



Restless legs syndrome and depression-anxiety disorder association in iron deficiency anemia patients

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ABSTRACT

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Restless Legs Syndrome (RLS) is a disorder in which the person experiences a strong urge to move their legs or other extremities during rest. This urge to move is associated with tingling, pulling or other unpleasant and uncomfortable feelings; it usually slowly increases in the affected limb and often affects sleep. The incidence in general population is 5-15%. Although the pathophysiology is not fully understood, it was thought to result from the iron and dopamine metabolism irregularities and also has a genetic component. There are publications that show the frequency of disease in patients with iron deficiency or renal failure reaches up to 80%. In this study, we investigated the incidence of restless leg syndrome in anemic patients without any other organic disease or drug use, which can cause restless legs syndrome. We also tried to find out if there is a relation between restless legs syndrome, ferritin levels, anxiety and depression. Our retrospective, cross sectional study was made in The Ministry of Health and family medicine, neurology and psychiatry outpatient clinics of Ordu University Education and Research Hospital. 47 patients who were admitted to above mentioned clinics whose ferritin levels were under 50 ng/ml without any other disease and were not on medication (including those indicated for iron deficiency anemia) was included in to the study. All patients were given the Beck depression inventory and Beck anxiety inventory. The patients were questioned in terms of the basic diagnostic criteria established by International Restless Legs Syndrome Study Group. Definitive diagnosis could be established by the patients that meet the four criterias for the diagnosis. International Restless Legs Scale applied to patients diagnosed with RLS. Of 47 patients, 39 were female and 8 were male. 28 (%59.6) of the patients met the criteria of RLS. 28 patients with a diagnosis of RLS; 4 of them mild, 11 of them moderate, 8 of them severe and 5 of them experienced very severe symptoms of RLS. The relationship between the RLS and ferritin levels were checked and there was no statistically significant difference between them. A significant difference was not found in Beck depression scores between patients with and without RLS, but when the groups were compared in terms of Beck anxiety score, there were a significant difference. There was no significant relationship between RLS severity and Beck depression or Beck anxiety scores. RLS can be seen in %5-15 of general population and it is much more likely to emerge in the presence of an organic problem such as iron deficiency anemia. The diagnosis of the disorder is set clinically and RLS had a different significance because it may cause sleep disturbances and psychiatric disorders. If not questioned, this problem, which is not easily noticeable, can lead to misdiagnosis and misinterpreted as an anxiety disorder or a primary sleep disorder. Therefore the symptoms that could be corrected only by iron deficiency treatment, could be inşamed further by giving antidepressants and hypnotics.

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Table 1. Patients' gender and sociodemographic data

	n	%
Gender		
Female	39	83
Male	8	17
Marital Status		
Married	35	74.5
Single	12	24.5
Education		
Illiterate	3	6.4
Primary school	20	42.6
Secondary school	7	14.9
High school	8	17
University/professional school	9	19.1
Profession		
Housewife	24	51.1
Officer	5	10.6
Private sector	3	6.4
Retired	4	8.5
Worker	7	14.9
Student	4	8.5

1. Introduction

Restless legs syndrome (RLS) is a disorder that causes a person to experience a strong urge to move his legs or other extremities while resting. This urge to move generally goes with a gradually growing tingling, pull or an ache-like unpleasant and disturbing feeling on the related extremity, and generally, it adversely affects sleep. Although generally the legs are affected by the RLS, there are also some studies reporting restless arms. These comfortless feelings subside temporarily through movement while it has a strong circadian rhythm growing worse in the evenings/at nights and often easing off after the sleep in the morning (Allen and Earley, 2001; Abetz et al., 2004).

The diagnostic criteria were determined by the International Restless Legs Syndrome Study Group (IRLSSG) in 1995 (Walters, 1995), which was revised by the National Institute of Health (NIH) in 2003 with the following criteria 1. The urge to move limbs together with paraesthesia/dysesthesia sensation 2. Inability to stay still and relief through motion (walking, flexing, scrubbing, etc.) 3. Aggravation of symptoms during the rest, subsidence by movement 4. Aggravation of symptoms during the evening-night hours (Allen et al., 2003). For the final diagnosis of the RLS, all the four diagnostic criteria must be among the patient's complaints.

