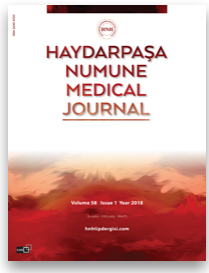
HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2024.51482
Haydarpasa Numune Med J 2024;64(4):517–525



hnhtipdergisi.com

ORIGINAL ARTICLE

Association between Cerebrovascular Disease and Restless Legs Syndrome

Cenk Murat Ünverdi, Kemal Tutkavul, Hülya Tireli

Department of Neurology, Haydarpasa Numune Training and Research Hospital, University of Health Sciences Türkiye, Hamidiye Medical Faculty, Istanbul, Türkiye

Abstract

Introduction: Restless legs syndrome (RLS) may increase the risk of developing cerebrovascular disease. Cerebral small vessel disease (CSVD) may present with clinically overt stroke. We aimed to determine whether RLS, when combined with other cardiovascular risk factors, caused an increase in CSVD burden in patients with a transient ischemic attack (TIA) or minor ischemic stroke (MIS).

Methods: Patients who were hospitalized with TIA or MIS were interviewed, and RLS was assessed using the diagnostic criteria defined in 2014 by the International RLS Study Group. One hundred nine patients were divided into two groups: those with and without RLS (n=30 and n=79, respectively). The demographics and stroke risk factors of the patients, along with the severity (International RLS Study Group Rating Scale (IRLSRS) scores) and duration of RLS (months) in the group with RLS, were recorded. CSVD burden was measured using neuroimaging at diagnosis via the Age-Related White Matter Changes (ARWMC) rating scale and compared between the two groups.

Results: There was no significant difference between the two groups in terms of demographics and stroke risk factors, but ARWMC scores were found to be significantly higher in the RLS group ($p<0.001$). There was no correlation between IRLSRS scores and ARWMC scores; however, a significant correlation was found between the duration of RLS and ARWMC scores in the RLS group ($p=0.033$).

Discussion and Conclusion: The presence and duration of RLS may be an independent propensity factor for CSVD in patients with TIA or MIS.

Keywords: Cerebral small vessel disease; Cerebrovascular disorders; Ischemic stroke; Restless legs syndrome.

The second most common cause of death and the most common reason for disability worldwide is cerebrovascular disease. Although mortality rates due to stroke tend to decrease worldwide, the absolute number of patients who have had a stroke, who die or become disabled due to stroke, is increasing every year [1].

Restless legs syndrome (RLS) is a sensorimotor disorder. It presents with the urge to move the legs, often because of displeasing sensations such as pain, itching, pulling, and tingling. RLS may be secondary to conditions such as iron deficiency anemia, end-stage kidney failure, or pregnancy, and it is associated with poor life quality, including insomnia,

Correspondence: Cenk Murat Ünverdi, M.D. Department of Neurology, Haydarpasa Numune Training and Research Hospital, University of Health Sciences Türkiye, Hamidiye Medical Faculty, Istanbul, Türkiye
Phone: +90 545 313 75 93 **E-mail:** unverdimurat@hotmail.com
Submitted Date: 05.12.2023 **Revised Date:** 03.06.2024 **Accepted Date:** 31.07.2024
Haydarpaşa Numune Medical Journal

depression, and anxiety [2]. The association between RLS and cerebrovascular disease remains controversial in the literature [3–6].

Cerebral small vessel disease (CSVD) affects the small arteries, arterioles, capillaries, and venules of the brain, resulting from several pathological processes and etiologies. It presents clinically with stroke, cognitive decline, dementia, psychiatric disorders, gait disturbance, and urinary incontinence. Neuroimaging reveals new small subcortical infarcts, lacunae, white matter hyperintensities (WMHs), perivascular spaces, and microhemorrhages [7].

This study aimed to determine whether RLS, when combined with other cardiovascular risk factors, led to an increase in CSVD burden in patients with minor ischemic stroke (MIS) or transient ischemic attack (TIA).

Materials and Methods

Study Population

Between July 2018 and November 2019, patients who were hospitalized at the University of Health Sciences, Hamidiye Faculty of Medicine, Haydarpaşa Numune Health Application and Research Center, Department of Neurology, with the diagnosis of TIA or MIS were examined consecutively. TIA is defined as a transient episode of neurological dysfunction resulting from focal central nervous system or retinal ischemia without acute infarction [8]. MIS is defined as an ischemic stroke with an admission National Institutes of Health Stroke Scale (NIHSS) score ≤5 [9] and with an admission modified Rankin Scale (mRS) score of 0 or 1 [10]. Patients were interviewed face-to-face by a neurologist (C.M.U.) under the supervision of a senior neurologist (H.T.), and RLS was questioned using the International RLS Study Group 2014 diagnostic criteria [11].

