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Original Article

Serum C-reactive protein/albumin ratio and restless legs syndrome

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ABSTRACT

Objectives: Our study aimed to assess the variation in serum C-reactive protein/albumin ratio (CAR), a biomarker of peripheral inflammation and oxidative stress, in patients with restless legs syndrome (RLS).
Methods: The study included a total of 380 individuals including 197 with RLS diagnosis. RLS diagnosis was determined according to the "International Restless Legs Syndrome Study Group" questionnaire. Disease severity was assessed according to the "International Restless Legs Syndrome Study Group Severity Scale".
Results: The mean age of patients with restless legs syndrome was 52.5 ± 12.7 years, while the mean age in the control group was 50.8 ± 11.2, with no statistically significant difference found ($p = 0.156$). The hemoglobin, iron and ferritin levels in the patient group were lower than in the control group ($p < 0.001$; $p < 0.01$; $p < 0.001$), with total iron binding capacity levels higher than the control group ($p < 0.001$). The mean ferritin in the RLS group (49.8 ± 51.2) was lower than the control group (76.9 ± 44.7). In patients, the c-reactive protein, albumin and c-reactive protein/albumin ratio were found to be 0.21 ± 0.18, 4.43 ± 0.31 and 0.07 ± 0.05, respectively. When compared with the control group, the patient group had high c-reactive protein (CRP), CAR and low albumin levels ($p < 0.001$). Among patients with "very severe" disease severity, ferritin levels were found to be lower than those with "moderate" disease severity. Additionally, patients with "very severe" disease had albumin levels which were significantly low compared to those with "mild" disease severity ($p < 0.05$).
Conclusion: Our study supports the hypothesis that serum albumin level, ferritin, CRP, and CAR may be associated with restless legs syndrome.

1. Introduction

Restless legs syndrome (RLS) is a clinical tableau characterized by the desire to move the legs and feelings of discomfort. It was described by Thomas Willis in 1672 and defined by Ekbom in 1945 [1–5]. The prevalence of RLS is from 1 to 20% in different populations [6,7].

The idiopathic form of RLS is most commonly observed. The central nervous system area of functional disorder in idiopathic RLS is not fully known. The most accepted hypothesis is that RLS pathophysiology is a disorder related to iron and dopamine use and storage. Iron is a co-factor of tyrosine hydroxylase, an enzyme necessary for dopamine synthesis [3,8]. Additionally, RLS is secondarily observed in many diseases led by iron deficiency anemia, Parkinson's disease (PD), rheumatoid arthritis and chronic renal failure [4,5].

Studies have shown that neuroinflammation and oxidative stress have an important place in the development and progression of chronic neurodegenerative diseases like idiopathic Parkinson's disease and Alzheimer type dementia, cardiovascular and inflammatory diseases and a variety of types of cancer [9–14]. The number of studies assessing inflammation and oxidative stress in patients with RLS diagnosis is limited. Varim et al., found that the neutrophil/lymphocyte ratio was high in RLS patients compared to controls and noted the importance of inflammation in the disease etiology [15]. Trotti et al., reported high c-reactive protein (CRP) levels and increased inflammation associated with RLS-periodic leg movements [16]. Most studies assessing serum albumin levels in RLS patients were performed on patients with chronic renal failure diagnosis and/or patients receiving dialysis treatment. The relevant

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studies associated low albumin levels with the presence and severity of RLS [17,18]. CRP/albumin ratio (CAR) can be used as a marker of systemic inflammation and oxidative stress.

In our study, the aim was to identify CAR levels as a marker of disease progression in RLS cases along with years of progression and, with the knowledge of correlations between disease severity and the relevant parameters, to collect data relevant to our hypothesis that these will guide research into disease etiology.

2. Material and method

The study included 197 RLS patients monitored and treated in the neurology clinics of Ordu University Education and Research Hospital and Ordu State Hospital and 183 healthy individuals abiding by the exclusion criteria chosen by a simple random sampling method.

Exclusion criteria were accepted as presence of chronic disease (apart from regulated hypertension), cigarette and alcohol use, presence of infectious disease, weight loss, obesity (body mass index above 30), polyneuropathy, lumbosacral radiculopathy, renal failure, chronic obstructive pulmonary disease, peripheral vascular disease, congestive heart failure, myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot-tapping, thyroid disease, pregnancy and use of neuroleptic or antidepressant medications.

