Sleep Medicine 60 (2019) 219–223

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Restless legs syndrome is associated with arterial stiffness and clinical outcome in stroke patients

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ARTICLE INFO

Article history:
Received 30 October 2018
Received in revised form
11 March 2019
Accepted 12 March 2019
Available online 20 April 2019

Keywords:
Restless legs syndrome
Arterial stiffness
Acute ischemic stroke

ABSTRACT

Objective: Restless legs syndrome (RLS) has been associated with vascular diseases, including cerebrovascular and cardiovascular diseases. Among the various mechanisms in RLS, peripheral vascular endothelial dysfunction in patients with RLS has recently been proposed as a vascular pathophysiology of RLS. This study investigated arterial stiffness related to RLS in acute ischemic stroke patients and its influence on stroke outcome.

Methods: RLS in patients with acute ischemic stroke was assessed based on the four essential criteria of the International Restless Legs Syndrome Study Group described in 2003. The patients' clinical and laboratory characteristics, arterial stiffness, small vessel disease occurrence, and burden on brain MRI were recorded. Stroke severity was determined using the National Institute of Health Stroke Scale (NIHSS), and clinical outcomes were determined using the modified Rankin Scale.

Results: Of 296 patients with acute ischemic stroke, 16 (5.4%) were diagnosed with restless legs syndrome. Logistic regression analysis showed that a 1 m/s increase in brachial arterial pulse wave velocity was associated with the diagnosis of RLS (odds ratio, 1.092; 95% confidence interval, 1.019–1.170, $p = 0.012$). Diagnosis of RLS in patients with acute ischemic stroke was associated with poor clinical outcome three months after stroke (modified Rankin Scale 3–6) (odds ratio, 4.263; 95% confidence interval, 1.229–14.792, $p = 0.022$) along with initial NIHSS score.

Conclusion: RLS in patients with acute ischemic stroke is associated with increased arterial stiffness and poor clinical outcomes.

1. Introduction

Restless legs syndrome (RLS) is a disorder in which the legs are urged to move by an unpleasant sensation, especially during rest [1]. Disorders in iron and dopamine, as well as other medical and neurological disorders, including cardiovascular and cerebrovascular diseases (CVDs), have been associated with the pathophysiological mechanisms of RLS [2,3]. Several studies have shown that RLS has been associated with CVDs, in that CVDs are risk factors for RLS, and conversely, RLS is a risk factor for these diseases [2,4–6]. Although diagnosis of RLS following acute ischemic stroke suggests that RLS may also be associated with stroke [7–11], evidence for a direct relationship is limited and uncertain [12,13].

While evidence is limited, various lesion locations in post-stroke RLS patients suggest that the mechanisms related to developing RLS in CVD patients may be more heterogeneous rather than being confined to only a specific lesion location [7,8,14–16]. Recently, vascular pathology in patients with RLS has been proposed [17–23]. Peripheral hypoxia, reduced intramuscular blood flow, and higher capillary tortuosity in patients with RLS suggest changes in peripheral microvasculature [19–22]. The alteration of the autonomic system in patients with RLS and periodic limb movements in sleep (PLMS) might enhance the vascular pathology of RLS [6,23,24]. These findings suggest that the vascular pathophysiology related to RLS may explain the association between RLS and stroke. However, vascular pathophysiology related to RLS in patients with stroke has not been investigated.

Brachial–ankle pulse wave velocity (baPWV) has been developed as a noninvasive method for measuring arterial stiffness that reflects the elasticity of the arterial wall. baPWV may be associated with atherosclerosis at various sites including peripheral arteries

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https://doi.org/10.1016/j.sleep.2019.03.027
1389-9457/

[25–27]. An increasing number of studies showed that baPWV is predictive of prognosis in patients with cerebrovascular disease or cardiovascular disease [28–30]. Based on the previous results of vascular pathology related to RLS [17,18,20], we have hypothesized that arterial stiffness in acute ischemic stroke patients may have an association with stroke-related RLS. In addition, we performed an exploratory analysis to determine whether RLS is related to clinical outcome in these patients.

