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The Interplay of Restless Legs Syndrome with Obsessive-Compulsive Disorder, Attention Deficit Hyperactivity Disorder, and Iron Levels: A Comprehensive Exploration

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ABSTRACT

Objective: The objective of this investigation was to assess the prevalence of obsessive-compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD) and examine their associations with serum iron levels among individuals diagnosed with restless legs syndrome (RLS).

Methods: Clinical data was collected using standardized self-administered questionnaires, including the Pittsburgh Sleep Quality Index (PSQI) for evaluating sleep quality, the Maudsley Obsessive Compulsive Inventory (MOCI) for assessing symptoms of OCD, and the Adult Attention Deficit Hyperactivity Disorder Self-Report Scale (ASRS) for evaluating symptoms of ADHD. Additionally, individuals diagnosed with RLS were evaluated using the International Restless Legs Syndrome Study Group (IRLSSG) RLS severity scale. This assessment was conducted within both a control group comprising 51 individuals diagnosed with RLS and a counterpart group consisting of 51 healthy subjects Serum iron and ferritin levels of RLS patients were recorded from the hospital database.

Results: A statistically noteworthy distinction was discerned in the incidence of symptoms related to OCD and ADHD within individuals diagnosed with RLS (*P* values = .039, .046, respectively). The RLS group exhibited a substantial impact on sleep quality in comparison to the control group (*P* = .0001). Conversely, there was no discernible difference in serum iron and ferritin levels between the RLS and control groups.

Conclusion: These findings suggest that OCD and ADHD symptoms are common among adult patients with RLS, independent of iron stores. This suggests that RLS, OCD, and ADHD share a common etiopathogenesis with dopamine and serotonin dysfunction.

Keywords: Attention deficit hyperactivity disorder, obsessive-compulsive disorder, restless legs syndrome, sleep quality

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INTRODUCTION

Restless legs syndrome (RLS) is a prevalent sensorimotor disorder marked by an urge to move the legs, accompanied by discomfort that diminishes with physical activity and exacerbates during evening hours and periods of rest. Its prevalence varies between 6% and 12% and is more common in women aged 45-64.[1] The diagnosis is based on the patient's history and the International RLS Study Group diagnostic criteria.[2] Restless legs syndrome can manifest as either primary or secondary in nature. Secondary etiologies encompass factors such as pregnancy, end-stage renal failure, iron deficiency anemia, polyneuropathy, or pharmacological agents.[3] While the precise etiology of primary RLS remains uncertain, brain iron deficiency is posited as a potential contributor to its pathogenesis based on findings from brain imaging and pathological observations.[4] Iron serves as a cofactor for tyrosine hydroxylase, an enzyme integral to the synthesis of dopamine. A deficiency in iron results in dysfunction within the dopaminergic system.[5] Animal investigations have demonstrated that a deficiency in iron disrupts the neurochemical dynamics of dopamine and serotonin within the brain.[6] The interplay among iron, dopamine, and serotonin in RLS may elucidate the pronounced impact observed with levodopa and dopamine agonists, as well as the exacerbation of symptoms upon the administration of selective serotonin reuptake inhibitors.[7]

A higher prevalence of psychiatric comorbidities is evident among individuals with RLS in contrast to the general population.[8] Among individuals diagnosed with RLS, the most prevalent psychiatric comorbidities include major depressive disorder and anxiety disorders.[9] Additional psychiatric disorders characterized by perturbations in monoaminergic neurotransmission, particularly involving serotonin and dopamine, such as obsessive-compulsive disorder (OCD), have demonstrated a higher prevalence among individuals diagnosed with RLS.[10] Dysfunction in the corticostriatothalamocort ical pathway is also hypothesized to play a role in the etiology of OCD.[11] Therefore, there may be a common etiologic mechanism for RLS and OCD.

