Original Article

Prevalence, severity and associated factors of restless leg syndrome in inflammatory bowel disease patients

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Abstract

Background: The association between restless leg syndrome (RLS) and inflammatory bowel disease (IBD) has often been an under-investigated and clinically misdiagnosed entity. An emphasis should be made on the severity and associated factors, as the prevalence of both entities is on the rise globally. In this study we aimed to investigate the prevalence, severity and associated risk factors of RLS in patients with IBD.

Methods: A multi-center, prospective cross-sectional study was conducted with age and gender matched controls in the ratio of 1:3. Cases of IBD were confirmed according to European Crohns and Colitis Organization guidelines. The study recruited 377 cases and 1131 age and gender-matched controls. RLS severity and prevalence was determined using a validated International Restless Legs Syndrome Study Group questionnaire. The anthropometric and blood biochemical measurements were retrieved from the patient's medical records. Associated factors were analyzed by regression analysis.

Results: The prevalence of RLS in patients with IBD and non-IBD control groups was 21.5% and 9.7%, respectively ($P = 0.001$). The severity index of RLS symptoms in all the three categories of mild, moderate and severe RLS was higher in the IBD group ($P = 0.001$). Obesity (BMI >30 Kg/m^2) was more prevalent in patients with IBD with RLS than without RLS (21.9%: 10.3%, $P = 0.009$). Ages between 46 and 59 years (OR = 18.7 [2.6–29.4], $P = 0.008$), obesity (OR = 22 [2.6–29.4], $P = 0.005$), higher TSH levels (OR = 1.7 [1.0–3.0], $P = 0.033$), and lower hemoglobin levels ($P = 0.028$) showed a greater risk associated with RLS.

Conclusion: Prevalence and severity of RLS was higher in patients with IBD. The risk factors for RLS in IBD include increasing age, obesity, higher TSH, and lower hemoglobin.

Keywords: Inflammatory bowel disease, prevalence, restless leg syndrome, risk factors, Saudi Arabia

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INTRODUCTION

Restless leg syndrome (RLS) is categorized as a chronic neurosensorimotor disorder that is characterized by both sensory and motor symptoms. Driven by an impulsive longing to the volitional movement of the legs, the episode is described as often accompanied by burning, tingling, pricking or painful sensation that worsens at rest and improves by movement, with a unique nocturnal occurrence.[1] The syndrome was first described by Willis in 1685, which was later extensively researched by Ekbom and first published in 1945.[2] Hence RLS is synonymous with Willis-Ekbom disease.

Epidemiological studies have reported a diverse global prevalence ranging from a lower range of 0.96–2.9% in Japan and India to a higher prevalence of 5%–29% in the general population of Western Europe, the United States, and Canada.[3-5] Primarily the syndrome may be idiopathic with no underlying causes often linked to familial disposition. However, evidence suggests that RLS may also be secondary to several other comorbid factors like ferritin and iron deficiency, renal insufficiency, pregnancy and eclampsia, multiple sclerosis, peripheral neuropathy, and gastrointestinal disorders like inflammatory bowel disease (IBD) and gastrectomy.[6] Both observational and analytical studies have shown the possible association between RLS and diabetes,[7] obesity,[8] pregnancy,[9,10] renal failure and hemodialysis,[11] low levels of ferritin or iron deficiency,[12] hereditary neuropathy,[13,14] medications like antidepressants, beta-blockers and anti-epileptics.[15,16] The association of the gastrointestinal disorder IBD with RLS is a less explored subject, and limited data are available to establish the possible association between them.

Becker and colleagues investigated the prevalence and severity of RLS in patients with IBD in Germany and found 9.4% of the Crohn's disease (CD) and 8% of the ulcerative colitis (UC) patients to have coexisting RLS with symptoms of moderate-intensity.[17] Although the prevalence in IBD was not different from their general population, an emphasis on clinical relevance and significance of RLS in IBD was made, which prompted an interdisciplinary approach in the management of IBD. Furthermore, Takahara *et al*.[18] conducted similar studies in Japanese patients with IBD and found a high prevalence of 20% and 17.6% of RLS in UC and CD patients, respectively, compared to the general population. Moreover, studies have shown significant differences in sleep disorders, fatigability, and poor quality of life (QoL) in patients with IBD having RLS, than those without RLS,[19,20] elucidating prompt diagnosis and management to improve QoL.