Patients were enrolled in the study if the following criteria were met: (1) patients diagnosed as having TIA or MIS on admission; (2) magnetic resonance imaging (MRI) and/or brain computed tomography (CT) performed within one week of symptom onset; (3) patients age >18 years. Patients were excluded from the study if they met one of the following criteria: (1) communication barrier due to cognitive impairment such as aphasia or neglect; (2) pre-stroke mRS score ≥2; (3) age <18 years; (4) moderate or severe iron deficiency anemia; (5) severe renal failure; (6) pregnancy; (7) post-stroke RLS. Patients were divided into two groups as those with and without RLS.

This study was approved by the Ethics Committee of the University of Health Sciences, Hamidiye Faculty of Medicine, Haydarpaşa Numune Health Application and Research Center, Türkiye (Approval Number: HNEAH-KAEK 2018/56-2218). The procedures used in this study adhere to the tenets of the Declaration of Helsinki. Written informed consent was obtained from each enrolled patient for participation in this study.

Clinical Data

Neurologic symptoms and signs of patients were recorded. Severity characteristics of acute cerebrovascular disease were assessed using pre-stroke mRS, admission mRS, and admission NIHSS. The demographics, stroke risk factors, and antihypertensive and antilipidemic drugs of the patients were recorded based on their medical history.

Patients who were diagnosed as having RLS were further evaluated. The RLS severity was investigated using the International RLS Study Group Rating Scale (IRLSRS) [12]. Additionally, the duration of RLS (months), lateralization of RLS symptoms, and the presence of arm symptoms were questioned.

Laboratory and Neuroimaging

Electrocardiography, transthoracic echocardiography, carotid color Doppler ultrasonography, and cranial and cervical CT/MRI angiography data of the patients performed on admission were evaluated in terms of carotid stenosis and source of cardioembolism [13]. In addition, serum levels of iron, ferritin, blood urea nitrogen, creatinine, hemoglobin, homocysteine, vitamin B12, glucose, glycated hemoglobin (HbA1c), total cholesterol, low-density lipoprotein, very low-density lipoprotein, high-density lipoprotein, and triglyceride were recorded.

MRI (standardized battery containing diffusion-weighted imaging [DWI], apparent diffusion coefficient [ADC], and fluid attenuated inversion recovery [FLAIR] sequences) was performed using a 1.5-T MRI scanner of General Electric Corporation, and CT was performed using a CT scanner of General Electric Corporation. When both MRI and CT were performed, MRI was used to acquire the data. CSVD burden was measured using the Age-Related White Matter Changes (ARWMC) rating scale. Firstly, white matter lesions in each region (right and left frontal, parietooccipital, temporal, and infratentorial) were assessed. No lesions, including symmetrical, well-defined caps or bands, were assigned a score of 0. Focal lesions were given a score of 1. Lesions beginning confluence were scored as 2, while diffuse involvement of the entire region with or without

involvement of U fibers received a score of 3. Secondly, lesions in the right and left basal ganglia were assessed. A score of 0 was assigned if no lesions were present. A single focal lesion (≥5 mm) was scored as 1. If there were multiple focal lesions, a score of 2 was given. Confluent lesions were scored as 3 [14]. Additionally, anatomic locations, vascular territories, and lateralization of acute stroke lesions were recorded. Furthermore, it was analyzed whether acute stroke lesions were lacunar, cortical, and symptomatic [15]. The neuroimaging data were assessed by a neurologist (C.M.U.), who was blinded to any information about the patients.

Statistical Analysis

Statistical analysis of our study was performed using the IBM SPSS Statistics 25.0 software package (IBM Corp., Armonk, NY). The Shapiro-Wilk test was used to assess whether the data were normally distributed. It was found that the data were not normally distributed ($p<0.05$), thus nonparametric tests were used. Median and interquartile range (IQR) values were calculated for presenting continuous variables and ordinal data of the study population. When comparing groups, median and rank values were calculated for continuous variables and ordinal data, and the Mann-Whitney U test was used. For comparisons of three or more groups, the Kruskal-Wallis H test was used. To compare categorical variables, the Chi-square test was used. To estimate the association between ARWMC scores and the duration and severity of RLS symptoms in the RLS group, the Spearman correlation test was used. The level of statistical significance was set at $p<0.05$.

Results

Demographics and Clinical Features

A total of 109 patients (64 males and 45 females) with TIA (12 patients) or MIS (97 patients) were included in

Table 1. Comparison of demographics and clinical features between groups with non-RLS and RLS

