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Elevated Cardiovascular Disease Risk in Patients with Restless Legs Syndrome

ABSTRACT

Objective: There are studies in the literature that link restless legs syndrome with increasing cardiovascular disease risk. The reason for this was that increased sympathomimetic activation in restless legs syndrome causes tachycardia, hypertension, and autonomic instability. We intended to assess the cardiovascular disease risk in patients with restless legs syndrome using electrocardiogram parameters.

Methods: The present investigation compared the demographic characteristics, electrocardiogram variables, and lab results of 40 patients diagnosed with restless legs syndrome with 43 healthy controls.

Results: Restless legs syndrome patients had a higher frontal QRS-T angle than healthy control patients. Restless legs syndrome patients had lower hemoglobin, neutrophil, lymphocyte, basophil, albumin, and high-density lipoprotein cholesterol levels. There was a significant increase in eosinophil, platelet, C-reactive protein, total cholesterol, low-density lipoprotein cholesterol, platelet-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, and C-reactive protein-to-albumin ratio values in patients with restless legs syndrome. The frontal QRS-T angle is highly correlated with the neutrophil-to-lymphocyte ratio ($P = .001$). Similarly, monocyte-to-lymphocyte ratio and C-reactive protein-to-albumin ratio values were significantly correlated with frontal QRS-T ($P = .011$ and $P = .24$).

Conclusion: The fact that frontal QRS-T angle and neutrophil-to-lymphocyte ratio were correlated in the restless legs syndrome group in our study suggests that the inflammatory process may have increased the risk of cardiovascular disease in restless legs syndrome patients. Our findings show that the frontal QRS-T angle is high in restless legs syndrome patients. We conclude that C-reactive protein-to-albumin ratio, neutrophil-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio are higher in the restless legs syndrome patient group and are related to cardiovascular disease risk.

Keywords: Restless legs syndrome, electrocardiogram, cardiovascular diseases, C-reactive protein, albumin

Introduction

Restless legs syndrome (RLS) is a disease of unknown etiology. Due to the uncomfortable feeling in the legs, patients have a great urge to move the lower extremities. It happens especially while sitting or lying down, and the complaints increase overnight. Patients have subjective complaints such as tingling, burning, pins and needles in the legs, and muscle tension. The prevalence of RLS rises as one ages and is estimated to be between 5% and 10%.[1]

Studies reporting the relationship between RLS and cardiovascular disease risk are available in the literature. The reason for this was that increased sympathomimetic activation in RLS causes tachycardia, hypertension, and autonomic instability. In addition, it is proposed that the risk of cardiovascular disease may be increased as a result of sleep fragmentation and insomnia in RLS patients.[2]

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The frontal QRS-T (fQRS-T) angle is an indicator showing ventricular depolarization and repolarization heterogeneity, and it shows the angular difference between QRS and T axes in the frontal plane. Several researches have reported that a wide fQRS-T angle increases sudden cardiac death.[3] The present investigation compared the demographic characteristics, electrocardiogram (ECG) variables, and lab results of 40 patients diagnosed with RLS with 43 healthy controls (HCs). We intended to assess the cardiovascular disease risk in patients with RLS using ECG parameters.

Methods

Study Design

Adıyaman University Non-Interventional Clinical Researches Ethical Review Committee approved the research methodology (Registration Date: 2021-02-16; IRB Number: 2021/02-39). The work was accomplished with the written agreement of all volunteers, and the Declaration of Helsinki was adhered to throughout the research procedure. The investigation is descriptive and cross-sectional in nature.

Study Group

This investigation involved 40 RLS patients identified according to updated International Restless Legs Syndrome Study Group guidelines criteria.[4] The study did not include participants with diabetes mellitus, hypertension, ischemic heart disease, arrhythmias, and valve disease. Forty-three HCs without mental illness or any organic condition were enrolled in the study. Those not between 18 and 65 years old were exempted from the study. Those in the control group did not use any regular medication. Eighteen of the RLS patients were using pramipexole. Restless legs syndrome patients were not using other drugs regularly. Sociodemographic features, smoking habits, complete blood count, biochemistry, blood pressure, and ECG results of the study subjects were recorded.

Electrocardiogram Analysis

The participants were monitored by a 12-lead ECG (Nihon Kohden, Tokyo, Japan) in a supine posture. The software generated the results of the QRS and QT intervals. The period between the appearance of a Q wave and the termination of an S wave is called the QRS duration. The QT interval is the period following the initiation of the QRS wave and the end of the T wave. The heart rate impacts how wide the QT interval is (rising heart rates decrease QT intervals, falling heart rates increase QT intervals). Due to this, it is necessary to customize it in accordance with the heart rate. The corrected QT (QTc) interval is estimated by assuming a constant heart rate of 60 per minute. The QRS and T axes were provided in the ECG display, and the precise gap between the QRS-axis and the T-axis was utilized in the recording to quantify the fQRS-T angle.

