ORIGINAL ARTICLE

Effects of Idiopathic Restless Leg Syndrome on Intima-Media Thickness of Carotid Artery: A Case Control Study

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Abstract

Purpose: Restless legs syndrome is claimed to be associated with a higher risk of cardiovascular diseases. Intima-media thickness has been reported to be the most valuable surrogate marker and predictor of atherosclerosis progression and upcoming cardiovascular diseases. In this study, we aimed to evaluate the relationship between restless legs syndrome and intima-media thickness of the carotid artery.

Materials and Methods: In this case-control study, a total of 23 patients with restless legs syndrome without other known risk factors of cardiovascular diseases were evaluated with regard to the intima-media thickness of the carotid artery by employing a high-resolution B-mode ultrasound study. The findings of the ultrasound study between the case and the control group were compared and statistically analyzed.

Results: Intima-media thickness was revealed to be of a lower value in subjects with restless legs syndrome (0.79 ± 0.10) compared to the control group (0.88 ± 0.13). Also, our study showed that older age and the presence of hypertension directly correlates with intima-media thickness.

Conclusion: It can be concluded that restless legs syndrome is associated with a lower intima-media thickness.

Keywords: Restless Legs Syndrome; Intima-Media Thickness; Carotid Artery Ultrasound.

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1. Introduction

Restless Legs Syndrome (RLS), also known as Willis-Ekbom disease, is a common neurological complaint in which excruciating sensation and the bothersome urge to move lower limbs suffer patients when an absence of movement occurs and worsens at night [1, 2].

Dopaminergic dysfunction in the Central Nervous System (CNS) is revealed to play a pivotal role, albeit the main pathogenesis is still vague [3]. The foremost medications prescribed in RLS are dopaminergic drugs, one of the side effects of which, is the alteration in blood pressure and peripheral vessel status [4, 5]. Pregnancy, iron deficiency, drugs, and chronic renal disease are of principal etiologies attributed to secondary RLS. Primary or idiopathic subtypes of RLS are those without any associated background conditions other than genetics [6, 7]. Some of the aforesaid associations of secondary RLS can potentially contribute to a higher risk of atherosclerosis while genetic factors, which are counted as the most prevalent risk factor of the primary RLS, are proven to be less associated with atherosclerosis [8, 9].

Intima-Media Thickness (IMT) has been reported to be the most valuable non-invasive surrogate marker and predictor of atherosclerosis and future risk of Cardiovascular Disease (CVD) in imaging, which is measured employing high-resolution B-mode ultrasound examination [10].

Association between a variety of diseases and IMT has been assessed, yet studies focusing on the effects of RLS on atherosclerosis of the carotid artery as a predictor of cardiovascular diseases are scarce. To the best of our knowledge, the obtained results of similar studies on this topic were not in the same direction and were controversial. Considering the fact that this relationship in secondary RLS can be difficultly assessed due to the existence of confounding factors, we aimed to design a study in which patients with primary RLS are investigated with regard to the intima-media thickness of the carotid artery.

2. Materials and Methods

2.1. Patients

A total of 23 patients with RLS diagnosed based on IRLSSG (International Restless Legs Syndrome Study Group) criteria were enrolled in this case-control study implemented in Mehraeen Hospital, Tehran, Iran, from May 2020 to September 2022. All patients with RLS referred to Mehraeen neurology clinic were recruited for evaluation of eligibility for enrollment.

Patients with secondary RLS, as well as those suffering from concomitant known CVD, stroke, and vascular diseases were excluded from the study. Patients with diabetes mellitus and dyslipidemia, as some of the most relevant risk factors contributing to atherosclerosis and upcoming CVD, were also kept out.

According to "RLS rating scale", the scaling system for evaluating the severity of RLS, which is almost a quantitative categorization rather than a clinical categorization with verified prognostic importance, patients with just "severe" and "very severe" symptoms were included in the current study and those with mild and moderate symptoms were not included.

A group of 30 patients referred to the radiology ward for Focused Assessment with Sonography in Trauma (FAST) with no history of CVD, Diabetes Mellitus (DM), or vascular diseases were enlisted as the control group. Patients in the control group were matched for age and gender.

Participants' demographic information, weight, height, smoking, drug history, history of diabetes mellitus, and other neurovascular diseases were recorded using a questionnaire. Lab data were extracted from patients' latest examinations, all of which were obtained during the year before the commencement date of our study. The blood pressure of the patients was measured using a digital blood pressure monitor (Withings, Issy-les-Moulineaux, France) after preparing a tranquil environment. Cut off range for hypertension was set as ≥135mmHg and ≥85mmHg for systolic and/or diastolic blood pressure, respectively. International approved diagnostic criteria were applied for the detection of patients with DM and dyslipidemia [11-13].

