermore, the time between cerebrovascular events and polysomnography was not associated with WMH burden or PLM index in our study (Table 3).

Our study had several limitations. We had a small sample size, but the novel possible relationship reported invites future replication in a larger sample. Furthermore, our study population only included patients presenting with TIA or minor stroke, limiting generalizability. However, our findings may be more generalizable in that our results do suggest that even after controlling for the presence of vascular risk factors (Table 4), PLMs may convey a significant risk for WMH burden. Furthermore, the use of a simple PLM index (ie, number of PLMs per hour of sleep) may not sufficiently reflect the clinical significance of PLMs, and other limb movement parameters (eg, periodicity and time distribution) may be particularly relevant.[40] Finally, we used a single night of polysomnography but there is evidence that the PLM index may vary from night-to-night in patients with[41] and without RLS.[42]

In conclusion, we demonstrate that elevated PLM indices are associated with greater WMHs in patients presenting with TIA or minor stroke, even after controlling for the effect of age, stroke volume, stroke severity, vascular risk factors, and the apnea-hypopnea index. While sleep-disordered breathing has been the most widely examined nocturnal phenomenon in the context of vascular disease, our results shed light on the potentially important, yet relatively underexplored, association of night-time PLMs with cerebrovascular disease. Large population-based prospective studies are needed to confirm the observed relationship between PLMs and WMHs, and establish the relative contribution of each directional relation. Since PLMs are common after stroke,[12] if PLMs are found to be a significant modulator of vascular disease they could potentially serve as a valuable therapeutic target for cerebrovascular

Table 4—Partial Spearman's Rank-Order Correlations Between PLM Index and WMH Burden After Controlling for Covariates (Age, Gender, BMI, NIHSS, Hypertension, Hyperlipidemia, Diabetes, Prior or Current Smoking History, and Coronary Artery Disease).

	Correlation with WMH burden (assessed using ARWMC scale)	
	ρ	*p*
AHI	−0.11	.62
RLS	0.30	.19
PLM	0.44	**.046**

ARWMC = age related white matter changes; BMI = body mass index; NIHSS = National Institutes of Health Stroke Scale; PLM = periodic limb movement; RLS = Restless Legs Syndrome; WMH = white matter hyperintensities. Significant *p* value is bolded.