	Non-RLS (n=79)	RLS (n=30)	p
Demographics			
Age, years	66 (60-73.5)	64.5 (54.25-70)	0.11[a]
Male, n (%)	50 (63)	14 (47)	0.13[b]
Urban life, n (%)	68 (86)	29 (97)	0.17[b]
Severity characteristics of acute stroke			
Pre-stroke mRS	0 (0-0)	0 (0-0)	0.42[a]
Admission NIHSS	1 (1-2)	2 (1-3)	0.15[a]
Admission mRS	1 (1-1)	1 (1-1)	0.84[a]
Stroke risk factors			
Hypertension, n (%)	56 (71)	21 (70)	0.93[b]
Diabetes mellitus, n (%)	41 (52)	14 (47)	0.67[b]
Hyperlipidemia, n (%)	62 (79)	24 (80)	0.86[b]
Body mass index	28.37 (25.55-31.22)	29.81 (27.68-33.57)	0.051[a]
Ex-smoker, n (%)	25 (32)	9 (30)	0.87[b]
Current smoker, n (%)	18 (23)	8 (27)	0.80[b]
Smoking exposure, n (%)	43 (54)	17 (57)	0.50[b]
Regular exercise, n (%)	18 (23)	2 (7)	0.06[b]
History of stroke or TIA, n (%)	18 (23)	8 (27)	0.80[b]
Coronary artery disease, n (%)	30 (38)	7 (23)	0.18[b]
Atrial fibrillation, n (%)	8 (10)	3 (10)	0.98[b]
Congestive heart failure, n (%)	10 (13)	2 (7)	0.51[b]
Significant valve disease, n (%)	4 (5)	1 (3)	0.58[b]
Carotid stenosis of ≥50%, n (%)	14 (18)	1 (3)	0.06[b]
Source of cardioembolism, n (%)	26 (33)	8 (27)	0.65[b]
Medication use			
Number of antihypertensive	1 (0-2)	1 (0-2)	0.93[a]
Antilipidemic, n (%)	35 (44)	15 (50)	0.67[b]

Unless other specified, the data are expressed as median (interquartile range); RLS: Restless Legs Syndrome; mRS: modified Rankin Scale; NIHSS: National Institute of Health Stroke Scale; TIA: transient ischemic attack; [a]Mann-Whitney U test; [b]Chi-square (X^2) test

Table 2. Comparison of blood parameters between groups with non-RLS and RLS

	Non-RLS (n=79)	RLS (n=30)	p
Iron, umol/L	15.04 (10.65-18.53)	13.25 (10.87-15.17)	0.13[a]
Ferritin, pmol/L	130.66 (60.64-240.63)	187.94 (127.01-330.39)	0.06[a]
BUN, mmol/L	6.07 (5.35-7.14)	5.71 (5-6.69)	0.32[a]
Creatinine, umol/L	78.68 (69.84-88.84)	72.49 (65.86-90.39)	0.33[a]
Hemoglobin, g/L	134 (122.5-146.5)	133 (125.25-146.25)	0.97[a]
Homocysteine, umol/L	13.04 (10.55-18.4) (n=58)	13.07 (9.83-14.55) (n=21)	0.31[a]
Vitamin B12, pmol/L	194.78 (145.72-246.5)	199.95 (181.5-262.11)	0.37[a]
Glucose, mmol/L	6.38 (5.24-10.07)	5.94 (5.2-9.63)	0.43[a]
HbA1c, %	6.3 (5.9-8.65)	6.1 (5.9-8)	0.62[a]
Total cholesterol, mmol/L	5.21 (4.47-6.16)	5.52 (4.56-6.03)	0.50[a]
LDL, mmol/L	3.03 (2.5-3.91)	3.42 (2.67-4.14)	0.21[a]
HDL, mmol/L	1.06 (0.87-1.23)	1.04 (0.84-1.16)	0.39[a]
VLDL, mmol/L	0.78 (0.52-1.09)	0.78 (0.57-1.28)	0.30[a]
Triglyceride, mmol/L	1.82 (1.14-2.44)	1.66 (1.28-2.79)	0.34[a]

The data are expressed as median (interquartile range); RLS: Restless Legs Syndrome; BUN: Blood Urea Nitrogen; HbA1c: Hemoglobin A1c; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; VLDL: Very Low-Density Lipoprotein; [a]Mann-Whitney U test.

our study. The median age of the study population was 65 (IQR: 59.5-72.5) years; 97 (89%) patients lived in urban areas. RLS was diagnosed in 30 (28%) of the 109 patients. Among the patients with RLS, nine (30%) had arm symptoms accompanying leg symptoms, four (13%) had left-sided symptoms only, and eight (27%) had right-sided symptoms only. The median RLS duration was 48 (IQR: 24-108) months, and the median IRLSRS score was 15 (IQR: 8-22).

The median pre-stroke mRS score of the study population was 0 (IQR: 0-0), the median admission NIHSS score was 2 (IQR: 1-2.5), and the median admission mRS score was 1 (IQR: 1-1).