2. Methods

2.1. Subjects

This single-center, observational study recruited consecutive acute ischemic stroke patients who were admitted to the Neurology Department of Chung-Ang University Hospital from November 2013 to October 2016. All acute ischemic stroke patients whose neurological symptoms developed within seven days were considered candidates for screening. All of the patients were diagnosed with acute cerebral infarction by brain magnetic resonance imaging (MRI) including diffusion weighted imaging. Patients unable to communicate due to loss of consciousness, aphasia, severe dysarthria, or cognitive impairment were excluded, along with those not willing to participate in this study. This study was approved by the Institutional Review Board of Chung-Ang University Hospital, and all participants provided written informed consent.

2.2. Clinical evaluations and diagnosis of RLS

RLS was diagnosed using the four essential criteria defined by the International Restless Legs Syndrome Study Group (IRLSSG, 2003) [31] by interview with one of two neurologists (S.H.H. and H.W.S.). The interview was performed within one week of admission. Patients with iron deficiency, uremia, peripheral neuropathy, and radiculopathy were excluded. In addition, patients with conditions mimicking RLS, due to leg muscle cramp, positional discomfort, venous stasis, or arthritic pain, were excluded during interviews. Therefore, the new consensus criteria for diagnosis of RLS were satisfied [32].

Initial stroke severity on the day of admission was evaluated using the National Institute of Health Stroke Scale (NIHSS). One of two neurologists (J.M.K. and K.Y.P.) classified subtypes of ischemic stroke according to the categorization system of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) [33]. History of diabetes mellitus (DM), dyslipidemia, ischemic heart disease (IHD), atrial fibrillation (AF), and hypertension were collected from medical records. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared (kg/m^2). Patients were categorized as underweight (<18.50 kg/m^2), normal (18.5–22.9 kg/m^2), overweight (23.0–27.5 kg/m^2), or obese (≥27.5 kg/m^2) using the World Health Organization Asian BMI cut-off points [34]. Laboratory evaluations included measurements of hemoglobin (Hb), creatinine (Cr), glycated hemoglobin ($HbA1_C$), total cholesterol, triglyceride (TG), and low-density lipoprotein (LDL) concentrations.

Stroke outcomes were evaluated using the modified Rankin Scale (mRS) at discharge and at the three-month follow-up visits [35]. A poor functional outcome three months after the onset of stroke was defined as an mRS ≥3.

2.3. Measurement of arterial stiffness

Arterial stiffness was assessed using a volume-plethysmography device (VP-1000; Collin, Komaki, Japan) that automatically calculated baPWV as the transmission distance divided by the transmission time between the right brachial and volume waveforms. The distance between the right brachium and each ankle was estimated from body height and was expressed in meters per second (m/s). Moreover, baPWV was reported as the average on both sides [36].

2.4. Imaging review and visual rating for burden of small vessel disease

Brain MRI including diffusion weighted imaging with a 3.0-T MR unit (Avanto, Philips, Eindhoven, The Netherlands) was performed to diagnose acute ischemic stroke. The burden of small vessel disease (SVD) was determined by assessing white matter hyperintensity in the axial fluid-attenuated inversion recovery images according to the scale of Fazekas, with grades 0–3 indicating the absence of SVD, punctate foci, beginning confluence of foci, and large confluent areas, respectively [37]. Neuroimaging was assessed by two neurologists (K.Y.P. and J.M.K.) blinded to the diagnosis of RLS.