Laboratory Analysis

Blood was collected during the patient's visit to the clinic. An Architect c8000 Chemistry System (Abbott Diagnostics, Abbott, IL, USA) was employed to calculate total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and fasting triglyceride levels. An automated hematology analyzer CELL-DYN Ruby (Abbott Diagnostics, Abbott Park, IL, USA), was utilized to count white blood cells (WBC), including lymphocytes, platelets, and hemoglobin. The ratio of neutrophils to lymphocytes (NLR), monocytes to lymphocytes (MLR), and platelets to lymphocytes (PLR) was calculated. C-reactive protein (CRP)-to-albumin ratio (CAR) and neutrophil-to-albumin ratio (NAR) were derived. The atherogenic index of plasma (AIP) is estimated as a log(fasting triglyceride/HDL-C).

Statistical Analysis

Data were evaluated with Statistical Package for Social Sciences (SPSS) version 26.0 (IBM SPSS Corp.; Armonk, NY, USA). Mean values and standard deviations were computed to express numerical parameters, and percentages were employed to express qualitative parameters. Whether the data conformed to a normal distribution was determined with the Kolmogorov–Smirnov test. Descriptive statistics that fit the normal distribution were expressed as mean (standard deviation). Descriptive statistics that did not fit the normal distribution were displayed as median [min–max]. Independent sample *t*-tests were conducted for continuous numerical variables. Mann–Whitney *U* tests were done for discontinuous numerical parameters. Chi-square tests were run to examine qualitative data. Spearman correlation coefficient was run to examine the association between fQRS-T angle, inflammatory parameters, and age. Statistical significance level was accepted as $P < .05$.

Results

The fQRS-T angle was wider in RLS patients than in HC (Table 1). The comparison of laboratory parameters is presented in Table 2. Accordingly, hemoglobin, neutrophil, lymphocyte, basophil, albumin,

Table 1. Comparison of Sociodemographic and ECG Parameters of Patients with RLS and Healthy Controls

	RLS Patients (n = 40) n (%)	HC (n = 43) n (%)	*P*
Age	37.98 (SD = 7.25)	38.68 (SD = 6.97)	.725[a]
Gender			.903[c]
Female	21 (52.5)	22 (51.2)	
Male	19 (47.5)	21 (48.8)	
Smoking	17 (42.5)	16 (37.2)	.623[c]
Heart rate, bpm	81 [62-124]	76 [54-115]	.082[b]
QRS, ms	89 [74-110]	88 [68-102]	.319[b]
QT, ms	363.10 (SD = 29.68)	363.07 (SD = 25.79)	.996[a]
QTc, ms	408.50 [377-480]	398 [366-485]	.067[b]
Frontal QRS-T angle (°)	48.55 (SD = 25.34)	23.19 (SD = 22.18)	***<.001***[a]

[a]Independent *t* test was used; [b]Mann–Whitney *U*-test was used; [c]Chi-square test was used.
$P < .05$ was accepted as statically significant.
ECG, electrocardiogram; HC, healthy controls; QTc, corrected QT interval; RLS, restless leg syndrome.

MAIN POINTS

- *Restless legs syndrome increases the risk of cardiovascular disease by causing low sleep quality, daytime sleepiness, mental tension and restlessness, and changes in autonomic activity.*
- *Impairment of immune system functions and increase in inflammatory processes can be observed in restless legs syndrome patients.*
- *Based on the relationship between inflammation markers and frontal QRS in this study, it can be said that inflammation increases the risk of cardiovascular disease in restless legs syndrome patients.*