The demographics, severity characteristics of acute stroke, stroke risk factors, and antihypertensive or antilipidemic

Table 3. Comparison of lesion characteristics of acute stroke between groups with non-RLS and RLS

	Non-RLS (n=79)	RLS (n=30)	p
Anatomical localizations			
Lobar, n (%)	34 (43)	10 (33)	0.39[b]
Centrum semiovale/corona radiata, n (%)	21 (27)	9 (30)	0.81[b]
Basal ganglia, n (%)	25 (32)	11 (37)	0.65[b]
Brainstem, n (%)	10 (13)	6 (20)	0.37[b]
Cerebellum, n (%)	6 (8)	1 (3)	0.67[b]
Vascular territories			
No acute stroke lesion, n (%)	7 (9)	5 (17)	0.47[b]
Anterior circulation, n (%)	49 (62)	15 (50)	
Posterior circulation, n (%)	18 (23)	9 (30)	
Anterior and posterior circulation, n (%)	5 (6)	1 (3)	
Lateralization			
No acute stroke lesion, n (%)	7 (9)	5 (17)	0.47[b]
Right hemisphere, n (%)	32 (41)	11 (37)	
Left hemisphere, n (%)	32 (41)	13 (43)	
Bilateral, n (%)	8 (10)	1 (3)	
Other			
Lacunar, n (%)	30 (38)	15 (50)	0.28[b]
Cortical, n (%)	42 (53)	10 (33)	0.09[b]
Symptomatic lesion, n (%)	62 (79)	24 (80)	0.55[b]

The data of acute stroke lesions are obtained from diffusion-weighted imaging or computed tomography; RLS: Restless Legs Syndrome; [b]Chi-square (X^2) test.

medication use showed no statistically significant differences between the non-RLS and RLS groups (Table 1).

Laboratory Characteristics and Neuroimaging of Acute Stroke

Examined blood parameters showed no statistically significant difference between the non-RLS and RLS groups (Table 2). Lesion characteristics of acute stroke also showed no statistically significant difference between the non-RLS and RLS groups (Table 3).

Cerebral Small Vessel Disease Burden

The median total ARWMC score in the RLS group was found to be significantly higher than in the non-RLS group (Fig. 1). In the RLS group, the rank values of median ARWMC scores were significantly higher in all areas except the left basal ganglia and the left infratentorial area than in the non-RLS group. In addition, the medians of the left and right hemisphere ARWMC scores were significantly higher in the RLS group than in the non-RLS group. Furthermore, the medians of the lobar (i.e., the sum of frontal, parietooccipital, and temporal areas) and extrapyramidal (i.e., the sum of basal ganglia and infratentorial areas) ARWMC scores were also significantly higher in the RLS group than in the non-RLS group (Table 4).

In the group with RLS, the duration of RLS (months) was significantly and positively correlated with ARWMC scores (r=0.39, p=0.03) (Fig. 2). However, the severity of RLS (IRLSRS scores) was not significantly correlated with ARWMC scores (r=0.05, p=0.79).

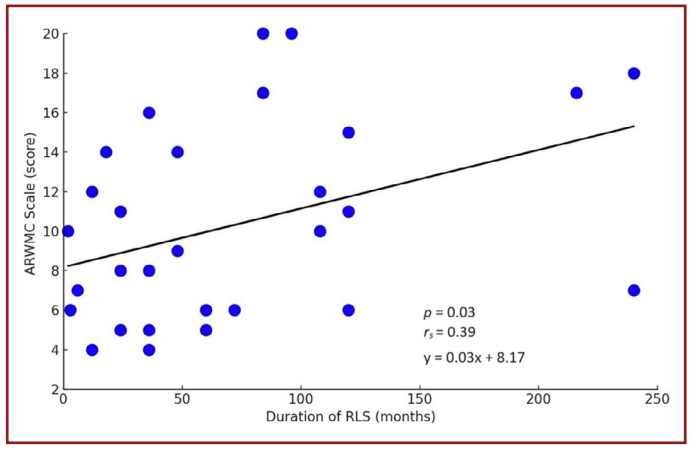


Figure 2. Correlation between duration of RLS and ARWMC scores in the group with RLS.

ARWMC: Age-Related White Matter Changes; RLS: Restless Legs Syndrome; r_s: Spearman's rank correlation coefficient.

Association between Lateralization of RLS Symptoms and Neuroimaging

Among the patients with RLS, the symptoms of RLS and the acute stroke lesions were on opposite sides in eight (27%) patients. The lateralization of RLS symptoms was not significantly associated with hemispheric ARWMC scores or lateralization of acute stroke lesions (Table 5).

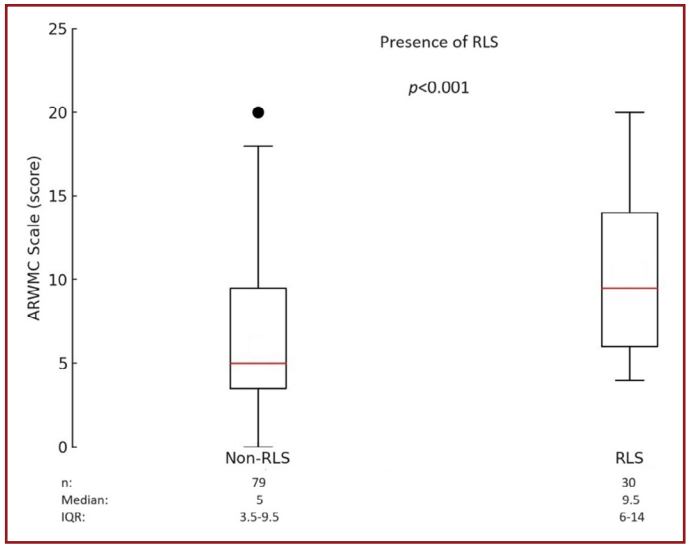


Figure 1. Comparison of total ARWMC scores between groups with and without RLS.