The prevalence rate of the RLS among the general population is 5-15% (Chokroverty, 2009). The disorder is more common among female when compared to male while its prevalence increases in parallel to the age. In the cases of genetic inheritance the symptoms may start at earlier

Table 2. RLS + and RLS-patient distribution

RLS	N	%
Positive		
Male	3	10.7
Female	25	89.3
Negative		
	19	40.4
Total	47	100.0

RLS: Restless legs syndrome

ages; even at a very young age (Ondo and Jankovic, 1996). It has two different forms as idiopathic and secondary while the secondary form is mostly related to anemia, end-stage renal failure, parkinson disease and pregnancy. Although the pathophysiology of the RLS has not been completely understood, it is thought that it may be secondary to the irregularity in the iron and dopamine metabolism. Additionally it has been shown that it has also a genetic component (Walters, 1995). There are some articles showing that the prevalence of the disease reaches to 80% among people with iron deficiency or with renal insufficiency (Holley et al., 1992; Stiasny et al., 2000). Through the advanced imaging methods, it has been revealed that there is decreased dopamine (D2) binding of the striatal receptors in the RLS patients (Trenkwalder et al., 2005). Iron is a required co-factor in the regulation of the dopamine synthesis and the dopamine receptors in the brain. It has been discovered that the levels of iron and ferritin are abnormally low in the cerebrospinal fluid of the RLS patients (Earley et al., 2000; Mizuno et al., 2005).

It has been already shown that the RLS is related to depression and anxiety (Tuncel et al., 2009). In the last few years, many clinic or community-based epidemiologic studies with different scales evaluating the symptoms of depression and anxiety revealed that the depression and anxiety symptoms are higher in the RLS patients than those in the control group (Mosko et al., 1989, Picchetti and Winkelman, 2005). The underlying mechanism of the pathophysiological link between the depression and the RLS has not been completely understood and there were only few studies on the subject. However hypofunction in the dopaminergic system has been considered/hypothesized as a common pathophysiology of both diseases (Allen et al., 2003; Barriere et al., 2005).

In the light of these findings we aimed: 1) To evaluate frequency of the RLS among the anemic patients who do not have an organic disease or do not use drugs that may secondary cause to the RLS, and to search whether there is a relation between the intensity of symptoms and the level of ferritin in the RLS patients. 2) To reveal the relation of RLS with the symptoms of anxiety and depression.

Table 3. RLS + and RLS - patients' age and gender distribution

	RLS + (n=28)	RLS - (n=19)	p
Age < 51	24/41 (58.5%)	17/41 (41.5%)	0.117
Age ≥ 51	4/6 (66.7%)	2/6 (33.3%)	0.221
Gender (M/W)	3/25	5/14	0.136

*Significant difference across groups, p<0.05. RLS: Restless legs syndrome

2. Material and method

In this study, 6123 patients (including 2315 male, 3808 female) were retrospectively analyzed who applied to the family practice clinic of our hospital between June, 1 2013-December, 31 2014. Among these patients 355 patients were diagnosed with anemia, considering the gender distribution 67 of them were male and 288 female. From 283 patients whom were invited to the hospital for an interview. 202 patients participated in the study voluntarily. From these patients 47 anemic patients whose ferritin level is below 50 ng/ml who do not have another chronic disease and patients who do not use any drugs for any reason including the anemia

Table 4. RLS distribution according to severity levels

RLS severity	%
Mild	14.3 (n=4)
Moderate	39.3 (n=11)
Intense	28.6 (n=8)
Severe	17.9 (n=5)

RLS: Restless legs syndrome

were included into the study. After an oral informing about the study, a written consent was taken from all the patients participated in the study that was accepted by the Ethical Committee of the University.

In order to exclude the reasons for the secondary RLS except for anemia, a detailed clinical interview and neurological examination was undertaken with the patients who had accepted to participate in the study. The participants were given a socio demographic form including age, gender, marital status, educational status and professional information, as well as a self-report on Beck depression and Beck anxiety scale. Then, the patients were inquired about the basic diagnostic criteria determined by the IRLSSG and diagnosed as RLS whose complaints fulfill 4 diagnostic criteria for the RLS (Hening et al., 2001) which were rated according to the IRLSSG's Rating Scale based on the symptom frequency, intensity and their effects on the quality of daily live and sleep of the patient (Allen et al., 2003).