2.5. Statistical analysis

The demographic and clinical characteristics of stroke in patients with and without RLS were compared using the Mann–Whitney *U* test for continuous variables and Fisher exact test for nominal variables. The relationships between variables, including baPWV and other vascular parameters and the presence of RLS, were determined by logistic regression analysis. The presence of RLS was considered the dependent variable. The independent variables included demographic variables (age, sex, BMI, hypertension, DM, IHD, AF, smoking status, dyslipidemia, and previous stroke history), laboratory variables (Hb, Cr, HbA1c, total cholesterol, TG, and LDL), arterial stiffness (baPWV), burden of SVD (Fazekas scale), TOAST classification, lesion location, and stroke severity (NIHSS). The association between stroke outcome (mRS ≥3) and RLS was tested using logistic regression analyses. Multivariable logistic regression analysis was used to further assess variables with p values < 0.1 according to univariable analysis. All data were analyzed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY) and the significance level was set at $p < 0.05$. Firth regression analysis was performed to compare logistic regression analysis for obtain odds ratio (ORs) in data of small events using R Statistical Software.

3. Results

Of the 296 eligible patients with acute ischemic stroke recruited to this study, 16 (5.4%) were diagnosed with RLS according to the IRLSSG criteria. Clinical characteristics and stroke locations in patients with RLS are described in Table 1. None of the patients diagnosed with RLS had been diagnosed with this disorder prior to admission or had taken medication for sleep disturbances. Lesions in the basal ganglia were found in two of the patients (12.5%).

No significant differences were observed between the demographic and laboratory characteristics, NIHSS scores (Mann–Whitney *U* test, $p = 0.404$), TOAST classification (Fisher exact test, $p = 0.830$), stroke lesion locations (Fisher exact test, $p = 0.460$), arterial stiffness measured by baPWV (Mann–Whitney *U* test, $p = 0.313$), and SVD burden (Fisher exact test, $p = 0.401$) between the patients with and without RLS. However, there was a trend showing a higher percentage of patients with an mRS ≥3 in the group of patients with RLS than in the group of patients without RLS (Fisher exact test, $p = 0.060$).

Logistic regression analysis showed that a 1 m/s increase in baPWV was associated with the presence of RLS (OR = 1.092; 95% confidence interval [CI] = 1.019–1.170, $p = 0.012$) (Table 2). None of

Table 1
Locations of ischemic stroke lesions in patients with restless legs syndrome.

No.	Sex	Age, y	Location of infarct	NIHSS at admission
1	F	79	Right corona radiata, external capsule, and posterior temporal subcortical white matter	1
2	M	69	Bilateral cerebellar hemispheres, vermis, and left lateral medulla	0
3	M	61	Right pons	0
4	M	60	Left corona radiata and putamen/external capsule	3
5	F	72	Right corona radiata	6
6	M	78	Left corona radiata	1
7	F	73	Left ventral pons	7
8	F	70	Left frontoparietal subcortical white matter and cortex	2
9	M	78	Left basal ganglia and corona radiata	4
10	M	88	Left corona radiata	3
11	M	53	Right parietal lobe including postcentral gyrus, and centrum semiovale	4
12	M	61	Left paramedian pons	0
13	M	64	Left temporo-parietal cortex	1
14	F	80	Right frontal, parietal and anterior insular cortex	10
15	F	79	Left medulla	8
16	M	69	Right corona radiata	2

F, female; M, male; NIHSS, National Institutes of Health Stroke Scale.

the other variables were significantly associated with the presence of RLS.

The associations between the stroke outcome (mRS ≥3) and the study variables, including RLS were also analyzed. The factors for univariable analysis included the presence of RLS, age, sex, hypertension, smoking status, levels of hemoglobin and TG cholesterol, baPWV, and NIHSS with p values of <0.1 (Table 3). When these factors were entered for multivariable analysis, the presence of RLS, age, and NIHSS score at admission were associated with poor clinical outcome, but baPWV was not (Table 4). Because a small event rate of RLS may affect the sensitivity or precision of the results of multivariable analysis, the number of independent variables was reduced; Firth regression analysis was performed using R Statistical Software [38]. The obtained estimate (OR = 1.26, 93% CI = 1.024–1.552) in Firth regression was comparable to the results obtained from the logistic regression analysis (OR = 1.28, 95% CI = 0.138–2.462).