ARWMC: Age-Related White Matter Changes; IQR: Interquartile Range; RLS: Restless Legs Syndrome.

Table 4. Comparison of ARWMC scores between groups with Non-RLS and RLS

	Non-RLS (n=79)	RLS (n=30)	p
Left frontal	1 (1-2)	2 (1-2)	**0.007[a]**
Right frontal	1 (1-2)	2 (1-2)	**<0.001[a]**
Left parietooksipital	1 (1-2)	2 (1-2)	**0.004[a]**
Right parietooksipital	1 (1-2)	2 (1-2)	**0.02[a]**
Left temporal	0 (0-0)	0 (0-1)	**0.01[a]**
Right temporal	0 (0-0)	0 (0-1)	**<0.001[a]**
Left basal ganglia	0 (0-1)	1 (0-2)	0.06[a]
Right basal ganglia	0 (0-1)	1 (0-2)	**0.02[a]**
Left infratentorial	0 (0-0)	0 (0-0)	0.93[a]
Right infratentorial	0 (0-0)	0 (0-0)	**0.04[a]**
Total	5 (3.5-9.5)	9.5 (6-14)	**<0.001[a]**
Left hemisphere	3 (2-5)	4.5 (3-7)	**0.002[a]**
Right hemisphere	3 (2-4.5)	4 (3-7.75)	**<0.001[a]**
Lobar	4 (3.5-7)	7 (5-10)	**<0.001[a]**
Extrapyramidal	1 (0-3)	2 (1-4)	**0.006[a]**

Data are expressed as median (interquartile range); ARWMC: Age-Related White Matter Changes; RLS: Restless Legs Syndrome; [a]Mann-Whitney U test.

Table 5. Association between lateralization of RLS symptoms and neuroimaging

	Left RLS (n=4)	Right RLS (n=8)	Bilateral RLS (n=18)	p
ARWMC scores				
Left hemisphere	5 (3.5-7)	5.5 (3-6.25)	4 (2.25-7)	0.88[c]
Right hemisphere	6 (3.5-8.5)	4.5 (4-6.25)	4 (3-7.5)	0.76[c]
Lateralization of acute stroke lesions				
No acute stroke lesion, n (%)	1 (25)	1 (13)	3 (17)	0.22[b]
Right hemisphere, n (%)	3 (75)	1 (13)	7 (39)	
Left hemisphere, n (%)	0 (0)	5 (63)	8 (44)	
Bilateral, n (%)	0 (0)	1 (13)	0 (0)	

Unless other specified, the data are expressed as median (rank); RLS: Restless Legs Syndrome; ARWMC: Age-Related White Matter Changes; [b]Chi-square (X^2) test; [c]Kruskal-Wallis H test.

Discussion

The main finding of our study revealed that among patients with TIA or MIS, the total CSVD burden was significantly higher in those with RLS than in those without RLS. This result was independent of demographics, severity characteristics of acute stroke, stroke risk factors, antihypertensive or antilipidemic medication use, blood parameters, and lesion characteristics of acute stroke because these factors did not differ significantly between the non-RLS and RLS groups. Our finding may be explained by several pathophysiologic mechanisms.

More than 80% of patients with RLS have accompanying periodic limb movements of sleep (PLMS) [2]. A significant increase in systolic and diastolic blood pressure and heart rate develops during concomitant PLMS in patients with RLS [16]. In addition, a non-dipper blood pressure profile develops at night in patients with RLS. The non-dipper nocturnal blood pressure profile is an independent risk factor for cardiovascular incidents and hypertensive target organ damage, even in normotensive individuals [17]. Moreover, hypertension is an important factor in the pathophysiology of arteriolosclerosis, which is responsible for the formation of CSVD due to cerebral autoregulation impairment [7,18]. Therefore, both hypertension and tachycardia attacks during concomitant PLMS, and the non-dipper blood pressure profile in patients with RLS, may increase the CSVD burden.

A study showed that limb movement-related cerebral hypooxygenation was seen in patients with PLMS [19]. Cerebral white matter is one of the most sensitive areas of the brain to hypoxia and hypoperfusion due to the watershed areas. White matter hyperintensities (WMHs) are one of the components of CSVD that develops due to chronic diffuse hypoperfusion [20]. Therefore, recurrent episodes of transient cerebral hypoxia associated with PLMS in patients with RLS may be one of the reasons for the increase in CSVD burden.