To analyze the data, the SPSS for Windows 11.0 statistical package was used. The data were given as average \pm standard deviation, median (min-max) and percentages. Shapiro-Wilk test was employed to test the normality of the patients' data. When it was seen that the normal distribution could not be done through the square root (SQRT) transformation that determines whether the data can be analyzed according to normal distribution, Mann Whitney U test, which is used to compare the data without normal distribution, was applied. To compare the qualitative data, the chi-squared test and Fisher Exact test were employed. The 95% confidence interval, $p < 0.05$ values were accepted as statistically significant.

3. Results

Table 1. shows the demographic data like marital status, educational and professional information, etc. of the total 47 patients, of which 39 (83%) were female and 8 (17%) were male. When analyzed in terms of the RLS diagnosis, it was seen that the 28 (59.6%) patients had all the RLS diagnostic criteria while the remaining 19 (40.4%) did not meet the RLS criteria.

When the gender distribution among the patients with the RLS diagnosis was studied, it was seen that 25 of them (89.3%) were female and 3 of them were male (Table 2). When the patients were analyzed according to their age group,

it was seen that there were 6 patients (12.8%) at the age of 51 and over, and 41 patients (87.2%) at the age range of 18-50. The 4 (%66.7) of the 6 patients at the age of 51 and over were diagnosed with the RLS, the number of the patients below the age 51 whom were diagnosed with the RLS was found out as 24 (58.5%) (Table 3).

According to the International Restless Legs Syndrome Study Group's Severity Rating Scale, it was discovered that the 4 of the 28 RLS patients (14.3%) experienced mild level, the 11 of them (39,3%) moderate level, the 8 of them (28.6%) intense level and the 5 of them (17,9%) experienced severe level RLS symptoms (Table 4). The relation between the patients' ferritin levels and the RLS was compared via Mann-Whitney U test but a statistical significant difference between them could not be established ($p=0.365$). Although there was not a significant difference between the patients with the RLS and those without the RLS in terms of the Beck depression points ($p=0,084$), it was discovered that the points of the Beck depression scale in the RLS patient group were 60% higher than the other group. There was no significant relationship statistically between the RLS severity that was measured according to the Beck depression scale point and the depression symptom severity.

On the other hand, when the RLS and the non-RLS groups were compared in terms of the Beck anxiety points, a statistically significant difference was identified ($p=0.011$). The Beck anxiety scale points of the patients with the restless leg syndrome were significantly higher than those of the patients without the restless leg (Table 5). Yet, there was not a significant relation between the patients' points from the restless leg severity scale and the points from the anxiety scale ($\chi^2=11.939$, $p=0.148$).

4. Discussion

The RLS is characterized with dysesthesia and abnormal feeling which is especially felt on legs. This abnormal sensation / dysesthesia creates an irresistible urge to move the related extremity and causes motor uneasiness. It is typical that this symptoms appear and/or increase during the rest and relieve through movement which has been considered as a diagnostic criteria for the illness (Kaynak, 2007). In the literature there are different reports on the frequency rate of the RLS which is changing between 3-15%. It has been shown that the RLS is available among the 25-45% of the patients with iron deficiency anemia, while 25% of the RLS patients may suffer from iron deficiency anemia (Hening et al., 2004). In our study, 28 of the 47 patients (59.6%) suffering from iron deficiency anemia were diagnosed as RLS. The rate seems to be higher than the rates reported in the literature. However, it can be hypothesized that the lesser number of patients may have caused this high rate. Since our hospital is a university

Table 5. The Beck depression, Beck anxiety and ferritin levels of the RLS patient group and the non-RLS patient group

Parameters	N	Mean	SD*	Median	Min	Max	P-values
RLS +	28	16.8	12,14	16.0	1	46	0.084
RLS -	19	10.6	6.71	12.0	0	21	
RLS +	28	19.7	12.20	16.5	7	57	0.011
RLS -	19	11.3	7.60	10.0	0	23	
RLS +	28	8.98	9.06	6.0	2	48	0.365
RLS -	19	11.13	9.19	7.0	1	35	

