J Surg Med. 2019;3(4):288-291.
DOI: 10.28982/josam.543100

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Investigation of inflammation with neutrophil/lymphocyte ratio in restless legs syndrome

İdiyipatik huzursuz bacaklar sendromunda enflamasyonun nötrofil/lenfosit oranları ile incelenmesi

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Ethics Committee Approval: Okmeydanı Training and Research Hospital, Date: 13.02.2019, No: B.30.2.ATA.0.01.00/60.
Etik Kurul Onayı: Okmeydanı Eğitim ve Araştırma Hastanesi, Tarih:13.02.2019, Sayı: B.30.2.ATA.0.01.00/60.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 3/26/2019
Yayın Tarihi: 26.03.2019

Abstract

Aim: Restless Legs Syndrome (RLS) is a chronic, progressive, sensorimotor disorder characterized by the urge to move legs and abnormal sensations in the limbs. The pathophysiology of RLS is not clear. In recent years, many studies have used different serum biomarkers to discuss pathophysiology or to follow up the diagnosis and treatment. There are not enough studies that entirely investigating the relationship between RLS and serum neutrophil/lymphocytes (N/L). Therefore, in this study it was aimed to examine the relationship between idiopathic RLS and serum N/L.

Methods: A case control study was planned. After sample size analysis, 93 patients with diagnosed RLS (study group) and age- and gender matching 50 healthy volunteers (control group) were included in the study. N/L ratio was compared between two groups.

Results: The median of N/L ratio was 2.58 in the RLS group and 2.72 in the control group. There was no statistically significant difference between the groups (P=0.89). The mean duration of disease was 3.2 (1.37) years in patients' group. Sleep disorders were found in 81.7% (n=76) of the patients, and similar complaints were observed on the upper extremities in 34.4% (n=32) of the patients. Severity scale of disease was determined according to the International Restless Legs Syndrome Study Group (IRLSSG). It was observed to be low severity of the symptom in 6.3%, middle severity of the symptom in 15.2%, severe severity of the symptom in 64.8%, high severity of the symptom in 13.7% of the patients. There was no correlation neither between duration of disease and N/L ratio (r:-0.117, P=0.28) nor between severity of the symptoms and N/L (r:0.68, P=0.41).

Conclusion: In this study, it was investigated the role of inflammation in the pathophysiology of RLS was evaluated with N/L ratio and it was not observed statistically significance on behalf of patients group.

Keywords: Restless legs syndrome, Neutrophil/lymphocyte ratio, Inflammation

Öz

Amaç: Huzursuz bacaklar sendromu (HBS); ekstremitelerde öncelikle bacaklarda hareket ettirme dürtüsü ve anormal duyularla karakterize, kronik, ilerleyici sensorimotor bir bozukluktur. HBS' nin patofizyolojisi net değildir. Son yıllarda birçok çalışmada patofizyoloji hakkında yorum yapabilmek ya da tanı ve tedavi takibi için farklı serum biyomarkerları kullanılmaktadır. HBS ve Nötrofil/Lenfosit (N/L) ilişkisini detaylı araştıran yeterli sayıda çalışma bulunmamaktadır. Bu nedenle çalışmamızda idiopatik HBS ile serum N/L arasında ilişkinin incelenmesi amaçlandı.

Yöntemler: Olgu kontrol çalışması planlandı. 93 HBS tanılı hasta (çalışma grubu) ile yaş ve cinsiyet açısından eşleştirilen 50 sağlıklı gönüllü (kontrol grubu) çalışmaya dahil edildi. İki grubun N/L oranları restrospektif olarak incelendi.