Nocturnal hypertension and nocturnal hypoxia in patients with RLS are explained by chronic sleep deprivation, PLMS-related autonomic fluctuations, and RLS-related sympathetic hyperactivity [21]. Various vascular changes that occur as a result of these mechanisms have been described in patients with RLS. One study found that vascular endothelial function was worse in patients with RLS than in healthy subjects [22]. Another study showed that RLS was associated with arterial stiffness in patients with stroke [23]. It has been reported that arterial stiffness is associated with CSVD [7]. These vascular changes in patients with RLS may explain the increase in CSVD burden.

Some studies have shown the association between PLMS and CSVD. Boulos et al. [24] found that the PLMS index was associated with WMHs in patients with first-ever MIS or high-risk TIA. In this study, no relationship was found between RLS and WMHs burden, but the authors stated that the power of the data was low. Additionally, Kang et al. [25] found that a high PLMS index was associated with increased WMHs, asymptomatic lacunar infarcts, perivascular spaces, and total CSVD burden, but not associated with cerebral microbleeds.

In our study, RLS duration was significantly and positively correlated with CSVD burden in the RLS group. However, RLS severity was not significantly correlated with CSVD burden in the RLS group. RLS severity data were obtained by measuring the RLS symptoms of the patients in the last week before the face-to-face interview using IRLSRS [12]. In contrast, RLS duration data were obtained by calculating the difference between the onset of MIS or TIA symptoms of the patients and the time when RLS symptoms first appeared. CSVD mainly develops as a result of chronic cerebral hypoperfusion [20]. Considering the

pathophysiology of CSVD, the results of our study show that the increase in the CSVD burden may be related to the total effect over time rather than the short-term severity characteristics of RLS. Studies in the literature also reveal the relationship between RLS duration and cardiovascular diseases and cerebrovascular diseases [26,27].

The pre-stroke RLS prevalence in patients with MIS or TIA was 28% in our study. Although the pre-stroke RLS prevalence in patients with stroke varies in the literature, it has been reported between 4.8% and 15% [3,4,23]. The population-based prevalence of RLS shows wide geographic variability. While the RLS prevalence is reported as high as 29% in North America and Western Europe, it is reported as low as 0.9% in Far East countries and as low as 0.037% in Africa [28–30]. The reported prevalence of RLS in our country is between 3.19% and 12.1% [31,32].

In this study, the pre-stroke RLS prevalence in patients with MIS or TIA is higher than the prevalence reported in patients with stroke in the literature. The comparison of the RLS prevalence in our study with those in other studies is hard because these studies are few, and the prevalence of RLS differs significantly between populations. Additionally, whereas patients with MIS or TIA were evaluated in our study, all patients with ischemic stroke/TIA or all patients with ischemic and hemorrhagic stroke were evaluated in other studies. Differences in the patient populations evaluated also make the comparison of the RLS prevalence in patients with stroke challenging.

The RLS prevalence in the study population is also higher than the population-based prevalence reported in our country. There may be several possible reasons for this high prevalence. The prevalence of RLS shows a strong increase, at a rate of 18-23%, in the elderly population [33]. In addition, Erden et al. [17] reported that the RLS prevalence in participants with a hypertension rate of 62.1% was 28.5% in our country, similar to our study. Furthermore, they found that the RLS prevalence in patients with hypertension was significantly higher than in patients without hypertension. Therefore, the RLS prevalence in our study may be related to the high median age of 65 years and the high rate of hypertension (71%) in the study population.

The median serum ferritin levels of RLS patients were numerically higher than those of non-RLS patients in our study (p=0.06, Table 2). Chenini et al. [34] reported no significant difference in serum ferritin levels between RLS patients and non-RLS controls. In their study, the median serum ferritin levels were numerically higher in RLS patients compared to non-RLS controls, consistent with our results. They suggested that serum ferritin remains important for RLS treatment.

Another finding of the present study showed that localization characteristics of acute stroke lesions did not differ between the non-RLS and RLS groups (Table 3). Additionally, the lateralization of RLS symptoms was not associated with hemispheric CSVD burden or lateralization of acute stroke lesions in the RLS group. These findings have been discussed in a few studies in the literature. Gupta et al. [4] revealed that subcortical stroke was significantly more common in those with RLS than in those without RLS in patients with subacute ischemic or hemorrhagic stroke. Moreover, they reported that the symptoms of RLS and the acute stroke lesions were on opposite sides in 68% of patients with RLS. In our study, the symptoms of RLS and the acute stroke lesions were on opposite sides in 27% of patients with RLS. By contrast, Han et al. [23] found no significant association between RLS presence and stroke lesion location in patients with acute ischemic stroke. Our results, unlike those in patients with subacute stroke, show that pre-stroke RLS in patients with acute MIS or TIA may be associated with vascular pathophysiology, possibly as a result of nocturnal hypertension and hypoxia rather than the location of stroke.

In general, median ARWMC scores were highest in the frontal and parietooccipital regions and lowest in the temporal and infratentorial regions (Table 4), as previously reported [14]. In CSVD, WMHs are many in the frontal and parietooccipital regions before appearing in the infratentorial region [7]. The course of CSVD may explain the distribution of WMHs.