In our cross-sectional study, each patient was given the IRSSSG survey, and the International Restless Legs Syndrome Study Group Rating Scale (IRLSSGRS) to determine the disease diagnosis and severity. Patient and control groups had venous blood samples taken after 12–14 h fasting for biochemical and hemogram studies.

2.1. 2012 revised IRLSSG diagnostic criteria for RLS

1. An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs.
2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
3. The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement (eg, walking or stretching) at least as long as the activity continues.
4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day.
5. The occurrence of the above features is not solely accounted for as symptoms primary to another medical or a behavioral condition (eg, myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping) [19].

Disease severity was assessed with the IRLSSGRS. The severity and effects on daily life activities of complaints are questioned in 10 items. Each question is scored with points from 0 to 4. A total of 1–10 points is accepted as a mild disease, 11–20 points are moderate, 21–30 points is severe, and points from 31 to 40 is a very severe disease [20].

2.2. Power analysis

The sample size for this study was estimated by a prior power analysis using G*Power 3.1 (Universität Düsseldorf, Düsseldorf) statistical software; assuming a large effect size ($d = 0.40$), $\alpha = 0.05$ and 1-$\beta = 0.99$, a minimum sample size of 152 (38 in each disease severity group) was required to detect the significance of the one-way ANOVA.

2.3. Statistical analysis

All data analyses were conducted using the SPSS v25 (IBM Inc., Chicago, IL, USA) statistical software package. Prior to the statistical analyses, the data were tested for normality using the Shapiro–Wilks test and for homogeneity of variance using Levene's test. An independent t-test was performed to compare the hematological parameters between patient and control groups. A one-way ANOVA was performed on the hematological parameters grouped by disease severity, and Tukey's posthoc test was performed if the differences were significant. A Chi-square test was conducted to analyze the significant difference between female and male frequencies. All comparisons were two-tailed and P-values less than 5% were considered statistically significant.

3. Results

The study included a total of 380 individuals with 197 RLS patients and 183 healthy control subjects. The mean duration of disease in patients was 6.18 (±3.73) years. The mean age in the RLS group was 52.51 (±12.73), and 50.7 (5 ± 11.19) years in the control group, with no statistical difference found ($p = 0.156$). In both groups there were more females compared to males; however, there was no significant difference found between gender distributions in the groups ($p = 0.769$) (Table 1).

In terms of hematological parameters, the RLS and control groups were compared with an independent samples t-test (Table 2). The hemoglobin, iron and ferritin levels in the RLS group were significantly lower compared to the control group ($p = 0.000$; $p = 0.004$; $p = 0.000$, respectively). The clearest difference was observed for ferritin levels; the mean ferritin in the RLS group (49.771 ± 51.158) was nearly 1.5 times lower than in the control group (76.899 ± 44.683). TIBC levels were found to be statistically higher than the control group ($p = 0.000$). When compared with the control group, the RLS group had significantly high CRP and CAR levels while albumin was found to be significantly lower ($p < 0.001$).

The hematological parameters in RLS patients were compared with disease severity using a one-way ANOVA. It was determined that the hemoglobin, iron, TIBC, CRP and CAR parameters did not vary according to disease severity ($p > 0.05$). Ferritin levels were determined to change according to disease severity ($p < 0.05$). The ferritin levels of patients with “very severe” disease were nearly half as low as ferritin levels of those with “moderate” disease severity ($p < 0.05$). Patients with disease severity of “mild” and “severe” did not have a statistically significant difference in ferritin levels ($p > 0.05$). In RLS patients, albumin levels appeared to be affected by disease severity ($p < 0.001$). The albumin levels of RLS patients with “very severe” disease were significantly low compared to those with “mild” disease severity ($p < 0.05$). There was no statistical difference in albumin levels in the mild, moderate and severe groups ($p > 0.05$) (Table 3).

Table 1
Demographic features of control and RLS groups.

	RLS (n = 197)	Control (n = 183)	P
Male	75 (38.1%)	67 (36.6%)	0.769 ^{NS}
Female	122 (61.9%)	116 (63.4%)	
Age	52.51 ± 12.73	50.75 ± 11.19	0.156 ^{NS}
DD (Year)	6.18 ± 3.73	–	

RLS: restless legs syndrome, Mean ± SD; χ^2, Chi-square test; t, Independent samples t-test; ^{NS}, Statistically not significant ($p > 0.05$), DD: disease duration.

