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Heart rate variability and analysis of rhythm in patients with restless legs syndrome: A prospective case-control study

Huzursuz bacaklar sendromlu hastalarda kalp hızı değişkenliği ve ritim analizi: Bir prospektif olgu-kontrol çalışması

Nuray Can Usta[1], Vildan Altunayanoğlu Çakmak[2], İsmet Durmuş[3], Murat Topbaş[4], Zeynep Kazaz[5], Oğuzhan Ekrem Turan[6]

Abstract

Aim: To investigate the involvement of cardiac autonomy by heart rate variability (HRV) analysis in patients with restless legs syndrome (RLS).

Methods: Patients with RLS and age/sex matched healthy controls were included in this prospective case-control study. The diagnosis of RLS was made according to the criteria determined by the International Restless Legs Syndrome Study Group. Demographic data and severity of disease were recorded. The HRV analysis was performed with a 24-hour electrocardiographic Holter monitoring in all patients and the control group.

Results: Sixty-five (of them, 50 female) patients and 58 (of them, 45 female) healthy individuals were enrolled into the study. Patients and control groups were similar for age and gender. No difference was found in the HRV analysis, except that the standard deviation of NN intervals (SDNN) at night was lower when RLS patients and the control group were compared (p=0.03). The HRV analyzes were compared according to disease severity, SDNN at night was significantly different between groups (p=0.03). In the pairwise comparison, the difference between the severe and very severe groups was significant (p=0.01) and severe group was lower than very severe group.

Conclusions: In the present study which evaluate the cardiac autonomic system with HRV in patients with RLS, a decrease in parasympathetic nervous system was found at night time.

Keywords: Restless legs syndrome, heart rate variability, autonomic dysfunction.

Öz

Amaç: Kalp hızı değişkenliği (KHD) analizi ile huzursuz bacaklar sendromu (HBS) hastalarında kardiyak otonomik tutulumu araştırmak.

Yöntemler: Prospektif olgu-kontrol çalışması tipindeki bu çalışmaya HBS hastaları ve yaş/cinsiyet uyumlu sağlıklı kontroller dahil edildi. HBS tanısı Uluslararası Huzursuz Bacaklar Sendromu Çalışma Grubu tarafından belirlenen kriterlere göre konuldu. Demografik veriler ve hastalığın şiddeti kayıt edildi. Tüm hasta ve kontrol gruplarında 24 saatlik elektrokardiyografik Holter monitörizasyonu ile HRV analizi yapıldı.

Bulgular: Çalışma grubunda 65 (50'si kadın), kontrol grubunda 58 (45'i kadın) hasta mevcuttu. Hastalar ve kontrol grupları yaş ve cinsiyet açısından benzerdi. HRV analizinde HBS hastaları ve kontrol grubu karşılaştırıldığında SDNN gece değerinin düşük olması dışında fark bulunmadı (p=0,03). KHD analizleri hastalık şiddetine göre karşılaştırıldığında SDNN gece değeri gruplar arasında anlamlı farklılık gösterdi (p=0,03). İkili karşılaştırmada şiddetli ve çok şiddetli gruplar arasındaki fark anlamlıydı (p=0,01) ve şiddetli grup, çok şiddetli gruba göre daha düşüktü.

Sonuç: HBS'li hastalarda HRV ile kardiyak otonom sistemi değerlendiren bu çalışmada, gece saatlerinde parasempatik sinir sisteminde azalma saptanmıştır.

Anahtar Kelimeler: Huzursuz bacaklar sendromu, kalp hızı değişkenliği, otonomik disfonksiyon.

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[1] University of Health Sciences, Trabzon Kanuni Training and Research Hospital, Department of Neurology, Trabzon, Turkey.

[2] Karadeniz Technical University, School of Medicine, Department of Neurology, Trabzon, Turkey.

[3] University of Health Sciences, Ahi Evren Thoracic and Cardiovascular Surgery Training and Research Hospital, Department of Cardiology, Trabzon Turkey.

[4] Karadeniz Technical University, School of Medicine, Department of Public Health, Trabzon, Turkey.

[5] Yıldırım Beyazıt University, Yenimahalle Training and Research Hospital, Department of Cardiology, Ankara, Turkey.

[6] Dokuz Eylül University Faculty of Medicine, Department of Cardiology, İzmir, Turkey.