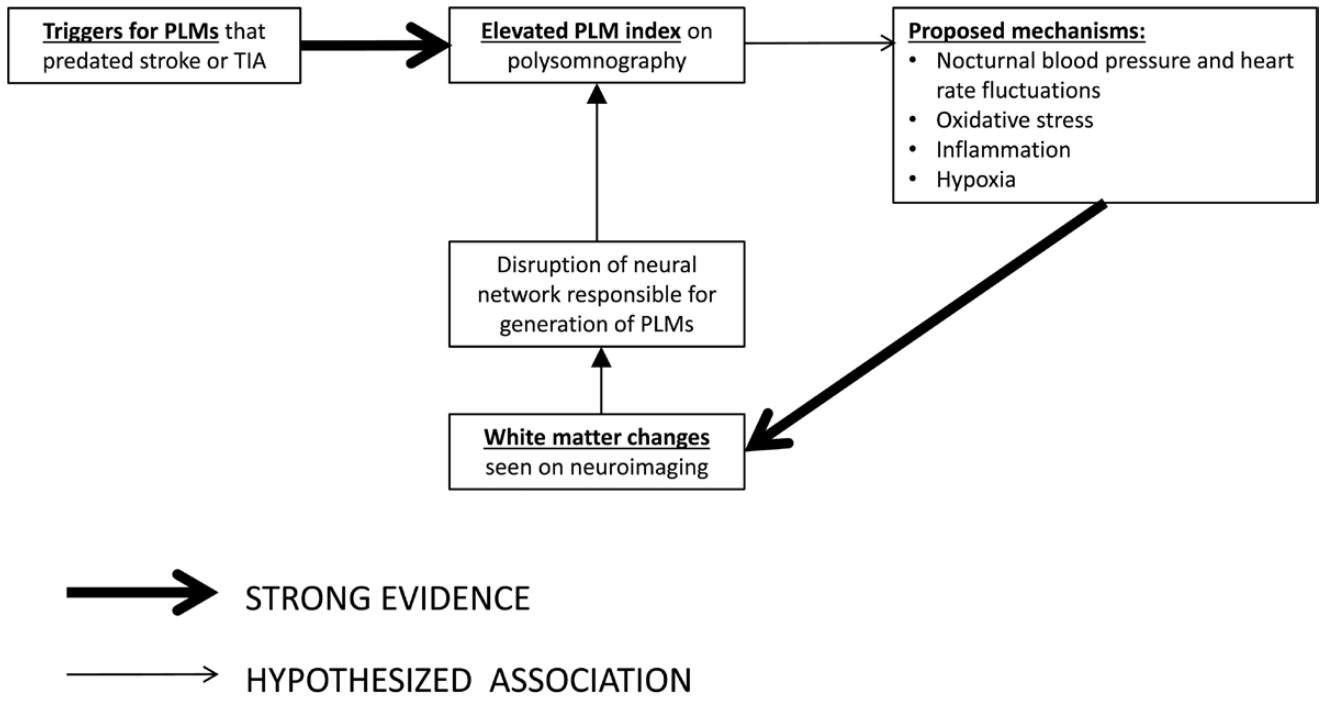

Figure 1—Postulated pathway for how periodic limb movements in sleep may be linked to white matter hyperintensities.

events. Of great interest is recent work that has demonstrated that PLM-associated BP elevations can be successfully managed using Rotigotine.[43]