Attention deficit hyperactivity disorder (ADHD) is a common childhood condition characterized by elevated levels of hyperactivity and impulsivity, resulting in deleterious impacts on both behavioral performance and attention.[12] However, ADHD symptoms are known to persist into adulthood.[13] The prevalence is 5%-7.1% in childhood and 2.5%-5% in adults.[14] Variables such as coexisting psychiatric disorders, primary sleep disturbances, concomitant utilization of psychotropic medications, and their impact on sleep patterns may exacerbate manifestations of ADHD. Nevertheless, it is imperative to underscore that these factors should not preclude the definitive diagnosis of ADHD.[15] Restless legs syndrome and periodic leg movements during sleep, along with sleep-disordered breathing, anxiety, and depression, exhibit independent associations with ADHD.[16]

The primary objective of this investigation is to assess and contrast the prevalence of ADHD and OCD between individuals diagnosed with RLS and a control group. The aim is to ascertain if these disorders exhibit a shared pathogenic basis and to scrutinize their potential correlation with serum iron levels.

MATERIAL AND METHODS

Approval from the Clinical Research Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital Hospital was obtained for this study (Approval No: 2021/359, Date: July 5, 2021). Informed consent forms were obtained from the study's patients and healthy volunteers.

Participants

Participants in this investigation were chosen from individuals seeking care at the sleep outpatient clinic during the period from July 1, 2021, to January 1, 2022. This study involved 51 patients and 51 healthy controls. The patient selection process involved the diagnosis of idiopathic RLS utilizing the diagnostic criteria set forth by the international RLS study group,[17] as ascertained through in-person evaluations. During the same study period, healthy individuals without known sleep disorders or sleep-related complaints from hospital staff and their relatives were included as the control group, with a similar age and gender distribution to the patients. Conditions resembling RLS were systematically assessed, and individuals presenting with secondary origins of RLS were intentionally omitted from the study. Exclusions encompassed conditions such as iron deficiency anemia, pregnancy, end-stage renal disease, diabetic neuropathy, abnormal neurological examination findings, or a documented history of medication usage known to induce or worsen RLS (e.g., neuroleptics or antihistamines) .[18] Nonetheless, individuals undergoing antidepressant therapy were not excluded from participation, provided that they had reported symptoms of RLS prior to the commencement of antidepressant medication.

Data Collection Tools

A screening questionnaire evaluating sleep quality, OCD, and ADHD was administered to both the patient and control cohorts. Furthermore, patients diagnosed with RLS underwent assessment utilizing the International Restless Legs Syndrome Study Group (IRLSSG) RLS severity scale. In this scale consisting of a total of 10 questions, each of which is graded 0-4 to determine the severity of RLS, 31-40 points are defined as very severe, 21-30 points as severe, 11-20 points as moderate and 0-10 points as mild RLS.[17] Increasing scores on the RLS severity scale determine the severity of RLS symptoms. Demographic data, serum ferritin, and iron values were recorded from the system.

For the evaluation of sleep quality, the Pittsburgh Sleep Quality Index (PSQI), whose validity and reliability were established by Ağargün et al within the Turkish population,[19] was administered to the participants. The PSQI questionnaire comprises 19 inquiries that assess the individuals' sleep experiences over the preceding month, with a maximum achievable score of 21. A cumulative score on the PSQI equal to or less than 5 signifies "adequate" sleep quality, whereas a score exceeding 5 denotes "suboptimal" sleep quality. In addition to the average scores of the PSQI, a comparative analysis was conducted on the mean values of its constituent components, encompassing subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, utilization of sleep medication, and daytime dysfunction. Maudsley Obsessive Compulsive Inventory (MOCI), developed by Hodgson and Rachman, was used to assess OCD. The scale consists of 37 questions to be answered as true or false. The MOCI can be scored between 0 and 37; the higher the score, the higher the frequency of obsessive-compulsive symptoms. The validity and reliability studies of the Turkish version of the MOCI were conducted by Erol et al.[20] The evaluation of ADHD was conducted utilizing the Adult Attention Deficit Hyperactivity Disorder Self-report Scale (ASRS). The ASRS is an 18-item self-report scale; 9 items are designed for attention deficit disorder symptoms,

and the other 9 are related to hyperactivity symptoms. The scale in question adopts a Likert-type format comprising 5 points, spanning from "never" to "very often." The psychometric characteristics specific to the Turkish version of the ASRS were established through an investigation conducted by Doğan et al on university students.[21] A comparative analysis was conducted between the patient and control groups, assessing parameters including MOCI and ASRS scores, along with serum iron and ferritin levels. The correlation between RLS severity scale scores and age, disease duration, PSQI, MOCI, ASRS scores, serum iron, and ferritin levels were evaluated in the RLS group.