NCU: 0000-0001-9238-1194
VAÇ: 0000-0003-2828-2583
İD: 0000-0001-8020-2945
MT: 0000-0003-4047-4027
ZK: 0000-0002-9250-4198
OET: 0000-0003-3557-1682

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Sorumlu yazar / Corresponding author:
Nuray Can Usta
Adres/Address: Trabzon Kanuni Eğitim ve Araştırma Hastanesi, Numune Kampüsü, Inonu Mah., 61250, Trabzon, Turkey.

e-mail: dr.nuraycan@hotmail.com
Tel/Phone: :+904622302300

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Introduction

The restless legs syndrome (RLS) is a movement disorder characterized by an abnormal sensation on the extremities, especially on legs. Complaints occur especially at rest or at night and they are relieved by movement [1]. There are two clinical forms of RLS including primary RLS and secondary RLS. Primary RLS appear in young adults with family history and secondary RLS appear in older adults with comorbidities such as iron deficiency, chronic renal failure or neurological diseases [2]. The prevalence of RLS varies between 5% and 10% [3]. The prevalence of RLS increases with age and predominance in female gender [4].

Although the pathophysiology of RLS is not fully explained, radiological examinations have revealed the dopaminergic hypofunction [5]. Spectroscopy studies suggested the presence of a decrease in postsynaptic D2 receptor number and affinity [6]. In PET studies; significant reductions in dopamine uptake have been demonstrated in the caudate nucleus and putamen [7].

Clinical studies suggested that RLS may also be a risk factor for cardiovascular diseases [8]. Many studies have reported a significant relationship between increased heart rate and cardiovascular mortality in RLS [9]. Increased nocturnal blood pressure and heart rate, hypertension, cardiovascular disease, and cerebrovascular disease frequency in RLS patients suggest autonomic dysfunction in RLS patients [10]. The sympathetic and parasympathetic nervous systems of the autonomic nervous system modulate the heart rate, and the changes in the heart rate over time provide information about the functioning of the autonomic nervous system [11]. Heart rate variability (HRV) is one of the noninvasive methods used to identify disorders affecting the autonomous system by quantitatively measuring the sympathovagal balance and the change between two heart beats [12, 13]. The aim of this study was to examine cardiac autonomic involvement by HRV analysis in RLS patients.

Material and methods

After local Institutional Review Board approval (2011/29), this prospective case-control was designed as a monocentric study and followed the principles of the Declaration of Helsinki. The study was performed between 01.03.2011-30.01.2012 in Karadeniz Technical University Sleep Polyclinic. The RLS patients and age/sex matched healthy controls were included in the study. Written informed consent were taken from the patients.

Inclusion criteria for the study group; regardless of etiology diagnosis of RLS and patients diagnosed with RLS should not have received any medical treatment for this disease or they should have had a break from their treatment for at least 3 months. Exclusion criteria for study group were; (1) age below 18 years, (2) presence of any sleep disorder (i.e. narcolepsy, sleep apnea); (3) any previously known cardiac disease (i.e. previous myocardial infarction, cardiac failure, cardiac arrhythmia); (4) use of medications that may affect the cardiac rhythm (i.e. anti-arrhythmic or anti-epileptic); (5) mental limitation to perceive the study; (6) disease duration of less than 1 year.

Inclusion criteria for control group were: (1) age above 18 years, (2) being healthy (3) having no exclusion criteria for study group.

Neurological examination and nerve conduction studies of the patients were performed. The diagnosis of RLS was made according to the criteria determined by the International Restless Legs Syndrome Study Group (IRLSSG) [14]. Demographic data of patients such as age, gender, concomitant diseases (hypertension, diabetes, hyperlipidemia, thyroid disease), and duration of the disease are recorded. The severity of RLS symptoms was assessed by using the IRLSSG rating scale (IRLS) with a sum of scores as mild (0–10), moderate (11–20), severe (21– 30), and very severe (31–40) [15].

The HRV analysis was performed with 24-hour electrocardiographic Holter monitoring in the patient and control groups of the study. Normal daily activities were monitored during Holter monitoring; the patient was instructed to avoid wetting the device and passing from X-ray devices. The whole day (24 hours) and night (6:00 PM-6:00 AM)/daytime (06:00 AM-6:00 PM) Holter recording of the patients were reviewed under following parameters; time domain parameters used the standard deviation (SD) of all normal to normal (NN) intervals (SDNN), the mean of the deviation of the 5-minute NN intervals over the entire recording (SDNN index), the square root of the mean squared differences of successive NN intervals (rMMSD), the proportion of adjacent RR intervals differing longer than 50 milliseconds in the 24-hour recording (pNN50) while frequency domain parameters used high frequency (HF) component (0.15–0.40 Hz), a low frequency (LF) component (0.04–0.15 Hz), very low frequency (VLF) component (0–0.4 Hz), Total Power (TP) (0–0.4 Hz) and LF/HF ratio [16]. Time domain parameters reflect both parasympathetic and sympathetic activities and are usually calculated as 24 hours. Frequency domain parameters usually provide information about the data in five-minute recordings. The TP is strongly associated with the risks of sudden cardiac death and all-cause death after myocardial infarction; VLF is an additional indicator of sympathetic function; LF reflects sympathetic and parasympathetic activities in short-term measurements and sympathetic activities in long-term measurements, HF reflects the parasympathetic or vagal activity of the autonomic nervous system. A higher LF/HF ratio means increased sympathetic activity or decreased parasympathetic activity [17].