The objectives of the study were explained to the research participants, and the patients were included in the study after obtaining written informed consent about the outlined sampling method. Also, all ethical considerations of Helsinki were observed.

2.2. Procedures

2.2.1. IMT Measurements

IMT measurements were taken employing high-resolution B-mode grayscale images provided by Mindray Resona I9 ultrasound scanner (Mindray Medical International Limited, Guangdong, China) equipped with a multi-frequency linear probe.

Carotid artery evaluation was performed bilaterally in a supine position, with minimal neck extension and a minimal tilt of the head toward the opposite side of the examining side. The examination frame was selected to be a continuous 10-millimeter-length portion of the Common Carotid Artery (CCA) that ends up at the point of 20mm proximal to the carotid bulb.

IMT, as the distance between the innermost two layers of the artery wall, was measured respecting the approved guideline presented by Mannheim Carotid Intima-Media Thickness and Plaque Consensus (Figure 1) [14, 15]. If the examination frame contains an atherosclerotic plaque which had been defined as a mural structure protruding ≥0.5mm into the lumen of the artery, the plaque would not be calculated as IMT and would be dismissed.

Maximum IMT was measured bilaterally and thickness of the side with the greater IMT was recorded.

2.2.2. Statistical Analysis

The data were analyzed employing SPSS v26 for Windows (SPSS Inc., Chicago, Ill., USA) with a significance level considered less than 0.05. Quantitative data were recorded as numbers and percentages. Categorical variables were analyzed using the Chi-square test and normally distributed continuous variables were compared utilizing a t-test. A multiple-regression model was used to explore the interplay among different variables in predicting IMT value. Additionally, a multivariable logistic regression model was used for predicting IMT considering RLS and other covariate/confounding variables.

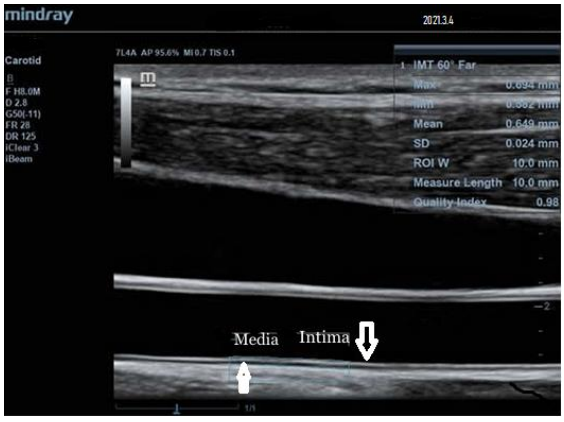

Figure 1. B-mode sagittal view of common carotid artery proximal to the bifurcation. The IMT was measured from the leading edge of the lumen-intima interface (larger arrow) to the leading edge of the media-adventitia interface (smaller arrow) of the far wall

3. Results

The demographic characteristics of the subjects are depicted in Table 1. A total of 53 subjects consisting of 23 clinically diagnosed primary RLS patients, as well as 30 control subjects were enrolled in this study.

The mean age in the case and the control group was revealed to be 57.20 ± 12.39 and 57.03 ± 10.46 (Table 1). No significant difference was detected in demographic characteristics and frequency of hypertension between the case and the control group (Table 1).

Table 1. Demographic characteristics and IMT of RLS and the control group

	RLS patients	Control group	p-value
Mean age ± SD, years	57.20 ± 12.39	57.03 ± 10.46	0.66
Male/Female ratio	13/10	17/13	0.45
BMI, kg/m^2	26.97 ± 2.51	27.11 ± 3.87	0.23
Hypertension	8(35%)	11(37%)	0.19
Cigarette smoker	6(26%)	7(23%)	0.11
Mean IMT ± SD, mm	0.79 ± 0.10	0.88 ± 0.13	0.03

Patients with RLS revealed to have a significantly lower mean IMT (0.79 ± 0.10) compared to the control group (0.88 ± 0.13) with a p-value of 0.03.

Age, RLS, hypertension, smoking, and BMI were evaluated as predictive of IMT measures. The results, which are depicted in Table 2 revealed age, RLS, and hypertension as possible predictors. The mean IMT was greater in older patients and patients with hypertension.

However, the RLS diagnosis correlated with a lower IMT value (Table 2).

Table 2. Correlation of IMT with other variants with multiple linear regression analysis

	Coefficients	Standard Error(SE)	p-value
Age	0.004	0.001	0.000
RLS	-0.065	0.024	0.000
Hypertension	-0.079	0.016	0.017
Cigarette smoking	0.019	0.047	0.41
BMI	–0.013	0.040	0.11

In order to determine the impact of RLS and other variables on IMT measures, as a dependent variable to show binary outcome, we performed a multivariable logistic regression model. Only RLS and HTN remained as a predictive variable of IMT and the impact of age was not proved. (Table 3). RLS and hypertension showed to result in higher IMT measures.