Large-scale, nationally representative prevalence studies from the region of Saudi Arabia do not exist, but a few sporadic studies were conducted among specific populations like pregnant/non-pregnant women,[21,22] institution employees,[23] or among general patients visiting primary health center,[24] with a prevalence of RLS ranging from 5% among general patients to 24% in pregnant women. However, RLS in IBD has never been previously investigated regionally. Although IBD has an idiopathic etiology, recent studies have suggested that RLS is probably one of its many extra-intestinal manifestations.[25] RLS is an under-investigated, misdiagnosed, and under-rated neurological disorder, especially when it is linked to gastrointestinal disorders such as UC and CD. Hence, this study was conducted with a primary aim to determine the prevalence of RLS in patients with IBD, and then to assess the severity of RLS and evaluate the associated factors. The findings may fill the gap in the existing literature and may provide valuable data for primary care physicians and specialists in understanding the contemporary trends of RLS in patients with IBD, that may involve a multidisciplinary approach involving gastroenterologists, and sleep medicine specialists, for coordinated management enhancing improved healthcare delivery.

METHODS

Study design and definitions

A multi-center, prospective cross-sectional study, with age and gender-matched controls for patients with IBD, was conducted across six hospitals from Central, Southern and Western regions of Saudi Arabia. Cases were defined on the basis of a confirmed diagnosis of IBD, with manifestations of either CD or UC according to European Crohns and Colitis Organization (ECCO) guidelines.[26] However, patients with a history of treatment with dopaminergic agents or anti-depressants and those with a history of psychiatric or neurological disorders were excluded. Controls included patients attending primary health care centers for non-gastrointestinal disorders without any symptoms that mimic RLS such as chronic neurological disorders, rheumatologic diseases, or psychiatric illnesses. The controls were matched with cases based on age and gender, in a ratio of 1:3 case: controls.

Diagnosis of RLS

RLS was diagnosed using a validated Arabic version of the International Restless Legs Syndrome Study Group (IRLSSG) questionnaire.[27] The questionnaire was interviewer-administered on the selected subjects. The IRLSSG questionnaire consists of five questions investigating RLS symptoms and their severity, five questions

assessing the impact of RLS symptoms on QoL and sleep. A diagnosis of RLS is made when the respondent answers in affirmative to all of the following four questions: (a) The urge to move one's legs, which is usually accompanied or caused by an uncomfortable sensation in the legs. (b) The urge to move the legs or unpleasant sensations beginning or worsening during periods of rest or inactivity. (c) The urge to move the legs or unpleasant sensations that are either partially or completely relieved by movement. (d) The urge to move the legs or unpleasant sensations that worsen in the evening or at night compared to during the day, or that occur only in the evening or night. In addition, the questionnaire also assesses the frequency of RLS. The IRLSSG severity scale for RLS (IRLS) is a 10-question scale to determine the severity of RLS symptoms. It includes five items about symptom frequency and intensity and five items focusing on the impact of symptoms on aspects of daily living and sleep. Based on the IRLS score, the severity of RLS is categorized; mild <10, moderate 11–20, severe 21–30, and very severe ≥31.[28,27]

Measurements of anthropometric and biochemical parameters

Anthropometric parameters like height in centimeters, weight in kilograms, and body mass index (BMI) in kg/m^2 and biochemical parameters like iron, ferritin, hemoglobin, magnesium, folate, vitamin B_{12}, and thyroid-stimulating hormone (TSH) were extracted from the patients' medical records.