Statistical Analysis

Statistical analyses in this study were conducted using the NCSS (Number Cruncher Statistical System) 2007 Statistical Software package program based in Utah, USA. Descriptive statistical methods, including interquartile range, mean, median, and standard deviation, were employed to assess the data. In the realm of statistical analysis, the normality of variable distributions was scrutinized through the Shapiro–Wilk test. When juxtaposing paired groups, the independent *t*-test was employed for variables exhibiting a normal distribution, the Mann–Whitney *U*-test was utilized for variables lacking normal distribution, and the Pearson's correlation test was applied to discern associations between variables. Comparisons between groups for non-numerical data were executed using a chi-square test. The predetermined threshold for statistical significance was set at $P < .05$.

RESULTS

Fifty-one patients (40 females, 11 males) who met the diagnostic criteria for primary RLS and 51 healthy individuals (30 females, 21 males) for the control group were selected by the study criteria. The average age of the 51 individuals diagnosed with RLS was 48.73 ± 10.11 years, while the control group exhibited a mean age of 45.25 ± 11.30 years. Additionally, the mean duration of RLS in the patient group was 7.08 ± 4.46 years (Tables 1, 2). The mean RLS severity score was 25.53 ± 9.36. According to the RLS severity score, 6% of the patients were mild, 16% moderate, 46% severe, and 32% very severe (Table 2).

Upon comparing the RLS cohort with the control group, no discernible distinctions were noted in terms of age and gender. The average scores of the PSQI, MOCI, and ASRS applied universally to all participants exhibited a statistically significant elevation in cases of RLS when compared to their healthy counterparts ($P = .0001$, $P = .039$, $P = .046$, respectively) (Table 1). Within the RLS cohort, the average scores of the PSQI and its subcomponents, namely subjective sleep quality, sleep latency, sleep efficiency, sleep disturbance, and utilization of sleep medication, demonstrated statistically significant elevation compared to the control group ($P = .0001$, $P = .0001$, $P = .001$, $P = .0001$, $P = .02$, respectively) (Table 1). There was no statistically significant distinction identified in terms of sleep duration and daytime dysfunction. No statistically significant disparity was evident between the RLS and control groups concerning serum iron and ferritin levels (Table 1).

A statistically significant positive correlation was identified in the RLS group between the severity scale scores of RLS and the scores of the PSQI, MOCI, and ASRS ($r = 0.474$, $P = .0001$; $r = 0.307$, $P = .029$; $r = 0.354$, $P = .011$, respectively). Conversely, no correlation was observed for age, disease duration, serum iron, and ferritin levels (Table 3).

Table 1. Comparison of RLS and Control Groups in Terms of Demographic Data, Laboratory Parameters, Sleep Quality, and Psychiatric Scales

		RLS (–) n = 51	RLS (+) n = 51	*P*
Gender	Female (%)	30 (58.82%)	40 (78.43%)	.055⁺ OR: 0.39 (0.16-0.93)
	Male (%)	21 (41.18%)	11 (21.57%)	
		Mean ± SD	**Mean ± SD**	
Age (years)		45.25 ± 11.30	48.73 ± 10.11	.105*
PSQI		6.57 ± 3.91	10.29 ± 3.66	.0001‡
Subjective sleep quality		1.33 ± 0.95	2.12 ± 0.65	.0001‡
Sleep latency		1.25 ± 0.96	2.04 ± 0.96	.0001‡
Sleep duration		0.82 ± 0.95	1.00 ± 1.04	.398‡
Sleep efficiency		0.12 ± 0.43	0.59 ± 0.88	.001‡
Sleep disturbance		1.55 ± 0.76	2.24 ± 0.65	.0001‡
Use of sleep medication		0.27 ± 0.80	0.82 ± 1.31	.02‡
Daytime dysfunction		1.27 ± 1.13	1.53 ± 1.12	.256‡
MOCI		13.63 ± 7.49	17.19 ± 7.83	.039‡
ASRS		27.71 ± 12.01	33.76 ± 14.92	.046‡
Fe (µg/dL)		83.15 ± 51.83	76.82 ± 38.85	.711‡
Ferritin (ng/dL)		64.01 ± 60.34	53.88 ± 51.15	.244‡

⁺Chi-square test, *Independent *t*-test, ‡Mann–Whitney *U*-test.
ASRS, adult attention deficit hyperactivity disorder self-report scale; Fe, iron; MOCI: Maudsley Obsessive-Compulsive Inventory; PSQI, Pittsburgh sleep quality index; RLS, restless legs syndrome.