Table 2
Hematological parameters in control and RLS groups.

	RLS (n = 197)	Control (n = 183)	Normal Limits	p
Hemoglobin (g ± dL)	13.18 ± 1.48 (9.2–16.8)	14.10 ± 1.07 (11.9–16.5)	12.2–18.1	<0.001
Demir (ug ± dl)	73.70 ± 29.59 (17.3–192.7)	82.30 ± 28.56 (11.3–183.7)	33.0–193.0	<0.01
TIBC (ug ± dl)	361.87 ± 51.83 (240.4–498.1)	343.67 ± 41.78 (237.1–427.1)	228.0–428.0	<0.001
Ferritin (ng ± ml)	49.77 ± 51.16 (3.8–250.9)	76.90 ± 44.68 (15.2–191.8)	30.0–400.0	<0.001
CRP (mg ± dl)	0.21 ± 0.18 (0.01–0.9)	0.16 ± 0.12 (0.01–0.48)	0.0–0.5	<0.01
Albumin (g ± dl)	4.43 ± 0.31 (3.8–5.2)	4.60 ± 0.25 (3.9–5.2)	3.5–5.2	<0.001
CAR	0.07 ± 0.05 (0.01–0.19)	0.04 ± 0.03 (0.002–0.129)	–	<0.001

CAR, C-reactive protein/albumin ratio; Mean ± Standard Deviation (Min.-Max.).

Table 3
Hematological parameters of RLS patients according to disease severity.

	Mild (n = 42)	Moderate (n = 47)	Severe (n = 49)	Very Severe (n = 59)	p
Hemoglobin (g ± dL)	13.41 ± 1.51 (10.8–16.8)	13.35 ± 1.92 (9.3–16.4)	13.34 ± 1.22 (9.2–16.5)	12.74 ± 1.16 (10.1–15.3)	0.057^{NS}
Iron (ug ± dl)	75.66 ± 26.50 (20.1–149.4)	79.09 ± 33.02 (22.2–183.7)	76.00 ± 31.03 (21.6–192.7)	66.11 ± 26.68 (17.3–141.1)	0.115^{NS}
TIBC (ug ± dl)	364.32 ± 37.63 (307.7–478.4)	359.97 ± 65.21 (242.2–497.2)	348.76 ± 52.70 (240.4–469.7)	372.52 ± 46.25 (260.5–498.1)	0.122^{NS}
Ferritin (ng ± ml)	48.44 ± 36.15 ^{ab} (5.8–137.1)	62.30 ± 61.89 ^{a} (4.0–241.3)	56.048 ± 64.23 ^{ab} (3.8–250.9)	35.53 ± 33.17 ^{b} (5.46–164.51)	0.042*
CRP (mg ± dl)	0.216 ± 0.169 (0.01–0.59)	0.198 ± 0.119 (0.01–0.53)	0.235 ± 0.210 (0.01–0.91)	0.210 ± 0.194 (0.01–0.82)	0.773^{NS}
Albumin (g ± dl)	4.62 ± 0.33 ^{a} (4.0–5.2)	4.37 ± 0.23 ^{ab} (4.0–5.0)	4.46 ± 0.31 ^{ab} (4.0–5.1)	4.33b ± 0.28 ^{b} (3.8–4.9)	0.000***
CAR	0.066 ± 0.046 (0.01–0.19)	0.072 ± 0.042 (0.01–0.16)	0.072 ± 0.046 (0.01–0.17)	0.079 ± 0.058 (0.01–0.20)	0.588^{NS}

CAR, C-reactive protein/albumin ratio; Mean ± Standard Deviation (Min.-Max.); *, Statistically significant (p < 0.05); ***, Statistically significant (p < 0.001); ^{NS}, Statistically not significant (p > 0.05); Means that do not share a letter are significantly different (p < 0,05).

4. Discussion

RLS (Willis-Ekbom disease) is a movement disorder characterized by an irresistible impulse to move the legs and accompanying sensorimotor symptoms. The etiology mainly includes dopaminergic mechanisms; it is proposed that glutamatergic, serotonergic and opioid neurotransmitter mechanisms are disrupted [21–24].