Sample size

The sample size was calculated based on the prevalence of RLS reported by Shen *et al*.[29] as 16.8% in the IBD group and 13% in the control group, with an odds ratio of 1.6, assuming an 80% statistical power and a 5% two-sided alpha with a case/control ratio of 1/3. The minimum required sample size for this study was 1380 (345 cases and 1035 controls). The sample size was calculated using the Epiinfo™ software.

Statistical analysis

Categorical data were summarized as frequencies and percentages, whereas continuous data were initially tested for normality using Kolmogorov–Smirnov or Shapiro–Wilk test. Continuous data were presented as mean and standard deviation. For comparison of categorical and continuous variables, we used the Chi-square test and Student's *t* test, respectively. Analysis of variance (ANOVA) was used to compare continuous variables across multiple groups (RLS severity subgroups). A multivariate binary logistic regression analysis was done to identify the associations of RLS within the IBD population. An alpha level below 0.05 was considered for statistical significance. The statistical analyses were performed using IBM SPSS™ software, version 23.

Ethical considerations

The study approval was obtained by the Institutional Review Board (IRB) committee of the College of Medicine with approval number 11-538, and written informed consent was obtained from the participants.

RESULTS

The study recruited 377 cases with IBD and 1131 age and gender-matched controls. The comparison of anthropometric measurements and prevalence of RLS are shown in Table 1. Age and gender were well-matched between the cases and controls. The non-IBD control group showed higher mean values of weight and BMI than the patients with IBD ($P = 0.001$). The prevalence of RLS in patients with IBD was 21.5%, whereas it was 9.7% for the non-IBD control group ($P = 0.001$). The severity of symptoms of RLS as mild, moderate, and severe was significantly higher in patients with IBD than those in the

Table 1: Comparison of variables between patients with IBD and controls

Variables	Mean±SD/*n* (%)		*P*
	Patients with IBD (*N*=377)	Controls (*N*=1131)	
Age	31.34±11.83	31.56±11.72	0.940
Height	169.1±82.43	163.91±8.69	0.074
Weight	64.74±18.44	70.98±17.6	<0.001
BMI	23.68±6.18	26.32±5.8	<0.001
Age (Grouped)			
<30	206 (54.6)	618 (54.6)	1.000
30–45	119 (31.6)	357 (31.6)	
46–59	45 (11.9)	135 (11.9)	
≥60	7 (1.9)	21 (1.9)	
Age>45			
Age≤45	325 (86.2)	975 (86.2)	1.000
Age>45	52 (13.8)	156 (13.8)	
BMI≥30			
BMI<30	291 (87.1)	858 (76)	<0.001
BMI≥30	43 (12.9)	271 (24)	
Hb (Grouped)			
No Anemia	200 (56.2)	1021 (90.3)	<0.001
Anemia	156 (43.8)	110 (9.7)	
Gender			
Female	179 (47.5)	537 (47.5)	0.989
Male	198 (52.5)	593 (52.5)	
Prevalence of RLS			
No	296 (78.5)	1021 (90.3)	<0.001
Yes	81 (21.5)	110 (9.7)	
RLS Severity			
None	295 (78.2)	1019 (90.1)	<0.001
Mild	31 (8.2)	26 (2.3)	
Moderate	37 (9.8)	73 (6.5)	
Severe	13 (3.4)	13 (1.1)	
Very Severe	1 (0.3)	0 (0)	

Data are represented as mean ± standard deviation, or *n* (%) as appropriate

control group ($P = 0.001$). Approximately 8.2% of patients with IBD had mild RLS compared with 2.3% in the control group. Approximately 9.8% of patients with IBD had moderate RLS compared with 6.5% in the control group. Similarly, severe RLS was found in 3.4% of patients with IBD and in 1.1% in the control group.

A comparison between patients with IBD with and without RLS is presented in Table 2. Although not significant, patients with IBD with RLS were shorter in height, weighed more, and had lower levels of ferritin. Obesity (BMI >30 Kg/m^2) was higher in patients with IBD with RLS than without RLS (21.9%: 10.3%, $P = 0.009$).