REFERENCES

1. Hornyak M, Feige B, Riemann D, Voderholzer U. Periodic leg movements in sleep and periodic limb movement disorder: prevalence, clinical significance and treatment. Sleep Med Rev. 2006; 10(3): 169–177.
2. Walters AS, Rye DB. Review of the relationship of restless legs syndrome and periodic limb movements in sleep to hypertension, heart disease, and stroke. Sleep. 2009; 32(5): 589–597.
3. Ferri R, Cosentino FI, Moussouttas M, et al. Silent Cerebral Small Vessel Disease in Restless Legs Syndrome. Sleep. 2016; 39(7): 1371–1377.
4. Winkelman JW. The evoked heart rate response to periodic leg movements of sleep. Sleep. 1999; 22(5): 575–580.
5. Pennestri MH, Montplaisir J, Colombo R, Lavigne G, Lanfranchi PA. Nocturnal blood pressure changes in patients with restless legs syndrome. Neurology. 2007; 68(15): 1213–1218.
6. Siddiqui F, Strus J, Ming X, Lee IA, Chokroverty S, Walters AS. Rise of blood pressure with periodic limb movements in sleep and wakefulness. Clin Neurophysiol. 2007; 118(9): 1923–1930.
7. Trotti LM, Rye DB, De Staercke C, Hooper WC, Quyyumi A, Bliwise DL. Elevated C-reactive protein is associated with severe periodic leg movements of sleep in patients with restless legs syndrome. Brain Behav Immun. 2012; 26(8): 1239–1243.
8. Bekci TT, Kayrak M, Kiyici A, et al. The relation between Lp-PLA2 levels with periodic limb movements. Sleep Breath. 2012; 16(1): 117–122.
9. Chappell DC, Varner SE, Nerem RM, Medford RM, Alexander RW. Oscillatory shear stress stimulates adhesion molecule expression in cultured human endothelium. Circ Res. 1998; 82(5): 532–539.
10. Koo BB, Blackwell T, Ancoli-Israel S, Stone KL, Stefanick ML, Redline S; Osteoporotic Fractures in Men (MrOS) Study Group. Association of incident cardiovascular disease with periodic limb movements during sleep in older men: outcomes of sleep disorders in older men (MrOS) study. Circulation. 2011; 124(11): 1223–1231.
11. Mirza M, Shen WK, Sofi A, et al. Frequent periodic leg movement during sleep is associated with left ventricular hypertrophy and adverse cardiovascular outcomes. J Am Soc Echocardiogr. 2013; 26(7): 783–790.
12. Coelho FM, Georgsson H, Narayansingh M, Swartz RH, Murray BJ. Higher prevalence of periodic limb movements of sleep in patients with history of stroke. J Clin Sleep Med. 2010; 6(5): 428–430.
13. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ. 2010; 341: c3666.
14. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. Lancet Neurol. 2013; 12(5): 483–497.
15. Brott T, Adams HP Jr, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke. 1989; 20(7): 864–870.
16. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991; 14(6): 540–545.
17. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J; Restless Legs Syndrome Diagnosis and Epidemiology workshop at the National Institutes of Health; International Restless Legs Syndrome Study Group. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med. 2003; 4(2): 101–119.
18. Winkelman JW, Shahar E, Sharief I, Gottlieb DJ. Association of restless legs syndrome and cardiovascular disease in the Sleep Heart Health Study. Neurology. 2008; 70(1): 35–42.
19. Budhiraja P, Budhiraja R, Goodwin JL, et al. Incidence of restless legs syndrome and its correlates. J Clin Sleep Med. 2012; 8(2): 119–124.
20. Allen RP, Picchietti DL, Garcia-Borreguero D, et al.; International Restless Legs Syndrome Study Group. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria–history, rationale, description, and significance. Sleep Med. 2014; 15(8): 860–873.
21. Iber C, Ancoli-Israel S, Chesson A, Quan SF. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. 1st ed. Westchester, IL: American Academy of Sleep Medicine; 2007:17–49.
22. Wahlund LO, Barkhof F, Fazekas F, et al.; European Task Force on Age-Related White Matter Changes. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke. 2001; 32(6): 1318–1322.
23. Harrell FE. *Regression Modeling Strategies*. New York City, NY: Springer; 2001:61.
24. Kario K, Pickering TG. Blood pressure variability in elderly patients. Lancet. 2000; 355(9215): 1645–1646.
25. Espinar-Sierra J, Vela-Bueno A, Luque-Otero M. Periodic leg movements in sleep in essential hypertension. Psychiatry Clin Neurosci. 1997; 51(3): 103–107.
26. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. Lancet. 2010; 375(9718): 938–948.
27. Kario K. Blood pressure variability in hypertension: a possible cardiovascular risk factor. Am J Hypertens. 2004; 17(11 Pt 1): 1075–1076.
28. De Keulenaer GW, Chappell DC, Ishizaka N, Nerem RM, Alexander RW, Griendling KK. Oscillatory and steady laminar shear stress differentially affect human endothelial redox state: role of a superoxide-producing NADH oxidase. Circ Res. 1998; 82(10): 1094–1101.
29. Puisieux F, Monaca P, Deplanque D, et al. Relationship between leuko-araiosis and blood pressure variability in the elderly. Eur Neurol. 2001; 46(3): 115–120.
30. Havlik RJ, Foley DJ, Sayer B, Masaki K, White L, Launer LJ. Variability in midlife systolic blood pressure is related to late-life brain white matter lesions: the Honolulu-Asia Aging study. Stroke. 2002; 33(1): 26–30.
31. Pizza F, Biallas M, Wolf M, Valko PO, Bassetti CL. Periodic leg movements during sleep and cerebral hemodynamic changes detected by NIRS. Clin Neurophysiol. 2009; 120(7): 1329–1334.
32. Salminen AV, Rimpilä V, Polo O. Peripheral hypoxia in restless legs syndrome (Willis-Ekbom disease). Neurology. 2014; 82(21): 1856–1861.
33. Giannaki CD, Zigoulis P, Karatzaferi C, et al. Periodic limb movements in sleep contribute to further cardiac structure abnormalities in hemodialysis patients with restless legs syndrome. J Clin Sleep Med. 2013; 9(2): 147–153.
34. Clemens S, Rye D, Hochman S. Restless legs syndrome: revisiting the dopamine hypothesis from the spinal cord perspective. Neurology. 2006; 67(1): 125–130.
35. Kim H, Yun CH, Thomas RJ, et al. Obstructive sleep apnea as a risk factor for cerebral white matter change in a middle-aged and older general population. Sleep. 2013; 36(5): 709–715B.
36. Davies CW, Crosby JH, Mullins RL, et al. Case control study of cerebrovascular damage defined by magnetic resonance imaging in patients with OSA and normal matched control subjects. Sleep. 2001; 24(6): 715–720.
37. Walters AS, Moussouttas M, Siddiqui F, et al. Prevalence of stroke in Restless Legs Syndrome: initial results point to the need for more sophisticated studies. Open Neurol J. 2010; 4: 73–77.
38. Innes KE, Selfe TK, Agarwal P. Restless legs syndrome and conditions associated with metabolic dysregulation, sympathoadrenal dysfunction, and cardiovascular disease risk: a systematic review. Sleep Med Rev. 2012; 16(4): 309–339.
39. Li Y, Walters AS, Chiuve SE, Rimm EB, Winkelman JW, Gao X. Prospective study of restless legs syndrome and coronary heart disease among women. Circulation. 2012; 126(14): 1689–1694.
40. Ferri R. The time structure of leg movement activity during sleep: the theory behind the practice. Sleep Med. 2012; 13(4): 433–441.
41. Sforza E, Haba-Rubio J. Night-to-night variability in periodic leg movements in patients with restless legs syndrome. Sleep Med. 2005; 6(3): 259–267.
42. Mosko SS, Dickel MJ, Ashurst J. Night-to-night variability in sleep apnea and sleep-related periodic leg movements in the elderly. Sleep. 1988; 11(4): 340–348.
43. Bauer A, Cassel W, Benes H, et al.; SP0977 Study Investigators. Rotigotine's effect on PLM-associated blood pressure elevations in restless legs syndrome: an RCT. Neurology. 2016; 86(19): 1785–1793.