Table 2
Univariable logistic regression model for presence of restless legs syndrome in acute ischemic stroke patients.

	OR (95% CI)	p
Demographics		
Age, y	1.018 (0.976–1.062)	0.406
Female sex	0.682 (0.241–1.929)	0.471
BMI	1.050 (0.910–1.211)	0.507
Hypertension	1.565 (0.492–4.984)	0.448
Diabetes mellitus	0.791 (0.248–2.524)	0.692
Ischemic heart disease	1.339 (0.289–6.206)	0.709
Atrial fibrillation	0.745 (0.206–2.693)	0.653
Current smoking	1.177 (0.396–3.497)	0.769
Dyslipidemia	0.966 (0.266–3.509)	0.958
Previous stroke history	1.205 (0.330–4.401)	0.778
Laboratory findings		
Hemoglobin, g/dL	1.013 (0.796–1.289)	0.917
Creatinine, mmol/L	1.023 (0.378–2.768)	0.964
HbA1c, %	1.171 (0.845–1.625)	0.343
Total cholesterol, mmol/L	0.991 (0.979–1.002)	0.119
LDL-cholesterol, mmol/L	0.989 (0.972–1.007)	0.221
TG-cholesterol, mmol/L	1.003 (0.998–1.008)	0.210
Arterial stiffness		
baPWV, m/s	1.092 (1.019–1.170)	**0.012**[a]
Fazekas grade	1.216 (0.707–2.092)	0.479
TOAST classification	0.862 (0.566–1.313)	0.489
Lesion location	1.204 (0.670–2.166)	0.535
Clinical findings		
NIHSS at admission	0.925 (0.813–1.052)	0.236

baPWV, brachial–ankle pulse wave velocity; BMI, body mass index; CI, confidence interval; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein; NIHSS: National Institutes of Health Stroke Scale; OR, odds ratio; TG, triglycerides; TOAST, Trial of Org 10172 in Acute Stroke Treatment.
$p < 0.05$ was set as significant and marked as bold.
[a] A 1-m/s increase in baPWV was associated with the presence of restless legs syndrome.

4. Discussion

This study showed that increasing 1 m/s of baPWV was associated with the presence of RLS in acute ischemic stroke patients. In contrast, the other vascular risk factors tested, as well as lesion location of acute stroke, were not associated with RLS. These findings indicate that arterial stiffness was associated with RLS in acute ischemic stroke patients. Further, baPWV was developed as a method for measuring arterial stiffness and has been shown in an increasing number of studies to be predictive of prognosis in patients with CVDs [28–30]. In a previous meta-analysis study,

Table 3
Univariable logistic regression model for poor prognosis (modified Rankin Scale ≥3) at three months after stroke.

	OR (95% CI)	p
Restless legs syndrome	2.643 (0.954–7.324)	0.062
Demographics		
Age, y	1.096 (1.066–1.128)	**<0.001**
Female sex	2.117 (1.293–3.466)	**0.003**
Underweight (BMI <18.50)	1.652 (0.612–4.455)	0.322
Overweight (BMI 23–27.49)	0.635 (0.365–1.105)	0.108
Obese (BMI ≥27.5)	0.511 (0.229–1.139)	0.101
Hypertension	1.565 (0.921–2.660)	0.098
Diabetes mellitus	0.845 (0.494–1.448)	0.541
Ischemic heart disease	1.157 (0.509–2.631)	0.729
Atrial fibrillation	1.353 (0.768–2.386)	0.296
Current smoking	0.333 (0.178–0.622)	**0.001**
Dyslipidemia	0.638 (0.334–1.218)	0.173
Previous stroke history	1.547 (0.818–2.926)	0.180
Laboratory findings		
Hemoglobin, g/dL	0.868 (0.773–0.975)	**0.017**
Creatinine, mmol/L	1.352 (0.834–2.192)	0.221
HbA1c, %	0.891 (0.724–1.096)	0.275
Total cholesterol, mmol/L	1.003 (0.997–1.008)	0.316
LDL-cholesterol, mmol/L	1.006 (0.998–1.014)	0.137
TG-cholesterol, mmol/L	0.996 (0.992–1.000)	**0.029**
Arterial stiffness		
baPWV, m/s	1.115 (1.059–1.173)	**<0.001**[a]
Clinical findings		
NIHSS at admission	1.132 (1.076–1.192)	**<0.001**