Furthermore, multivariate logistic regression analysis was performed to determine the associations of RLS in patients with IBD, as shown in Table 3. The most powerful predictors of RLS were obesity (OR = 22 [2.6–29.4], $P = 0.005$) and age between 46 and 59 years (OR = 18.7 [2.6–29.4], $P = 0.008$). Higher TSH also showed more risk (OR = 1.7 [1.0–3.0], $P = 0.033$).

DISCUSSION

Recent studies have reported a rising prevalence of IBD over the last three decades.[30-34] Intestinal and extra-intestinal manifestations of IBD have been thoroughly investigated; however, its association with RLS is less explored. The current study adds vital data to the existing literature from the Middle East and Arab world.

The principal finding of the study is a higher prevalence of RLS in patients with IBD than in non-IBD controls. The severity index was also higher in IBD cases than in controls. These findings concur with a previous Korean study by Yun and his colleagues,[35] who reported RLS to be 2.59 times more common in IBD than in the non-IBD group (9.7% vs 3.8%; $P < 0.001$), However, the reported prevalence in our study is much higher than the Korean population, which could be related to the differences in the studied population and the diagnostic assessment criteria used. Furthermore, Weinstock *et al*. conducted pioneering research to establish the relationship between IBD and RLS in the United States population.[36] In the prospective multi-center study, Weinstock found a 30% prevalence of RLS in 272 consecutive CD patients visiting the clinics and concluded that RLS frequently occurs in CD, and as a possible extra-intestinal manifestation. Another recent study from Germany by Becker *et al*.[17] agrees with our findings.

This study also documented the predictors of RLS in IBD. Age between 46-59 years, obesity, higher TSH levels, and lower hemoglobin were associated with greater risk of RLS. With an odds ratio (OR) of 22 and 19, obesity (BMI >30 kg/m^2) and increasing age showed the highest risk associated with RLS. However, this study did not show a female predisposition in contrast to other global studies.[35,37,38] On the contrary, a regional study showed male predilection over females for RLS.[39] The

Table 2: Comparison between patients with IBD, with and without RLS

Variables (Mean ± SD)	IBD with RLS *N* = 81	IBD without RLS *N* = 296	*P*
Age	31.69 ± 11.83	31.21 ± 11.7	0.73
Height	164.63 ± 9.42	170.26 ± 9.4	0.72
Weight	68.41 ± 19.76	64 ± 18.17	0.08
Body Mass Index (BMI) kg/m^2	24.8 ± 6.34	23.37 ± 6.11	0.10
Thyroid Stimulating Hormone (mIU/L) (mmIU/Lml/UI	2.7 ± 1.75	2.45 ± 1.57	0.29
Ferritin (ng/ml)	62.42 ± 60.84	67.65 ± 60.26	0.95
Folate (mcg)	25.02 ± 8.76	24.97 ± 10.29	0.84
Vit B_{12} (ng/ml)	322.45 ± 401.96	253.53 ± 129.69	0.90
Transferrin (mg/dl)	2.71 ± 0.77	2.53 ± 0.63	0.16
Magnesium (mg/dl)	0.8 ± 0.1	0.82 ± 0.09	0.44
Iron (Fe) (mg/dl)	9.9 ± 5.43	10.31 ± 13.23	0.36
Hemoglobin (g/dl)	12.77 ± 21.13	12.51 ± 22.05	0.35
Age (Grouped)			
<30	50.6%	55.7%	0.772
30–45	35.8%	30.4%	
46–59	12.3%	11.8%	
≥60	1.2%	2%	
BMI ≥ 30 Kg/m^2			
BMI < 30	78.1%	89.7%	0.009
BMI ≥ 30	21.9%	10.3%	
Gender			
Female	49.4%	47%	0.699
Male	50.6%	53%	

Data are represented as mean ± standard deviation, or *n* (%) as appropriate.