DISCUSSION

In our study, sleep disorders, OCD, and ADHD were more common in RLS patients, but no relationship was found regarding disease duration, serum iron, and ferritin levels.

Restless legs syndrome is characterized by uncomfortable and abnormal sensations and irresistible urges to move the legs. Restless legs syndrome can have a pronounced impact on both sleep and quality of life. Symptoms intensify during periods of rest in the evening or at night and are alleviated, either wholly or partially, through physical movement. When the patient's symptoms occur during sleep, the person wakes up and moves during the night, causing sleep to be interrupted. A study found that 92.9% of RLS patients

Table 2. Evaluation of Family History and RLS Severity in the RLS Group

		n	%
RLS severity scale categorical classification	1-10	3	6.00
	11-20	8	16.00
	21-30	23	46.00
	31-40	16	32.00
Family history	Yok	34	66.67
	Var	17	33.33
		Minimum/Maximum	**Mean ± SD**
RLS severity scale score		4/42	25.53 ± 9.36
Duration of disease (year)		1/15	7.08 ± 4.46

RLS, restless legs syndrome.

Table 3. Correlation Between RLS Severity and Age, Disease Duration, Sleep Quality, MOCI, ASRS, Serum Iron, and Ferritin Levels

		RLS Severity Score
Age	*r*	0.270
	P	.056
Duration of disease	*r*	0.112
	P	.433
PSQI total score	*r*	**0.474**
	P	**.0001**
MOCI	*r*	**0.307**
	P	**.029**
ASRS	*r*	**0.354**
	P	**.011**
Fe (µg/dL)	*r*	–0.212
	P	.139
Ferritin (ng/dL)	*r*	–0.239
	P	.091

Pearson's correlation test. Values in bold indicate statistical significance.
ASRS, adult attention deficit hyperactivity disorder self-report scale; Fe, iron; MOCI: Maudsley Obsessive-Compulsive Inventory; PSQI, Pittsburgh sleep quality index; RLS, restless legs syndrome.

had poor sleep quality.[22] Research has demonstrated that challenges in sustaining sleep and the incapacity to resume sleep after nocturnal awakenings are more prevalent among individuals with RLS in comparison to the broader population.[23] In polysomnographic studies conducted on patients with RLS, a shortening in total sleep duration (mean 326.3 min), a decrease in sleep efficiency (mean 73.2% vs. 86.6%), and an increase in the number of awakenings (mean 12.2 vs. 7.4) were observed compared to healthy individuals (383.3 min). In addition, a decrease in subjective sleep quality and efficiency was demonstrated using the PSQI compared with those without RLS.[24] Sleep onset time is longer, and average sleep duration is shorter in individuals with RLS, which has been reported to cause severe impairments in physical and social functions.[25] In our study, in addition to the PSQI averages in the RLS group, subjective sleep quality, sleep latency, sleep efficiency, sleep disturbance, and use of sleep medication averages among the PSQI subcomponents were statistically significantly higher than the control group. No statistically significant difference was observed between the means of sleep duration and daytime dysfunction among the PSQI subcomponents. Moreover, within the cohort experiencing RLS, a statistically significant positive correlation was observed between the severity scale scores of RLS and the scores obtained from the PSQI.