Bulgular: N/L'nin ortanca değeri hasta grubunda 2.58 ve kontrol grubunda 2.72 idi. Hasta ve kontrol grubu arasında istatistiksel olarak anlamlı bir farklılık yoktu (P=0.89). Çalışmamızda hasta grubunda hastalık süresinin ortalama 3,2 (1,37) yıl olduğu tespit edildi. Olguların %81,7'sinde (n=76) uyku bozukluğu, %34,4'ünde (n=32) üst ekstremitelerde benzer yakınmaların olduğu görüldü. Hastalığın şiddet skalası Uluslarası Huzursuz Bacaklar Sendromu Çalışma Grubu (IRLSSG)'na göre belirlendi. Semptomların şiddetinin dağılımı %6,3'ünde hafif, %15,2'sinde orta, %64,8'inde ciddi, %13,7' sinde ağır şiddette olduğu izlendi. Hastalık süresi ile N/L arasında anlamlı korelasyon yoktu (r:-0.117, P=0,28). Semptomların şiddeti ile N/L arasında istatistiksel olarak anlamlı korelasyon görülmedi (r:0.68, P=0,41).

Sonuç: Bu çalışmada, HBS patofizyolojisinde enflamasyonun rolü N/L oranı ile birlikte değerlendirilmiş ve hasta grubunda enflamasyon lehine istatistiksel olarak anlamlı bir ilişki gözlenmemiştir.

Anahtar kelimeler: Huzursuz bacaklar sendromu, Nötrofil/lenfosit oranı, Enflamasyon

How to cite / Atıf için: Sonkaya AR, Ceylan M. Investigation of inflammation with neutrophil/lymphocyte ratio in restless legs syndrome. J Surg Med. 2019;3(4):288-291.

Introduction

RLS is a chronic neurologic disorder of sensorimotor system with circadian features manifested by the need or urges to move the extremities to stop unpleasant sensations in the evenings or rest. [1,2]. RLS, also known Wills-Ekbom Disease, was defined the first time by Dr. Ekbom in 1945 [3].

Diagnosis criteria of RLS have been developed by the International Restless Legs Syndrome Study Group (IRLSSG) and still these diagnosis criteria have been used [4]. Although, incidence of RLS has been found as between 0.25% and 15.3% in studies, it is more common in women [5,6]. RLS is divided into two forms as of primary and secondary. Family history in primary RLS, also known as idiopathic form, is remarkable. Allen et al. [7] reported that the first-degree relatives of patients with primary RLS were in a much higher risk group for RLS than their second-degree relatives, and that this form of familial features had an earlier onset. Although secondary or symptomatic RLS tends to late-onset and faster progression than idiopathic RLS, there is no clear difference between seconder and idiopathic RLS with regards to characteristics of symptoms [8]. Studies on the pathogenesis of the disease have focused on iron metabolism, changes in dopaminergic system, hypoxic / inflammatory response and genetics [9,10]. It has been reported that RLS is more common in cases where peripheral oxygen saturation decreases, such as chronic obstructive pulmonary disease and obstructive sleep apnea [11,12] and improvement of RLS symptoms with correction of peripheral hypoxia [13]. Hypoxia in pathophysiology of RLS was supported with post-mortem studies [14].

The serum neutrophil/lymphocytes (N/L) ratio has been used as a marker of systemic inflammation recently. N/L measurements cost less than other inflammatory markers, and it is practical and easy to perform [15].

Zahorec [16] was the first, reporting the relationship between neutrophils and lymphocytes during the inflammatory response. Neutrophils, lymphocytes, and other white blood cells are essential proinflammatory and anti-inflammatory cells [16,17]. Neutrophils are the paramount cells in causing inflammatory response during acute phase reactions. Lymphocytes constitute the main components of both the humoral and cellular responses [18,19]. Stress response of circulating lymphocytes results in a rise in the neutrophil count and reduction in the lymphocyte count. Therefore, the ratio of these two subgroups of white blood cells (N/L ratio) is used as an inflammatory marker [16]. It was examined the relationship between N/L ratios and some diseases [20-22].

Although different results were indicated in many studies which investigated the relationship between RLS and N/L ratios, it was not examined the relationship between severity of disease symptoms and N/L ratios [22]. Therefore, in this study we aimed to investigate the relationship between idiopathic RLS, severity of its symptoms and serum N/L.