Table 3: Associations of RLS among Patients with IBD using regression analysis

Variables in the Equation	*P*	OR [95% C.I.]
Age group (46-59) years	0.008	18.7 [2.1-26.2]
BMI≥30 kg/m^2	0.005	22.3 [2.6-29.4]
Height	0.027	0.9 [0.8-0.9]
TSH	0.033	1.7 [1.0-3.0]
Lower hemoglobin	0.028	0.9 [0.8-0.9]

difference in population characteristics may explain some of the differences as the above studies included the general population, whereas our study was specifically in patients with IBD.

Additional analysis of our study population showed that although the mean BMI of patients with IBD was significantly lesser than the control group, the mean BMI of IBD with RLS was higher than IBD without RLS, although not at the level of statistical significance. Moreover, the proportion of obese subjects was higher in IBD with RLS than in the non-RLS group (21.9%: 10.3%; $P = 0.009$). Consistency was observed with studies hypothesizing possible risk between obesity and RLS in the general population.[40,41] Gao *et al*.[40] showed a multivariate-adjusted OR of 1.4 (CI 1.3–1.6; $P < 0.001$) for RLS among subjects with BMI greater than 30 kg/m^2, concluding that both general obesity and abdominal adiposity increase the risk of developing RLS. A strong correlation between obesity and RLS was observed in many analytical studies in different populations, enumerating a fivefold risk of developing RLS among obese subjects.[8]

This study found subjects with increased TSH at 1.7 times more risk to develop RLS in patients with IBD. The intensity of the TSH profile increases with an increase in RLS symptoms, thus making TSH a precipitating factor.[42] Whether it is a coincidence or a cause-effect relationship, the ascending levels of TSH in the evenings and worsening symptoms of RLS is an issue warranting specific in-depth research. In addition, having lower levels of hemoglobin posed an additional risk for RLS. However, the effect of severity of anemia by gender on RLS in patients with IBD was not explored and may be a subject of interest in future studies.

The other established risk factors of RLS, like low ferritin concentration and other micronutrient deficiencies, did not appear significant in our study. Although lower levels of ferritin were found in IBD with RLS subjects than without RLS, the association did not reach the level of statistical significance, yet a considerable clinical significance cannot be ruled out. On the contrary, the mean vitamin B_{12} values were higher in IBD with RLS patients. These findings suggest that patients with IBD might have already been on micronutrient supplementation therapy. This is considered one of the study limitations.

Although the causative pathway and the pathophysiology are beyond the scope of our study, it is important to mention possible underlying mechanisms established by scientific and epidemiologic studies. It is hypothesized that polyneuropathy is the possible explanation for RLS in patients with IBD[43] as many studies have shown neuropathy to be consistent with IBD.[44,45] However, further studies are warranted in establishing the causative mechanism as many co-existing factors like vitamin B_{12} and ferritin deficiency also pose significant risks.

The study had several strengths and limitations. Our study population included a wide sample from different regions, making it more representative of the general population of Saudi Arabia. The age and gender matching between cases and controls was accurate. The sample size was also adequate to meet the requirements. Standardized diagnostic criteria from the IRLSSG questionnaire were used to diagnose RLS, whereas the standard ECCO guidelines were adopted for the diagnosis of IBD. The mean anthropometric and biochemical blood readings were extracted from the medical records. However, the study excluded the recording of other comorbid conditions that may confound the results. An in-depth analysis of hemoglobin deficiency based on age and gender was not performed. In addition, forward-looking causative studies are highly recommended to show the association and causative link between the two disease entities.

CONCLUSION

Our findings show a significant association between IBD and RLS. Obesity, older age, high TSH, and lower hemoglobin were precipitating factors of RLS in patients with IBD. We found no significant gender predisposition to RLS in patients with IBD. Further research is highly recommended to establish the causative link between RLS and IBD, which could prove beneficial in the prevention and management of RLS in patients with IBD. RLS cannot be neglected by gastroenterologists when diagnosing and treating patients with IBD.

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Conflicts of interest

There are no conflicts of interest.

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