There are some limitations to our study. The patients were not questioned for obstructive sleep apnea syndrome and PLMS. However, age, obesity, diabetes mellitus, hypertension, congestive heart failure, atrial fibrillation, and stroke, which are among the risk factors for obstructive sleep apnea syndrome and/or PLMS, showed no difference between the non-RLS and RLS groups [2,35]. Recall bias may have been present because the duration of RLS was questioned retrospectively. The study population includes only patients presenting with MIS or TIA, which limits generalizability. Lastly, because our study is cross-sectional, the direction of the relationship between RLS and CSVD in terms of cause and effect could not be determined. There are various studies in the literature on RLS development after stroke [36–38]. However, other studies show that RLS increases the risk of developing cardiovascular disease and cerebrovascular disease [27,39]. Moreover, Denis et al. [40]

indicated that RLS is associated with poorer outcomes after ischemic stroke at 3 months. The findings of our study and the data in the existing literature show that the presence and duration of RLS may increase the CSVD burden, rather than the CSVD burden causing the development of RLS.

Conclusion

This study reveals that the presence and duration of RLS may be an independent propensity factor for CSVD in patients with MIS or TIA. The significantly higher ARWMC scores in the group with RLS in almost all cerebral areas indicate a widespread increase in CSVD burden. This finding supports the role of nocturnal hypertension and hypoxia seen in patients with RLS in the pathophysiology of CSVD. Future prospective studies will help test the hypothesized direction of the relationship between RLS and CSVD based on pathophysiology.

Acknowledgement: The authors thank F. Nihan Ready for her statistical support and David Francis Chapman for his editing and proofreading.

Ethics Committee Approval: The study was approved by University of Health Sciences, Hamidiye Faculty of Medicine, Haydarpaşa Numune Health Application and Research Center, Ethics Committee (No: HNEAH-KAEK 2018/56-2218, Date: 15/06/2020).

Peer-review: Externally peer-reviewed.

Use of AI for Writing Assistance: Not declared.

Authorship Contributions: Concept – C.M.Ü., K.T., H.T.; Design – C.M.Ü., K.T., H.T.; Supervision – C.M.Ü., K.T., H.T.; Fundings – C.M.Ü., K.T.; Materials – C.M.Ü., K.T., H.T.; Data collection &/or processing – C.M.Ü., K.T., H.T.; Analysis and/or interpretation – C.M.Ü., K.T., H.T.; Literature search – C.M.Ü., K.T.; Writing – C.M.Ü.; Critical review – C.M.Ü., K.T., H.T.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18:459–80.
2. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J, et al. 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;4:101–19.
3. Schlesinger I, Erikh I, Nassar M, Sprecher E. Restless legs syndrome in stroke patients. Sleep Med 2015;16:1006–10.
4. Gupta A, Shukla G, Mohammed A, Goyal V, Behari M. Restless legs syndrome, a predictor of subcortical stroke: A prospective study in 346 stroke patients. Sleep Med 2017;29:61–7.
5. Walters AS, Moussouttas M, Siddiqui F, Silveira DC, Fuentes K, Wang L, et al. Prevalence of stroke in Restless Legs Syndrome: Initial results point to the need for more sophisticated studies. Open Neurol J 2010;4:73–7.
6. Bassetti CLA, Randerath W, Vignatelli L, Ferini-Strambi L, Brill AK, Bonsignore MR, et al. EAN/ERS/ESO/ESRS statement on the impact of sleep disorders on risk and outcome of stroke. Eur J Neurol 2020;27:1117–36.
7. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: Insights from neuroimaging. Lancet Neurol 2013;12:483–97.
8. Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, et al. Definition and evaluation of transient ischemic attack: A scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke 2009;40:2276–93.
9. Yakhkind A, McTaggart RA, Jayaraman MV, Siket MS, Silver B, Yaghi S. Minor stroke and transient ischemic attack: Research and practice. Front Neurol 2016;7:86.
10. Amarenco P, Lavallée PC, Labreuche J, Albers GW, Bornstein NM, Canhão P, et al. One-year risk of stroke after transient ischemic attack or minor stroke. N Engl J Med 2016;374:1533–42.
11. Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW, et al. 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;15:860–73.
12. Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, et al. Validation of the International Restless Legs Syndrome study group rating scale for restless legs syndrome. Sleep Med 2003;4:121–32.
13. Ay H, Benner T, Arsava EM, Furie KL, Singhal AB, Jensen MB, et al. A computerized algorithm for etiologic classification of ischemic stroke: The Causative Classification of Stroke System. Stroke 2007;38:2979–84.
14. Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjögren M, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 2001;32:1318–22.
15. Staals J, Makin SD, Doubal FN, Dennis MS, Wardlaw JM. Stroke