Materials and methods

N/L ratios of 93 patients with diagnosed idiopathic RLS (42 male + 51 female) in neurology polyclinic according to the IRLSSG, and 50 healthy volunteers (24 male + 26 female) aged between 18 and 65 years were evaluated retrospectively from January 2018 to November 2018. Additionally, disease duration of patients with RLS, upper limb involvement, and presence of sleep disorder and severity of symptoms were compared to the N/L ratios. Severity scale of disease was determined according to the IRLSSG. When falling asleep latency (prolonged sleep latency) is longer than 30 minutes and/or waking up 3 or more than 3 in staying sleep were considered as a sleep disorder [23]. Participants with polyneuropathy, lumbosacral radiculopathy, amyotrophic lateral sclerosis, multiple myeloma, multiple sclerosis, Parkinson disease, poliomyelitis, diabetes mellitus, uremia, amyloidosis, cancer, peripheric vascular disorders, pneumopathy, congestive heart failure, Cushing syndrome, hyper or hypothyroidism, pregnancy, lactation, chronic kidney failure, use of neuroleptic or antidepressant, smoking, steroid treatment (by any means), systematic inflammatory disorders and hematologic disorders were excluded. N/L ratios were obtained by dividing the absolute number of neutrophils by the number of lymphocytes. Local ethics committee approval was taken from Ataturk University Faculty of Medicine (Protocol No: B.30.2.ATA.0.01.00/60).

Statistical analysis

All statistical analyses were performed using Medcalc statistical software (version. 12, Ostend, Belgium). D'Agostino Pearson Test was used to determine whether the variables were normal distribution or not. Since D'Agostino-Pearson test is based on the fact that when the data is normally distributed the test statistic has a chi-square distribution with two degrees of freedom, it is recommended [24]. While data with normal distribution were expressed as mean, standard deviation, as for non-normal distribution data were expressed as median and interval. The independent samples t-test was used in comparisons of normal distribution variables. Non-normal distribution of the data was compared using the Mann Whitney U test. Nominal variables were compared with chi-square test. Pearson Correlation was used to analyze the correlation between the numerical parameters. P <0.05 value was considered statistically significant.

Results

One hundred forty-three participants including 93 patients with idiopathic RLS and 50 controls were included in the study. Both groups had similar sociodemographic features. Sociodemographic features such as age, sex, marital status, etc. of both groups and biochemical and hemogram examinations of the routine examinations were compared (Table 1).

The median of N/L ratio was 2.58 in the RLS group and 2.72 in the control group. There was no statistically significant difference between the groups (P=0.89). The mean duration of disease was 3.2 (1.37) years in patients' group. Sleep disorders were found in 81.7% (n=76) of the cases and similar complaints were observed in 34.4% (n=32) of the upper extremities. It was observed to be low severity of the symptom in 6.3%, middle severity of the symptom in 15.2%, severe severity of the symptom in 64.8%, high severity of the symptom in 13.7% of the cases. There is no significant correlation neither between duration of disease and N/L ratio (r:-0.117, P=0.28) nor between severity of the symptoms and N/L (r:0.281, P=0.41).

Table 1: A comparison between sociodemographic features and laboratory database in RLS patients and healthy subjects

	RLS (n=93)	Control (n=50)	*P*-value
Age, mean (SD)	38.5 (12.4)	36.38 (11.8)	0.28
Sex			
male	42 (45.2)	24 (48)	0.89
female	51 (54.8)	26 (52)	
Marital status			
Married	65 (69.9)	33 (66)	0.81
Single	28 (30.1)	17 (34)	
Occupation			
House wife	32 (34.4)	15 (30)	0.91
Civil Servant	13 (14)	8 (16)	
other	19 (20.4)	11 (22)	
Health-care professional	16 (17.2)	9 (18)	
student	13 (14)	7 (14)	
Education level			
Non-educated	9 (20.0)	7 (15.6)	0.75
≤8 years educated	7 (15.6)	11 (24.4)	
8-12 years educated	9 (20.0)	8 (17.8)	
>12 years educated	20 (44.4)	19 (42.2)	
Economic situation			
Low	40 (43)	17 (34)	0.67
Middle	21 (25.6)	18 (36)	
High	32 (34.4)	15 (30)	
Hemoglobin, mean (SD)	14.6 (2.7)	14.1 (2.1)	0.64
B12 vitamin, mean (SD)	283.7 (119.7)	278.1 (113.4)	0.87
Folic acid, mean (SD)	9.5 (5.3)	7.9 (4.1)	0.06
Serum iron, mean (SD)	64.2 (47.1)	81.9 (39.7)	0.03
UIBC, mean (SD)	293.1 (87.4)	248.4 (74.2)	0.04
Ferritin, mean (SD)	54.7 (89.7)	50.8 (67.1)	0.79
N/L ratio median (reference range)	2.058 (1.4-3)	2.072 (1.4-2.9)	0.89