Statistical Analysis

The statistical analysis was performed through SPSS for Windows (version22.0). Descriptive analyses were presented by mean ± standard deviation. Quantitative data distribution was tested with the Shapiro Wilk test and data distribution was proper for non-parametric test. The Mann-Whitney U test was used for quantitative comparison of two independent groups. The Kruskal Wallis test was used for three independent groups. Bonferroni correction was used for pairwise comparisons. Chi square test was used to compare the qualitative data. Spearman's correlation analysis was used to examine the association of two quantitative data. Any p-value below 0.05 ($p<0.05$) was considered as statistically significant.

Results

Totally 123 participants were included in the study. There were 65 (50 females, 15 males) patients in the study group and 58 (45 females, 13 males) individuals in the control group ($p=0.932$). The mean age was 49±12.2 years in the study group and 46±10.7 years in the control group ($p=0.173$). The concomitant diseases were hypertension in 17 (26.4%) patients, thyroid disease in 9 (9.2%) patients, diabetes mellitus in 5 (7.7%) patients, and hyperlipidemia in 4 (6.2%) patients. The mean disease duration was 7.12±7.24 (1-44) years. Neurological examination and neural conduction studies of the patients included in the study were within normal limits.

Table 1. Heart rate variability parameters in restless legs syndrome and control group.

Parameter	RLS severity groups				RLS Groups (n=65)	Control group (n=58)	p
	Moderate RLS (n=18)	Severe RLS (n=36)	Very-severe RLS (n=11)	p			
SDNN (total), ms	151.0±42.8	134.7±35.4	150.8±24.6	0.102	141.9±36.5	144.8±43.9	0.275
SDNN (daytime), ms	129.0±35.1	130.7±36.0	133.1±23.2	0.681	130.6±33.5	131.3±37.5	0.773
SDNN (night), ms	135.2±46.4	115.4±26.8	144.7±31.5	0.037	125.8±35.6	137.5±41.2	0.037
rMSSD (total), ms	31.5±10.3	29.4±12.8	34.0±12.6	0.260	30.8±12.1	32.9±12.8	0.360
rMSSD daytime),ms	28.0±8.6	27.7±12.7	30.2±13.0	0.534	28.2±11.6	30.5±13.7	0.448
rMSSD (night), ms	34.8±13.8	30.9±14.1	37.3±13.3	0.172	33.1±13.9	35.2±14.9	0.390
pNN50 (total), %	8.9±6.4	7.5±8.4	11.6±8.5	0.191	8.6±8.0	9.5±8.8	0.651
pNN50 (daytime), %	6.1±5.0	6.2±7.3	8.2±8.6	0.498	6.5±6.9	7.3±7.3	0.618
pNN50 (night), %	11.8±9.7	10.1±12.9	15.3±9.9	0.161	11.4±11.6	12.2±11.5	0.612
SDANN Index total)	139.6±41.6	123.7±34.4	141.0±28.1	0.154	131.0±36.0	136.2±41.3	0.265
SDNN Index (total)	58.3±18.0	50.0±12.2	56.5±11.4	0.133	53.4±14.3	57.1±16.4	0.133
HF (total), ms2	229.6±149.3	229.6±244.5	312.6±234.3	0.292	243.6±219.5	257.4±232.3	0.871
HF (daytime), ms2	163.5±93.1	167.9±156.6	231.2±195.4	0.573	254.4±214.4	209.1±208.3	0.750
HF (night), ms2	286.4±211.3	262.0±283.8	384.9±279.8	0.234	289.6±264.9	300.0±269.3	0.911
LF (total), ms2	732.2±469.4	473.7±224.5	718.7±376.9	0.061	586.7±352.7	660.4±403.8	0.246
LF (daytime), ms2	682.9±495.0	444.0±227.4	611.9±312.9	0.123	538.6±347.1	622.0±394.8	0.165
LF (night), ms2	773.0±457.8	502.0±253.7	819.1±559.1	0.041	630.7±380.7	688.8±443.0	0.469
LF/HF (total)	3.4±1.1	3.0±1.3	3.0±1.7	0.371	0.1±1.3	0.64±2.0	0.891
LF/HF (total)	4.2±1.9	3.5±1.7	3.6±1.8	0.380	0.0±1.8	0.71±3.9	0.696
LF/HF (night)	3.2±1.1	2.8±1.2	2.9±1.8	0.491	0.1±1.3	0.57±3.2	0.746
VLF (total), ms2	2655.6±1655.3	1794.0±908.8	2258.5±853.1	0.072	2111.2±1198.7	2406.79±1409.3	0.191
VLF (daytime), ms2	2505.3±1652.5	1835.1±902.6	2063.6±725.7	0.171	2309.4±2296.3	2396.35±1473.9	0.232
VLF (night), ms2	2794.0±1737.3	1784.7±1034.9	2449.6±1122.1	0.038	2176.7±1338.1	2368.75±1458.9	0.386
Total power (total)	3648.3±2219.1	2514.7±1166.8	3318.5±1308.1	0.061	2964.6±1608.4	3348.64±1937.0	0.248
Total power (daytime)	3374.9±2187.6	2489.5±1156.1	2930.6±1128.5	0.362	2809.3±1533.3	3300.31±2053.4	0.191
Total power (night)	3916.4±2401.9	2538.9±1298.2	3419.1±1486.3	0.041	3032.63±1748.2	3387.63±2020.4	0.291