Table 2. Comparison of Laboratory Parameters of Patients with RLS and HC

	RLS Patients (n = 40)	HC (n = 43)	*P*
Hemoglobin, mg/dL	13.85 (SD = 1.90)	15.02 (SD = 1.95)	***.007***[a]
WBC, 10^3/μL	7.73 [4.07-12.9]	7.89 [4.42-14.34]	.392[b]
Neutrophil, 10^6/μL	4.36 [1.92-9.72]	4.33 [2.08-9.09]	.877[b]
Lymphocyte, 10^3/μL	2.20 (SD = 0.58)	2.56 (SD = 0.81)	***.026***[a]
Monocyte, 10^3/μL	0.62 (SD = 0.21)	0.53 (SD = 0.21)	.090[a]
Eosinophil, 10^3/μL	0.17 (SD = 0.13)	0.12 (SD = 0.10)	***.010***[a]
Basophil, 10^3/μL	0.04 (SD = 0.04)	0.08 (SD = 0.04)	***<.001***[a]
Platelet, 10^3/μL	269 [156-428]	233 [172-343]	***<.001***[b]
CRP, mg/dL	0.25 [0.10-0.60]	0.10 [0.10-0.20]	***<.001***[b]
Albumin, mg/dL	4.20 [3.30-4.80]	4.30 [3.60-5.30]	***.006***[b]
Total cholesterol, mg/dL	182 [94-284]	169 [109-307]	***.029***[b]
LDL-C, mg/dL	106.15 (SD = 34.69)	76.37 (SD = 29.45)	***<.001***[a]
HDL-C, mg/dL	50.38 (SD = 14.06)	63.19 (SD = 12.98)	***<.001***[a]
Triglyceride, mg/dL	90 [39-888]	104 [45-737]	.788[b]
NLR	2.04 [0.64-6.08]	1.81 [0.90-5.89]	.444[b]
PLR	129.22 [67.93-307.44]	95.94 [59.42-324.26]	***.001***[b]
MLR	0.25 [0.11-0.79]	0.22 [0.01-0.93]	***.020***[b]
CAR	0.05 [0.02-0.14]	0.02 [0.02-0.05]	***<.001***[b]
NAR	1.06 [0.44-2.31]	1.03 [0.48-2.11]	.506[b]
AIP	0.39 (SD = 0.42)	0.25 (SD = 0.31)	.186[a]

[a]Independent *t*-test was used; [b]Mann–Whitney *U* test was used.
P < .05 was accepted as statically significance.
AIP, atherogenic index of plasma; CAR, C-reactive protein-to-albumin ratio; CRP, C-reactive protein; HC, healthy controls; HDL, high density cholesterol; LDL-C, low density cholesterol; MLR, monocyte-to-lymphocyte ratio; NAR, neutrophil-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; RLS, restless leg syndrome; WBC, white blood cells.

Table 3. Correlation Analyses of Frontal QRS-T Angle with Age and Inflammatory Parameters in RLS Patients

	Frontal QRS-T Angle
Age	*r* = 0.107
	P = .509
NLR	*r* = 0.623
	P ≤ .001
PLR	*r* = 0.223
	P = .167
MLR	*r* = 0.397
	P = .011
CAR	*r* = 0.355
	P = .024
NAR	*r* = 0.161
	P = .146
AIP	*r* = −.218
	P = .178

Spearman correlation coefficient was used. *P* < .05 was accepted as statically significant.
AIP, atherogenic index of plasma; CAR, C-reactive protein to albumin ratio; MLR, monocyte-to-lymphocyte ratio; NAR, neutrophil-to albumin ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; RLS, restless leg syndrome.

and HDL-C values were statistically lower in RLS patients. Eosinophil, platelet, CRP, total cholesterol, LDL-C, PLR, MLR, and CAR values were significantly higher in RLS patients. The correlation analysis of fQRS-T angle with age and inflammation parameters in RLS patients is shown in Table 3. Accordingly, fQRS-T and NLR are highly correlated ($P < .001$). Monocyte-to-lymphocyte ratio and CAR values were also significantly correlated with fQRS-T ($P = .011$ and $P = .024$, respectively).

Discussion

Our study is the first in the literature investigating the fQRS-T angle on ECG in the RLS patient group. The fQRS-T angle was significantly wider in the RLS patient group.

Aro et al.[5] the first to analyze the connection between fQRS-T angle and cardiovascular death, stated that a wide fQRS-T angle was predictive of arrhythmic deaths. However, it was not crucial in demonstrating non-arrhythmic deaths.[5] The same investigators found that those with wide fQRS-T angles had a higher cardiac risk than those with long QT syndrome or left ventricular hypertrophy, which is thought to show the best mortality risk on ECG.[6] This increased risk of cardiovascular disease is likely related to alterations in the T wave axis, and an atypical T wave axis carries a double risk of arrhythmic death. Beyond the current study's results, previous studies have indicated that T-axis shift is an important risk factor for cardiac mortality in the elderly population.[7]

It is thought that the QRS-axis shift is commonly associated with left anterior hemiblock and carries a more benign prognosis regarding cardiac risk. As a consequence, the predictive meaning of the fQRS-T angle is that it shows the ventricular repolarization abnormality due to the abnormal T-axis. As a result, the wide fQRS-T angle may predispose to ventricular conduction abnormalities, which can be life-threatening. It has been shown that there is a tendency to ventricular arrhythmias in patients with cardiac disease and those with wide fQRS-T angles. A study conducted in a population undergoing implantable cardioverter-defibrillator (ICD) due to nonischemic cardiomyopathy showed that those with fQRS-T angle >90 are an independent indicator in predicting appropriate shock, resuscitated cardiac arrest, and all-cause death.[8] In another ICD study conducted on patients with ischemic heart disease, a wide fQRS-T angle indicated ventricular arrhythmias.[9]