baPWV, brachial–ankle pulse wave velocity; BMI, body mass index; CI, confidence interval; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein; NIHSS: National Institutes of Health Stroke Scale; OR, odds ratio; TG, triglycerides.
$p < 0.05$ was set as significant and marked as bold.
[a] A 1-m/s increase in baPWV was associated with poor clinical outcome three months after stroke (modified Rankin Scale ≥3).

Table 4
Multivariable logistic regression model for poor prognosis (modified Rankin Scale score ≥3) at three months after stroke.

	OR	95% CI	*p*
Restless leg syndrome	4.263	1.229–14.792	**0.022**
Age, y	1.083	1.046–1.121	**<0.001**
Females	1.491	0.721–3.081	0.281
Hypertension	1.079	0.549–2.123	0.825
Current smoking	0.901	0.385–2.110	0.811
Hemoglobin, g/dL	1.002	0.850–1.181	0.981
TG-cholesterol, mmol/L	0.997	0.993–1.002	0.300
baPWV, m/s	1.033	0.970–1.009	0.315
NIHSS score at admission	1.163	1.092–1.238	**<0.001**

Multivariable analysis included variables with p values < 0.1 on univariable logistic regressions.
baPWV, brachial–ankle pulse wave velocity; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; TG, triglycerides.
p < 0.05 was set as significant and marked as bold.

increasing 1 m/s of baPWV increased 12%, 13%, and 6% of total cardiovascular events, cardiovascular mortality, and all-cause mortality [28]. Vascular pathology has been proposed to be a cause of RLS, and studies have shown an increased arterial stiffness in patients with PLMS and obstructive sleep apnea [24]. Thus, a relationship between arterial stiffness and various sleep disorders has been suggested [17,18,20,24]; however, no previous study has examined arterial stiffness in RLS patients. Several mechanisms may explain the association of arterial stiffness with RLS observed in the present work. Patients with RLS experience changes in the peripheral microvasculature, including reduced blood flow, higher capillary tortuosity, and hypoxia in the legs [18,19,21]. Peripheral microangiopathy may reduce local blood flow and increase hypoxia in the legs, thereby inducing symptoms of RLS [22]. Iron deficiency, one of the main pathophysiological mechanisms underlying RLS, may also induce hypoxia in leg muscles, giving rise to RLS symptoms [39]. Increased peripheral arterial stiffness, therefore, may cause local hypoxia in the legs, resulting in RLS symptoms. A recent study showing impaired vascular endothelial function in patients with RLS supports the notion that RLS is induced by conditions causing hypoxia, such as impaired vascular supply to the leg muscles [17]. PLMS is highly comorbid with RLS [1]; the alteration of the autonomic system in patients with RLS and higher arterial stiffness in patients with PLMS also may enhance the vascular pathology of RLS patients [6,23,24]. Taken together, the predictive value of baPWV for RLS in ischemic stroke patients provides vascular pathophysiology of RLS. Nevertheless, although increasing 1 m/s of baPWV was associated with the presence of RLS in acute ischemic stroke patients, there was no significant difference between value of baPWV between two groups with and without RLS. The lack of a significant difference may have been due to the low power of the nonparametric test in between-group comparisons, because of the small number of patients in the RLS group.