Table 3. Multivariable logistic regression for the prediction of IMT

Parameters	P-value	OR (95%CI)
Age (years)	0.85	1.04 (0.82-1.12)
Male gender (yes or no)	0.06	1.21 (0.98-1.30)
BMI (kg/m^2)	0.63	1.09 (1.01-1.18)
Cigarette Smoking (yes or no)	0.07	1.18 (0.89-1.35)
HTN (yes or no)	0.00	1.91 (1.45-2.18)
RLS (yes or no)	0.01	0.71 (0.55-0.82)

4. Discussion

In the current study, we investigated the relationship between idiopathic RLS and IMT in order to predict the potential future risk of CVD. An abundance of studies suggested that IMT value can be supposed as a surrogate marker for subclinical atherosclerosis and CVD.

Our results revealed that the IMT value was significantly lower in the RLS group compared to the control group. On the other hand, multiple studies insisted on the high prevalence of CVD in patients with RLS. It seems like the aforementioned inconsistency is owing to the fact that we primarily kept out patients with DM, dyslipidemia, and secondary RLS; moreover, we did not consider patients with Periodic Limb Movements Disorder (PLMD) as a critical confounding factor, which might be regarded in those studies [16].

Impaired dopaminergic metabolism as an etiology is attributed to RLS [17]. An identical hypothesis exists for Parkinson's Disease (PD) [18], which prompts a similar perspective of both diseases with regard to treatment approaches and prognosis. As so, shoulder-to-shoulder evaluation of these two diseases could be of noticeable importance. Studies on atherosclerosis progression in PD showed a lower risk of atherosclerosis in these patients which is along the same line as our results for patients with RLS [19]. Few uncertain assumptions have been made about the reasons for lower atherosclerosis incidence in PD, the two cardinal points of which include the protective nature of impaired dopamine metabolism, and hypotension induced as a side effect of dopamine agonist treatments [20].

Previously, in several studies, it was observed that IMT value was greater in patients with hypertension or pre-hypertension status compared to those without hypertension [21–23]. Similarly, we found that those with hypertension could potentially have a higher IMT value which was consistent with the results of other research.

To the best of our knowledge, to date, only two studies have assessed the potential relationship between the primary RLS and the IMT, which were conducted by Park *et al.* [24], in 2012 and by Janes *et al.* [25], in 2021. The latter showed higher IMT values in patients with RLS. Nonetheless, in the former, IMT was revealed to be of lower values in patients with idiopathic RLS. Likewise, in the current study, lower IMT values were detected in RLS patients. This inconsistency in the achieved results of different studies might confer with some differences in study design conducted by Janes et al. They had implemented different exclusion/inclusion criteria by which patients with PLMD (periodic limb movement disorder) were enrolled, but in our investigation, we did not consider patients with overt PLMD. Additionally, a dissimilar measurement approach was used by Janes et al., as they assessed IMT in 1 and 3 cm distance from the carotid bulb while we

did it in about 2 cm from the bulb of the carotid artery. In the current study, IMT measurements were performed by an expert radiologist manually, while software-assisted measurement methods provided by artificial intelligence were utilized in Park's and Jane's studies. Also, other factors could have potentially interfered with the results; in Jane's study, most of the patients had moderate to severe symptoms of RLS whilst we selected patients with severe and very severe symptoms and this can suggest the potential effect of disease severity on the IMT increase. It is of great importance to mention that neither of the studies conducted by Jane and Park nor ours, had considered the possible impact of different medications and the duration of the disease. Lacking data about disease duration is an unavoidable part of RLS since patients claim vague statements about the date of symptoms' onset. On the other hand, varied medications could lead to varied effects on IMT, which were not identical in each patient.

Contrary to our results, in Park's study, hypertension did not show a correlation with IMT values. This discrepancy might be due to the fact that although they had excluded patients with concurrent PLMD, they had not excluded patients with DM and dyslipidemia which could have separate potential impacts on the blood pressure status and atherosclerosis progression [26–28].

We encountered limitations during the study period. This was a single-center study and selection bias was inevitable. Although patients recruited for this study were referred to a referral center, collecting subjects fulfilling all of our inclusion criteria was difficult and has led to the small sample size of the current study. As previously mentioned, we did not consider treatment approaches in our study that might have affected the results, especially due to its impact on blood pressure. Also, according to the fact that assessing all of the possible confounding variables was not attainable with a sole questionnaire and required detailed investigation, all confounding factors were not feasible to be evaluated. Hence, it is recommended that studies with greater sample sizes, consideration of the effects of the different medications, and all confounding factors be designed.

5. Conclusion

Our results show that patients with primary restless legs syndrome have a lower intima-media thickness compared to the control group and it can possibly decline RLS as a predictive factor for future vascular damage.

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