In today's computerized ECG systems, the spatial QRS-T angle cannot be included in the output. Conversely, the QRS and T axes are instantly visible from a standard 12-lead ECG, and the fQRS-T angle is simply estimated. The fQRS-T angle threshold value has been evaluated differently according to various studies, and the ideal cutoff level may also vary between genders. On the basis of prior researches, fQRS-T angle ≥100 was defined as abnormal.[5]

Restless legs syndrome is a sensory-motor condition involving the need to move the legs, generally followed by discomfort and sleep disturbance.[10-12] Patient complaints are prominent in the evening and usually occur at rest or in motionless situations, and partial or complete relief can be achieved by walking and leg movements.[11-13] It has been reported that RLS is twice as frequent in females as in males.[12] Sleep disturbance accompanies 60%-90% of RLS patients.[14] Although Dr. Karl Ekbom first described it in 1945, the syndrome's

pathophysiology has not been determined.[15] Although iron deficiency, dopaminergic activation imbalance, and genetic factors are at the forefront of the pathogenesis of the disease, a growing body of literature supports the idea that inflammation also has a part in the pathogenesis.[11-13,16,17]

The higher incidence of RLS in diseases like rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel diseases, and HIV infection supports the role of inflammatory mechanisms.[17,18] Circulating leukocytes are essential in the immune system's response to systemic inflammation. It has been reported that a decrease in lymphocyte number and an increase in the neutrophil number are associated with the severity of the clinical condition in inflammatory diseases. It has been stated that NLR can be taken as a more appropriate indicator of inflammation than the change in the number of neutrophils or lymphocytes.[19,20] It has been previously shown that platelets interact with leukocytes and are effective in releasing mediators that trigger inflammation.[21] It was reported that erythrocyte distribution width (RDW) level is positively correlated with CRP and erythrocyte sedimentation rate (ESR) levels.[22] Also, it has been reported in other studies that monocytes are involved in the release of pro-inflammatory cytokines, that an increase in HDL-C has an anti-inflammatory effect, and that an increase in uric acid and bilirubin levels causes inflammation.[23] Several studies investigated PLR in systemic inflammatory diseases, and it was thought that PLR could be used as an inflammatory indicator and could be associated with disease severity and prognosis.[24-26]

Many studies point to the connection between RLS and inflammatory markers and the elevated risk of hypertension, cerebrovascular, and cardiovascular issues in those with RLS. Jung-Won Shin et al[27] investigated differentially expressed proteins and revealed the relationship between complement C3, complement C4A, alpha-2 HS glycoprotein, alpha-2 macroglobulin precursor with iron deficiency, and inflammatory pathways in patients with RLS.[27] Two cross-sectional studies in a large cohort reported a strong relationship between RLS and cardiovascular diseases.[28,29] Olgun Yazar et al[30] showed higher CAR values in RLS patients.

Studies have reported that RLS is 4 times more common in multiple sclerosis (MS) patients than in the normal population.[31] This increase in the prevalence of RLS in MS with immunological activation supports the hypothesis that inflammatory processes play a role in the pathogenesis of RLS. In MS, cytokines such as interleukin-6 and tumor necrosis factor-α are thought to cause iron reduction in some brain areas by causing iron uptake into the cell. It is suggested that RLS symptoms may develop accordingly.[32]

The fact that fQRS-T angle and NLR were correlated in the RLS group in our study suggests that the inflammatory process may have increased the risk of cardiovascular disease in RLS patients. In addition, the correlation of CAR and MLR with fQRS-T angle may indicate the importance of calculating novel inflammation indicators and fQRS-T angle for cardiovascular risk determination.

The most substantial limitations of our study were that it was a monocentric, retrospective study, and the sample size was relatively low. In our opinion, examining venous blood samples taken in the morning hours in this study is a limitation. Since RLS symptoms occur primarily at night, it would be more appropriate to examine blood parameters at night in these patients.

As a result, we concluded that the fQRS-T angle was high in RLS patients, and we concluded that CAR, NLR, and MLR were higher in the RLS patient group and correlated with the elevated risk of cardiovascular disease.

Ethics Committee Approval: *Ethical committee approval was received from the Adıyaman University Non-Interventional Clinical Researches Ethical Review Committee (Approval No: 2021/02-39).*

Informed Consent: *Written informed consent was obtained from all participants who participated in this study.*

Peer-review: *Externally peer-reviewed.*

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