FUNDING

During this study, MIB was supported by a Focus on Stroke 2010 Research Fellowship, which was funded by the Heart and Stroke Foundation of Canada, the Canadian Stroke Network, and the Canadian Institutes of Health Research; he was also supported by fellowship funding from the Canadian Partnership for Stroke Recovery. RHS is supported by the Heart and Stroke Foundation of Canada New Investigator Award and Barnett Award, and this work was supported by operating grant funding from the Heart and Stroke Foundation and the Canadian Institute of Health Research.

ACKNOWLEDGMENTS

The authors thank Dana Jewell for scoring the polysomnograms, and Yomi Gammada, Joshua Wortsman, Benjamin Corrigan and Paul Wolfe for their assistance with participant recruitment. The authors also thank the staff of the Sunnybrook Health Sciences Centre sleep laboratory, stroke clinics, and the study participants.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication August, 2016
Submitted in final revised form November, 2016
Accepted for publication December, 2016
Address Correspondence to: Mark I. Boulos, MD, MSc, Sunnybrook Health Sciences Centre, Room A442—2075 Bayview Avenue, Toronto, ON M4N 3M5, Canada. Telephone: 416-480-4473; Fax: 416-480-5753; Email: mark.boulos@sunnybrook.ca

DISCLOSURE STATEMENT

ASL has engaged in consulting activities for UCB S.A. and Merck & Co. Inc. ASW has served as a consultant on RLS to UCB Pharma and MundiPharma, and has also received grant funding for investigator-initiated projects from both companies. ASW has also participated in a study initiated by UCB. All other authors report no conflicts of interest.