CRP is an acute phase protein synthesized by hepatocytes in response to cytokines during inflammatory processes; it is known as a biomarker of acute inflammation. However, many studies have reported CRP is associated with chronic inflammation [10]. CRP also plays a direct participatory role in pathological processes [25]. Moreover, CRP levels have been shown to increase in chronic neurological diseases like hemorrhagic cerebrovascular disease, Alzheimer's disease (AD) and PD [10–12,26–28].

Hypoalbuminemia is a negative acute phase protein showing inflammation and is linked to oxidative stress. Homocysteine, uric acid (UA) albumin, and bilirubin are defined as laboratory parameters linked to oxidative stress and low UA; albumin and bilirubin levels are defined as risk factors for many neurodegenerative diseases including PD [7,29,30].

Hemogram and biochemical tests provide important data related to a variety of blood cell features including CRP and albumin levels and are easily accessible, cheap and simple to administer. CRP/albumin ratio levels are used as prognostic markers in chronic neurological diseases [10,27,28]. It is important to note that they are easily accessible compared to other inflammatory cytokines including IL-6, IL-1β, and TNF-α [13,26,31,32].

In our study, the CRP and CAR levels were found to be high, and albumin levels were found to be low for RLS patients compared to the control group. Additionally, in parallel with the increase in disease severity in our patients, there was a statistically significant level of reduction in serum ferritin and albumin levels observed. A significant proportion of diseases known to be associated with RLS are inflammatory or infectious [33]. In the literature, we found no study that assessed serum CAR as a biomarker of inflammation and oxidative stress in RLS patients. There are a limited number of studies assessing inflammation in RLS patients. Varım et al., in a study of 75 newly-diagnosed RLS patients and 56 healthy control cases found that the neutrophil/lymphocyte ratio (NLR) was statistically significantly high in the patient group compared to the control group and noted the importance of inflammation in disease etiology [15]. Another study by Tak et al., in 2018 of 62 RLS patients and 40 healthy controls, reported no significant difference in NLR and platelet lymphocyte ratios in both groups [34]. A 2012 study by Trotti et al., compared the periodic leg movement (PLM) of 137 RLS patients with CRP levels and stated RLS-PLM were associated with high CRP levels and increased inflammation [16]. A study by Higuchi et al., assessing the incidence of RLS and inflammation biomarkers in hemodialysis patients showed the RLS subgroup had significantly higher levels of CRP in serum [35]. Two different studies identified significant correlations between the presence of RLS and increased CRP [36,37]. The majority of studies assessing the serum albumin levels in RLS patients were performed on patients with a chronic renal failure diagnosis and/or undergoing dialysis treatment. The relevant studies correlated low albumin levels with HBS presence and severity [17,18]. In our study, similarly, serum albumin levels were low in RLS patients compared to the control group, and this drop was shown to parallel the increase in disease severity.

Our study found hemoglobin and ferritin values were low, and TIBC levels were high in the RLS group compared to the control group, in agreement with literature data. Iron is a cofactor of tyrosine hydroxylase with duties in dopamine synthesis [38]. There are many studies showing that disrupted iron metabolism in the brain plays a role in RLS pathophysiology. Individuals with low serum ferritin levels are more likely to have RLS [17,18,39,40]. It is known that iron deficiency plays an important role in the pathophysiology of RLS [41]. In addition to, neuropathologic studies found reduced iron, ferritin and other protein concentrations associated with iron homeostasis in the substantia nigra of RLS patients [42,43]. Experimental models resembling RLS show there is a significant interaction between iron deficiency and the dopaminergic system in RLS pathogenesis [44].

The most important limitation of our study is that anthropometric and demographic features were not assessed in the patient and control groups and the medications used by RLS patients were

not evaluated within the scope of our study. The cross-sectional nature of our study limits our ability to determine a causative relationship between the variables. Furthermore, our sample size is relatively small. Another limitation is that oxidative stress biomarkers like uric acid, bilirubin and homocysteine were not assessed. As a result, there is a need for prospective, more comprehensive and broad population studies to assess the correlation between RLS and serum inflammatory biomarkers.

5. Conclusion and recommendations

Our study supports the hypothesis that there may be an association between serum CAR and restless legs syndrome. There is a need for more studies to validate our findings using longitudinal data.

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The study was approved by Ordu University Education and Research Hospital ethics committee with decision number 2018/164 and conducted in compliance with Helsinki criteria. Consent was not required as files were retrospectively screened.

Conflict 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.2019.02.022.

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