subtype, vascular risk factors, and total MRI brain small-vessel disease burden. Neurology 2014;83:1228–34.
16. Cassel W, Kesper K, Bauer A, Grieger F, Schollmayer E, Joeres L, et al. Significant association between systolic and diastolic blood pressure elevations and periodic limb movements in patients with idiopathic restless legs syndrome. Sleep Med 2016;17:109–20.
17. Erden EC, Erden İ, Türker Y, Sivri N, Dikici S, Ozşahin M. Incremental effects of restless legs syndrome on nocturnal blood pressure in hypertensive patients and normotensive individuals. Blood Press Monit 2012;17:231–4.
18. Liu Z, Ma H, Guo ZN, Wang L, Qu Y, Fan L, et al. Impaired dynamic cerebral autoregulation is associated with the severity of neuroimaging features of cerebral small vessel disease. CNS Neurosci Ther 2022;28:298–306.
19. 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;120:1329–34.
20. Li Q, Yang Y, Reis C, Tao T, Li W, Li X, et al. Cerebral small vessel disease. Cell Transplant 2018;27:1711–22.
21. Chiaro G, Manconi M. Restless legs syndrome, periodic limb movements during sleep and cardiovascular risk. Auton Neurosci 2019;220:102554.
22. Koh SY, Kim MS, Lee SM, Hong JM, Yoon JH. Impaired vascular endothelial function in patients with restless legs syndrome: A new aspect of the vascular pathophysiology. J Neurol Sci 2015;359:207–10.
23. Han SH, Park KY, Kim JM, Youn YC, Shin HW. Restless legs syndrome is associated with arterial stiffness and clinical outcome in stroke patients. Sleep Med 2019;60:219–23.
24. Boulos MI, Murray BJ, Muir RT, Gao F, Szilagyi GM, Huroy M, et al. Periodic limb movements and white matter hyperintensities in first-ever minor stroke or high-risk transient ischemic attack. Sleep 2017;40:zsw080.
25. Kang MK, Koo DL, Shin JH, Kwon HM, Nam H. Association between periodic limb movements during sleep and cerebral small vessel disease. Sleep Med 2018;51:47–52.
26. Ferri R, Cosentino FI, Moussouttas M, Lanuzza B, Aricò D, Bagai K, et al. Silent cerebral small vessel disease in restless legs syndrome. Sleep 2016;39:1371–7.
27. 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;126:1689–94.
28. Innes KE, Selfe TK, Agarwal P. Prevalence of restless legs syndrome in North American and Western European populations: A systematic review. Sleep Med 2011;12:623–34.
29. Cho SJ, Hong JP, Hahm BJ, Jeon HJ, Chang SM, Cho MJ, et al. Restless legs syndrome in a community sample of Korean adults: Prevalence, impact on quality of life, and association with DSM-IV psychiatric disorders. Sleep 2009;32:1069–76.
30. Burtscher C, Baxmann A, Kassubek J, Hornyak M, Matuja W, Schmutzhard E, et al. Prevalence of restless legs syndrome in an urban population of eastern Africa (Tanzania). J Neurol Sci 2014;346:121–7.
31. Aksoy S, Eker E, Oymak S, Karaman HIO. Prevalence of restless legs syndrome : A cross - sectional population - based study from northwest of Turkey. Sleep Biol Rhythms 2021;19:453–8.
32. Sevim S, Dogu O, Camdeviren H, Bugdayci R, Sasmaz T, Kaleagasi H, et al. Unexpectedly low prevalence and unusual characteristics of RLS in Mersin, Turkey. Neurology 2003;61:1562–9.
33. Gossard TR, Trotti LM, Videnovic A, St Louis EK. Restless legs syndrome: Contemporary diagnosis and treatment. Neurotherapeutics 2021;18:140–55.
34. Chenini S, Delaby C, Rassu AL, Barateau L, Vialaret J, Hirtz C, et al. Hepcidin and ferritin levels in restless legs syndrome: A case-control study. Sci Rep 2020;10:11914.
35. Patel SR. Obstructive sleep apnea. Ann Intern Med 2019;171:ITC81–96.
36. Woo HG, Lee D, Hwang KJ, Ahn TB. Post-stroke restless leg syndrome and periodic limb movements in sleep. Acta Neurol Scand 2017;135:204–10.
37. Tuo H, Tian Z, Ma X, Cui Y, Xue Y, Che J, et al. Clinical and radiological characteristics of restless legs syndrome following acute lacunar infarction. Sleep Med 2019;53:81–7.
38. Zorgor G, Kabeloglu V, Soysal A. Restless legs syndrome after acute ıschemic stroke and its relation to lesion location. Sleep Biol Rhythms 2022;20:551–60.
39. Molnar MZ, Lu JL, Kalantar-Zadeh K, Kovesdy CP. Association of incident restless legs syndrome with outcomes in a large cohort of US veterans. J Sleep Res 2016;25:47–56.
40. Denis C, Jaussent I, Guiraud L, Mestejanot C, Arquizan C, Mourand I, et al. Functional recovery after ischemic stroke: Impact of different sleep health parameters. J Sleep Res 2024;33:e13964.