Values are provided as Mean ± Standard deviation.

SDNN: Standard deviation (SD) of all normal to normal (NN) intervals, SDNN index: The mean of the deviation of the 5-minute NN intervals over the entire recording, rMMSD: The square root of the mean squared differences of successive NN intervals, pNN50: The proportion of adjacent RR intervals differing by >50 milliseconds in the 24-hour recording, HF: High frequency, LF: Low frequency, VLF: Very low frequency, TP: Total power.

No statistical difference was found in the HRV analysis, except that the SDNN night value was lower when RLS patients and the control group were compared (p=0.037) (Table 1). When patients were divided according to disease severity, 18 patients had mild, 36 patients had severe, and 11 patients had very severe disease; however, there was not any patient with mild disease. Since HRV analyzes were compared according to disease severity, SDNN night was significantly different between groups (p=0.037). In the pairwise comparison, the difference between the severe and very severe groups was significant (p=0.013), and severe group was lower than very severe group. LF night (p=0.041) and VLF night (p=0.03) values were significantly different between three groups but no difference was found in terms of in pairwise comparisons (p>0.016). In addition, there was no correlation between disease duration and HRV parameters (p>0.05).

Discussion

The aim of the present study was to show the effect of autonomic dysfunction through comparison of HRV parameters in RLS patients with healthy controls. It was found that SDNN night value, which is a time domain parameter as an indicator of the cardiac effects of parasympathetic modulation and circulation dynamics, was significantly lower in RLS patients when compared to the control group.

Contradictory results were detected in manuscripts on HRV findings in the literature. Yıldız et al. [18] found in their study that SDNN, SDANN, and SDNN indexes were significantly lower and LF/HF ratio, which is an indicator of sympathetic nerve activity, was significantly higher in RLS patients when compared to the control group. Barone et al. [19] and Cikrikci et al. [20] detected no difference in HRV analysis. In these studies, the changes in the disease severity and duration in the HRV analysis data were not examined. It was found in our study that the disease duration and severity had no effect [18-20]. We have detected a significant decrease in the value of SDNN night. The circadian rhythm of the symptoms in RLS and the increase at night time may be associated with lower SDNN night value. This may be related to the fact that the pathogenesis is still not fully elucidated. We could not find a difference in the increased VLF, LF, LF/HF ratio parameters showing sympathetic activity in our study; however, the decrease in the SDNN night value associated with decrease parasympathetic activity indicates the need for further researched on this subject.

There have been studies in the literature investigating cardiac autonomic dysfunction in RLS patients with other techniques besides HRV. In a study evaluating cardiovascular

baroreflex gain with the Modified Oxford technique, increased sympathetic system activation was shown in RLS patients [21]. There are studies showing that, irritable bowel syndrome and other autonomic dysfunctions are seen more frequently in RLS patients besides cardiac autonomic dysfunction [22, 23]. Cardiac autonomic dysregulation with HRV may be an indicator of increased sympathetic system. Increased sympathetic activation can cause endothelial damage, atherosclerosis, and cardiac death [24]. It can be concluded that RLS disease, which increases the risk of cardiovascular disease, may have effects up to mortality.

Cardiac parasympathetic autonomic dysfunction was shown at night time; however, cardiac sympathetic autonomic dysfunction could not be demonstrated in HRV analyzes in this study.

As the limitations of the study, there was not any significant correlation between HRV analysis data for disease duration and severity. This may be caused by exclusion of the patients with a longer disease duration since they received treatment for RLS. Furthermore, the study group was relatively smaller. Comparison with HRV analyzes of the patients included in the study after treatment and follow-up periods may provide a better assessment of cardiac autonomic dysfunction in RLS patients.

In conclusion, in this study examining the cardiac autonomic system with HRV in patients with RLS, a decrease in parasympathetic nervous system was detected at night time. Therefore, there is a need for further studies with larger series and including control HRV analyses.

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