According to Mann-Whitney U test. Mean values provided for non-categorical data; RLS: Restless legs syndrome; SD: Standard deviation

hospital, our patient population is generally composed of complicated cases. Thus, although we have interviewed 355 patients with iron deficiency anemia, we were able to include only a limited number of patients which were suffering from iron deficiency anemia, (patients) with no other disease and who does not get any treatment including also iron deficiency. Epidemiological studies show that the RLS prevalence is the highest at old ages though it can appear at any age (Saraçgil et al., 2012). We have divided the patients into 2 groups as 'the age 51 and over' and 'younger than 51' and found out that the RLS prevalence rate in the first group is 66.7% while it is 58.5% in the second age group. Although there was not a statistically significant difference between the prevalence rates of the RLS between these two groups ($p=0.695$), it has been determined that the RLS prevalence rate is 8% higher in the "age 51 and over group", which is in accordance with the literature. However, as underlined in many studies showing the effect of age on the RLS prevalence, the small number of the patients at the age of 51 and over group ($n=6$) is an important restriction (Garcia-Barreguera et al., 2006). When the gender distribution among the patients was studied, it is seen that 39 of them were female (83%) and 8 of them were male (17%) which may have lead to a pseudo-high effect showing the number of female with RLS are significantly higher than the male which can be due to the small number of our patients although this was in accordance with the recent literature showing that females are significantly more affected than male. Yet, when the literature is studied, there are studies that report 3% of the adult male and 25% of female are diagnosed with iron deficiency anemia (Beutler et al., 1995). When these rates are considered, the rates in our study seem consistent with those reported in the literature. However regarding the RLS prevalence rate among the patients, it has been shown that 3 (10.7%) and 25 (89.3%) of RLS patients were male and female, respectively. In the literature, it is highlighted that the RLS prevalence is 2 times higher among female (Allen et al., 2005).

The relation between the RLS severity which is determined by the IRLSSG severity scale, and the ferritin levels have been analyzed among the RLS patients; which revealed no statistically significant difference. In the same way, there was no relation between the RLS and the ferritin level. This findings support the reports of Ozcan et al that in addition to the Fe deficiency, there are many other factors including the genetic predisposition that may play an important role in the pathogenesis of RLS (Özcan et al., 2013).

In the last few years, there have been conducted a few studies that evaluate the depression and anxiety symptoms in the RLS patients. According to these studies, the depression and anxiety symptoms in the group diagnosed with the RLS are significantly higher than the control group (Picchietti and

Winkelman, 2005; Tuncel et al., 2009). Tuncel et al evaluated 20 RLS and 20 control patients with Hamilton Depression (HAM-D) and Hamilton Anxiety (HAM-A) scales, and revealed that the scale points of the RLS patients are higher than those of the control group. In the epidemiological study conducted by Sevim et al which covered 3234 participants of whom 103 patients were diagnosed with the RLS showed HAM-A and HAM-D scales were significantly higher than the control group (Sevim et al., 2004). In order to evaluate the depression and anxiety symptoms in anemic patients who have no other diseases, we have performed Beck Depression and Beck Anxiety scales. Although there was not a statistically significant difference in terms of Beck depression points between the RLS patient group and the non-RLS patient group ($p=0.084$), it has been shown that the points of the Beck depression scale in the RLS patient group were 60% higher than the other group. However when we compared the RLS severity and the the Beck Depression scores we have found no significant relation between these two groups. Moreover when we compared the Beck Anxiety scores of the RLS patient group with the non-RLS group, we have found a statistically significant difference between these two groups ($p=0.011$) although Sevim et al. (2004) have found no significant relation between the the RLS severity scores and the anxiety severity levels which included scanning of 3234 adults through the Hamilton-Anxiety and Hamilton-Depression scales.

The relation between depression and the RLS has not been well understood; still there are some studies suggesting that both disorders may share a common dopaminergic hypofunction (Hening et al., 2001; Allen et al., 2003). Similar to a "chicken or egg" relation between depression and RLS, Picchietti and Winkelman, hypothesized a third disorder that may lead to both depression and the RLS (Picchietti and Winkelman, 2005). The overlapping of the anxiety and depression symptoms determined by the scales with the RLS symptoms can be responsible for this confusion (Picchietti and Winkelman, 2005). The RLS disorder, which can easily be disregarded if not searched in detail, is seen at the rate of 5-15% in the general population while it may be more common when an organic problem like anemia is high in the society (Chokroverty, 2009). In the case of a wrong diagnosis, symptoms that can be aggravated secondary to unnecessary use of antidepressant or hypnotic drugs can be eliminated only through an iron deficiency treatment.

Currently, there is no routine search in the clinic practice to evaluate the anxiety and depression symptoms or their severity in relation to the RLS disorder. Through our study, we aimed to draw the attention of the clinicians to the psychiatric disorders that may accompany to the RLS that can be easily misinterpreted as symptoms for a psychiatric disorder.

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