This study found that 5.4% of acute ischemic stroke patients had RLS. The prevalence of RLS in patients with stroke has been variably reported to range from 2.31% to 15%, which is similar to the disorder prevalence in the general population [4,9,16]. The prevalence of RLS in the general population has been reported to range from 0.9% to 9.5% in our country, which is lower compared to that in Western countries [40,41]. Because few direct comparative studies have assessed the prevalence of RLS in stroke patients, and because this prevalence ranges widely among populations [4], it is difficult to compare the prevalence of RLS in our study with the rates observed in other studies. In addition, RLS was diagnosed in the subacute stage of stroke in the previous study, in contrast to our study, in which diagnosis of RLS was performed in the acute stage of stroke. The difference in patient population may affect the prevalence of RLS. Additional studies are required to determine the prevalence of RLS in specific disease entities compared to that in the general population.

With regard to the topographical distribution of cerebral infarction, our study found that RLS was not associated with any specific lesion localization. Only two of the 16 patients with RLS had lesions in the basal ganglia, with other patients having lesions in the cerebral cortex, subcortical white matter, brainstem, and cerebellum. The stroke location was not related to the diagnosis of RLS. This finding is different from that of the previous study, in which RLS occurred mainly in patients with subcortical infarction, especially in the basal ganglia [9]. The results of our study provide that RLS in acute stroke patients may be associated with vascular pathophysiology rather than the stroke location, which is different from that in the subacute stage or chronic stage of stroke patients [9,42].

We found that RLS in acute ischemic stroke patients was related to poor outcomes (mRS ≥ 3) three months after stroke, with the likelihood of poor outcome being 4.3-fold higher in patients with RLS than in patients without RLS. The number of patients with poor clinical outcome tended to be higher in the group with RLS than in the group without RLS, although the difference was not statistically significant. We also found that age and NIHSS score at admission predicted clinical outcomes in acute stroke patients, which are widely known as prognostic factors in stroke patients. In the previous studies, RLS has had a negative impact on clinical recovery from ischemic stroke or on stroke-related quality of life several months after the acute stage of stroke [43,44]. The mechanism of influence of RLS on stroke outcome is uncertain. Increased blood pressure, which may reflect sympathetic hyperactivity, has been seen in patients with RLS [45]. Accordingly, the previous study proposed that poorer clinical outcomes in stroke patients with RLS may be related to increased sympathetic activity [43]. Our result indicating that each 1-m/s increase in baPWV increases the likelihood of developing RLS supports this hypothesis. Arterial stiffness, as determined by baPWV, might be associated with sympathetic nervous system activity [46,47]. The relationship between RLS, sympathetic hyperactivity, and arterial stiffness may explain the poorer outcome in acute stroke patients with RLS.

This study had several limitations. First, this study recruited only patients with relatively mild neurological deficits, because patients who were not able to communicate well owing to aphasia, cognitive impairment, neglect syndrome, or altered mental status were excluded from the study, as diagnosis of RLS relies on interview. Therefore, the prevalence of RLS in our overall patient population may have been underestimated and the exclusion bias could not be removed from this study. In addition, we did not include details on the severity and duration of symptoms, although detailed interviews excluded RLS mimics and satisfied new RLS diagnostic criteria [32]. This may have limited the understanding of the exact nature of patients with RLS in our study. There may also be concerns about introduction of bias due to unequal group sizes between patients with and without RLS. In addition, the exclusion of RLS mimics and patients with iron deficiency, uremia, peripheral neuropathy, and radiculopathy in our study may have introduced a bias, as the differentiation may have become more artificial than actual [2]. However, according to the newly revised criteria [32], it is important to distinguish RLS mimics, as we did in our study. Exclusion of RLS mimics and patients with secondary RLS could also have reduced the heterogeneity of the group. Finally, because this study was cross-sectional in nature, the cause-and-effect relationships between cerebrovascular factors and RLS are uncertain.

5. Conclusion

This study demonstrated that increased arterial stiffness was associated with RLS in acute ischemic stroke patients and that RLS was related to these patients' clinical outcomes. These findings suggest a new vascular pathophysiological mechanism of RLS and highlight its clinical importance in stroke patients.

Conflict of interest

The authors declare that there are no conflicts of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.03.027.

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