Obsessive-compulsive disorder represents a substantial public health concern, exhibiting a prevalence within the range of 0.8%-3.2%. This condition gives rise to a decline in the quality of life, functional impairment, and disabilities across occupational and social domains.[26] It is characterized by recurrent obsessions and behaviors such as counting, checking, washing, and hoarding.[27] It tends to be frequently associated with conditions such as depression, panic disorder, eating disorders, social phobia, Tourette syndrome, and alcohol dependence.[28] It has been documented that an imbalance in serotonergic and dopaminergic activities within the central nervous system may play a role in the pathophysiology of various types of OCD.[29] Apart from anomalies in iron metabolism, dopaminergic dysfunction, and genetic alterations contributing to the etiology of RLS, dysfunctions in serotoninergic, glutamatergic, and opioid neurotransmitter mechanisms have also been proposed.[30-32] In addition to the commonalities in neurotransmitter mechanisms between RLS and OCD, it is known that psychiatric conditions such as psychosomatic diseases, anxiety disorders, impulse control disorders, and depression may accompany these 2 conditions.[10] A study in which RLS patients with and without dopamine agonist (DA) treatment were compared with healthy individuals found that MOCI subscores of suspiciousness and cleanliness were high.[33] In another study comparing primary RLS patients who did not receive medical treatment and who used dopamine agonists with healthy individuals, no difference was found in terms of the scores of the MOCI. However, it was noteworthy that some patients were more disadvantaged in the decision-making task under uncertainty despite receiving low-dose DA treatment.[34] Mazurie et al determined that OCD symptoms exhibited no variations among individuals with RLS, those without any sleep-related disorders, and those diagnosed with obstructive sleep apnea syndrome. Furthermore, the severity of RLS, irrespective of gender, demonstrated no significant association with the MOCI score.[35] In addition, dopaminergic agents used in the treatment of RLS have been reported to be associated with impulse control disorders with standard etiologic features with OCD.[36] Our study observed that the mean MOCI scores in RLS cases were statistically significantly higher than in healthy individuals. Furthermore, within the RLS cohort, a statistically significant positive correlation was established between the severity scale scores of RLS and the MOCI scores.

Restless legs syndrome is reportedly more prevalent among adolescents and adults diagnosed with ADHD.[37] While the coexistence of RLS and ADHD remains a subject of ongoing discussion, the potential linkage between these conditions, potentially indicative of a shared regulation of brain iron homeostasis and dopaminergic dysfunction, lends support to the conjecture positing a neurodevelopmental facet in the pathogenesis of RLS. The correlation between RLS and ADHD may arise from their shared associations with suboptimal sleep quality and iron deficiency.[38] Cortese et al suggested that these disorders may be related to iron deficiency because they affect the function of dopaminergic systems, leading to decreased levels of catecholamines, especially dopamine and serotonin.[13] Subsequent to a 12-week regimen of iron supplementation, a notable enhancement in ASRS scores was discerned among children diagnosed with ADHD, contrasting with the absence of such improvement in the placebo group.[39] It is recognized that conditions leading to sleep disruptions have the potential to induce or contribute to behavioral issues associated with mood alterations and diminished attention.[40] Consequently, there exists a plausible scenario wherein RLS precipitates ADHD and analogous symptomatic expressions. Nevertheless, certain investigations posit the likelihood of an interconnected physiopathological relationship between ADHD and RLS. In adults, the expansion of echogenic substantia nigra serves as a structural biomarker indicating dysfunction within the nigrostriatal dopaminergic system. A transcranial ultrasonography investigation revealed that the area of the substantia nigra was more pronounced in children diagnosed with ADHD compared to their counterparts in the healthy control group.[41] Our study identified a statistically significant positive association between the scores on the RLS severity scale and the ASRS. However, no correlation was discerned in relation to serum iron and ferritin levels.

The incidence of RLS rises proportionately with advancing age. Within an investigation examining RLS symptoms among participants aged 18-64 years diagnosed with ADHD, findings indicated

that individuals exhibiting RLS were of advanced age and demonstrated a higher prevalence of ADHD in comparison to those devoid of RLS symptoms. Hence, the presence of adult ADHD exhibited statistically significant elevations in fulfilling diagnostic criteria for RLS when alternative causative factors were excluded from consideration.[42] Our study observed no correlation between RLS severity scale scores and age in the RLS group.

Compared with the control group, OCD and ADHD scores were significantly higher, and sleep quality was significantly impaired in RLS patients. While there was no disparity in serum iron and ferritin levels between the RLS and control groups, these 3 conditions may have a shared etiopathogenesis in relation to dopamine and serotonin dynamics. This correlation could be due to the limited number of cases or the possibility that serum iron levels alone do not account for the etiology. Therefore, future studies must investigate whether these diseases are comorbid with a common etiology or pathophysiology and examine standard genetic components and brain iron levels.

Limitations

The constraints inherent in our study include the reliance on scales for the assessment of attention deficit and obsessive features rather than clinical diagnoses. Additionally, it should be noted that the study is limited by a relatively small number of cases.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (Approval No: 2021/359, Date: July 5, 2021).

Informed Consent: Written informed consent was obtained from the patients and healthy volunteers who participated in this study.

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