RLS: Restless legs syndrome, SD: Standard deviation

Discussion

Although various assumptions such as dopaminergic hyperstimulation, iron deficiency, insensitivity of dopaminergic receptors in the tubero-infundibular area have been suggested, still the pathophysiology of RLS is not clear enough [25]. Nevertheless, in recent years, the role of systemic inflammation in the pathogenesis of RLS has been discussed in some studies. The coexistence of RLS with some diseases associated with systemic inflammation such as systemic lupus erythematosus, rheumatoid arthritis, human immunodeficiency virus infection, and inflammatory bowel disease was shown, and it has been pointed out the association of RLS with immunologic and inflammatory mechanisms [26,27].

N/L is drawn attention as a new, cost-effective, and simple to perform method that providing the assessment of inflammation. High levels of N/L were determined in acute or chronic inflammatory situations such as acute pancreatitis, chronic tonsillitis, acute mesenteric ischemia, coronary artery disease, diabetes mellitus, heart failure and malignancies [22]. Also, N/L was assessed in some central or systemic neurologic diseases such as ischemic and hemorrhagic cerebrovascular diseases, myasthenia gravis and multiple sclerosis and was demonstrated the relation with prognosis [28]. On the other hand, in some studies have been demonstrated that the RLS was more common in neurologic conditions where the N/L was observed increment [29]. The only one study in the literature was evaluated the inflammation with N/L in patients with RLS demonstrated higher N/L values in the RLS group, and it was discussed the effect of inflammation in the etiology [30]. In this study we evaluated the N/L to investigate the role of inflammation in etiology of RLS and found no significant increment in the RLS group fort this parameter.

It is known that there is an improvement in symptoms with dopaminergic agonists in RLS as well as exacerbations with anti-dopaminergic agents. While this exacerbation is explicitness in dopamine antagonists that can cross the blood brain barrier such as metoclopramide, no exacerbation is seen with dopamine antagonists that cannot cross the blood brain barrier. This shows that RLS is not a peripheral, but it is central nervous system (CNS) dysfunction [31]. In one study carried out by Patton et al. [14] demonstrated higher levels of HIF1α, which acts as a regulator in inflammation in the substantia nigra of patients with RLS, indicating the effect of inflammation at cellular level. Contrary to this study, Varım et al. [30] indicated the high-level N/L ratios in RLS in their study. With the difference of Varım et al. [30], in this study, N/L ratios were found lower in patients and no statistically significant difference compared to healthy controls. Low N/L values in patients with RLS may suggest that systemic inflammation does not have a role in etiology, rather than inflammatory changes in RLS. In addition, hematologic parameters such as neutrophil and lymphocyte counts can easily be affected by various conditions such as ethnicity, age, sex, eating habits, and environmental factors or our small sample group may be influence to our results.

Vitamin B12, folate, and ferritin levels were found normal in the study which was carried out by Varım et al. [30], but in their study these values were significantly different between the patient and control groups. We did not find such a difference in our study. Although ferritin levels were lower in the RLS group compared with the control group, the difference was not statistically significant. This result may be related with the replacement treatments that patients might have taken before.

Conclusion

We investigated the role of inflammation in the pathophysiology of RLS was evaluated with N/L ratio and it was not observed statistically significance on behalf of patients group. This result may be related with non-evaluation of other biomarkers such as C-reactive protein, sedimentation and interleukin 6 and also small sample group. It is thought that multicenter and longitudinal studies on the larger sample groups can be beneficial for the literature.

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The National Library of Medicine (NLM) citation style guide is used in this paper.
Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine