Inflammatory bowel disease and restless leg syndrome

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ABSTRACT

الأهداف: ارتبط مرض الأمعاء الإلتهابي (IBD) بمتلازمة تململ الساق (RLS) حيث تهدف هذه الدراسة إلى استكشاف مدى الانتشار والتنبؤات السريرية وشدة حدوث متلازمة تململ الساق لدى مرضى الأمعاء الإلتهابية بالنسبة لمجموعة المقارنة.

المنهجية: أجرينا الدراسة في الفترة ما بين يناير وديسمبر من عام 2019 باستخدام استبيان الكشف عن متلازمة تململ الساق لمجموعة أمراض الأمعاء الإلتهابية ومجموعة المقارنة. حيث تم تطبيق تحليلات الانحدار اللوجستي للتحقيق في الارتباطات بين التركيبة السكانية للمرضى والسمات السريرية وتشخيص متلازمة تململ الساق.

النتائج: تم دراسة 218 مريضًا بامراض الأمعاء الإلتهابية و211 مريضا من مجموعة المقارنة بعد استبعاد 6 مرضى يعانون من الانزعاج الموضعي و 4 مرضى يعانون من التنصت المعتاد على القدم حيث كان متوسط العمر 30.2±11.7 سنه ونسبة الإناث 64%. كما تبين ان نسبة انتشار متلازمة تململ الساق هي (7.34%) لدى مرضى الأمعاء الإلتهابية و (8.06%) لدى مجموعة المقارنة. و كانت درجة شدة متلازمة التململ بسيطة لدى (7.34%) ومتوسطة لدى 25% وشديدة لدى 6.3% من مرضى أمراض الأمعاء الإلتهابية. كما تبين ان نسبة الإرتباط مع أمراض الأمعاء الإلتهابية اقل من مرضى مجموعة المقارنة عند تحليل نتائج مرضى متلازمة تململ الساق. كما نتج عن تحليل الإنحدار اللوجستي بان نقص فيتامين B12 له علاقة بمتلازمة تململ الساق لدى مرضى الأمراض الإلتهابية.

الخلاصة: لم يتم العثور على فرق في معدل انتشار متلازمة تململ الساق بين مرضى الأمراض الإلتهابية ومرضى مجموعة المقارنة. كما تبين ارتباط نقص فيتامين ب 12 بحدوث متلازمة تململ الساق.

Objectives: Inflammatory bowel disease (IBD) has been associated with restless leg syndrome (RLS). This study aims to explore the prevalence, clinical predictors, and severity of RLS in IBD patients compared to controls.

Methods: We conducted a case-control study between January and December of 2019 comparing IBD patients with controls. Assessment of RLS was performed using the previously validated diagnostic restless leg syndrome questionnaire (RLSQ). Logistic regression analyses were applied to investigate associations between patient demographics and clinical features and RLS diagnosis.

Results: A total of 218 IBD patients and 211 healthy controls were incorporated after excluding 6 patients with positional discomfort and 4 patients with habitual foot tapping. The mean age was 30.2±11.7 and 64% were females. The prevalence of RLS was 16/218 (7.34%) and 17/211 (8.06%) among cases and controls, respectively. Based on the RLSQ severity score, 6/16 (37.5%), 4/16 (25%) and 1/16 (6.3%) of the IBD patients with RLS had mild, moderate and severe RLS; respectively. The odds of IBD were lower among patients with confirmed RLS (OR=0.90, 95% CI=0.44-1.84, *p*=0.78). In the logistic regression analysis, only vitamin B12 deficiency (OR=10.20, 95% CI=1.40-74.10, *p*=0.022) was associated with RLS diagnosis among IBD patients.

Conclusion: No difference was found in the prevalence of RLS between IBD patients and non-IBD controls. Vitamin B12 deficiency was associated with RLS diagnosis among patients with IBD.

Inflammatory bowel disease (IBD) is a family of chronic inflammatory disorders that cause inflammation of the gastrointestinal tract. It comprises two main conditions: ulcerative colitis (UC) and Crohn's disease (CD). Approximately 30% of IBD patients suffer from extra-intestinal manifestations (EIMs), which can involve the rheumatologic, musculo-cutaneous, and hepato-biliary systems.[1,2] Anemia is a common manifestation of IBD that can be attributed to iron, folate (folic acid), or vitamin B12 deficiencies.[3]

Patients with IBD may develop neurological symptoms as part of the disease itself or through secondary complications, such as anemia. Perhaps one of its most distressing neurological manifestations is restless leg syndrome (RLS), which is a movement disorder characterized by an uncomfortable sensation in the legs which engenders restlessness temporarily relieved by movement. This discomfort takes place most commonly during night and when resting, and often disturbs sleep.[4] Iron deficiency anemia (IDA) has been strongly associated with RLS.[5,6] The RLS can be primary, i.e., idiopathic, or secondary, and is believed to be caused by both genetic and environmental factors.[7] The most common secondary causes of RLS include iron deficiency and kidney disease; other causes include cardiovascular disease, arterial hypertension, diabetes, liver cirrhosis, migraine, Parkinson's disease, and pregnancy.[7-9] In a previous study conducted in Saudi Arabia, the prevalence of RLS among IBD patients was estimated to be 21.5%, compared to 9.7% in controls.[10] Another study reported a 10% prevalence rate of RLS in North America and Europe, which is much higher than the prevalence rate reported by studies from Asian countries (0.6-1.8%).[9] In contrast to many findings in Asian countries, the prevalence of RLS has been reported to increase with age in Europe, North America, and Saudi Arabia,[10,11] and women have a higher prevalence of RLS compared to men.[11,12] Moreover, it has been suggested that patients with RLS have poorer health and quality of life.[11] This study describes the prevalence, clinical predictors, and severity of RLS in IBD patients compared with healthy controls.

Methods. We conducted a case-control study comparing healthy controls with IBD patients seen at the outpatient department of King Abdulaziz

University Hospital (KAUH), Jeddah, Kingdom of Saudi Arabia between January and December of 2019. Ethical approval was obtained from the Research Committee at the Biomedical Ethics Unit at KAUH (Reference #147-19). Written consent was obtained for all participants. All patients diagnosed with UC or CD were identified and recruited with no age restrictions. Diagnosis of CD and UC was based on standard clinical criteria. Clinical, laboratory, endoscopic, radiologic, and histologic data were collected. Patients with symptoms consistent with habitual foot tapping or positional discomfort were excluded. Controls with a history of habitual foot tapping, positional discomfort neuroleptic-induced akathisia, peripheral neuropathy and radiculopathy, diabetes mellitus (DM), Parkinson's disease, end stage renal failure, rheumatoid arthritis (RA), scleroderma, hyperparathyroidism, symptomatic peripheral neuropathy, migraine, attention defect, multiple sclerosis, pregnancy, organ failure, lung transplantation, pre-existing fibromyalgia, tremors, or bruxism were excluded.

Restless leg syndrome diagnosis and evaluation. Assessment of RLS was performed using the restless leg syndrome questionnaire (RLSQ),[13,14] which is a self-rating questionnaire that comprises 3 parts: the first part explores administrative, demographic, past medical history of any chronic illness and medication history, smoking habits, physical examination (anthropometric measures), and laboratory results of vitamin D; the second part is composed of the RLS diagnostic criteria items 1-4 (**Table 1**); and the third part addresses each criterion through a set of closed questions, requiring "YES" or "NO" answers. All of the criteria must have been met for a diagnosis of RLS. Family history and assessment of the severity of the symptoms was estimated by the third part of the questionnaire, which comprised a severity rating scale and an inquiry about family history of RLS. This consisted of 10 questions, where each item had a set of five responses to choose from: 0=none, 1=mild, 2=moderate, 3=severe, 4=very severe. A total score could range between 0 and 40, which was subcategorized as follows: a score of 0 was none, a score of 1-10 was mild, a score of 11-20 was moderate, a score of 21-30 was severe, and a score of 31-40 was very severe.

Selection of controls. Controls free of any GI symptoms that did not have a previous diagnosis of IBD were randomly selected and recruited from the outpatient clinics and from social media platforms.

Outcomes. The primary outcome of the study was to estimate the prevalence of RLS among IBD cases relative to controls. The secondary outcome was to identify predictors of RLS (and severe RLS) among patients with IBD.

Sample size calculation and statistical analysis. For sample size calculation, we hypothesized that the incidence of RLS detection (outcome) in patients with IBD (exposure) is twice as high as the baseline incidence rate of RLS in the general population (20% versus 10%). Assuming a type 1 error of 0.05 and 80% power to detect RLS, we estimated that 219 IBD patients and 219 healthy controls would be needed to detect an odds ratio (OR) of at least 2 (2-sided). This was calculated using OpenEpi, version 3 based on the reported prevalence rate in Saudi Arabia.[15]

Descriptive statics were used for quantitative variables, including means, standard deviations (SD), and minimum and maximum values or medians with inter quartile ranges (IQR), and summarized where appropriate. For qualitative variables we used frequencies measurement. McNemar's test was incorporated to estimate the odds of IBD (exposure) vs. no IBD (no

Table 1 - The restless leg syndrome diagnostic criteria. shall we add

1. Do you experience an urge to move the legs that is usually accompanied by an uncomfortable and unpleasant sensation in the legs?
2. Do you experience an urge to move your legs or an unpleasant sensation that begins or worsens during periods of rest or inactivity, such as lying or sitting?
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as that activity continues.
4. Do you experience an urge to move your legs or an unpleasant sensation that is worse in the evening or at night than during the day or only occurs in the evening or night?.

*All 4 criteria must be fulfilled for the diagnosis of restless leg to be made. **Adapted from Allen et al, official journal of the Movement Disorder Society. 2011;26(1):114-20.

exposure) in RLS patients (cases) relative to healthy controls.

Logistic regression was applied to investigate associations between patient clinico-demographics features and RLS among patients with IBD; OR with 95% confidence intervals (CI) were reported. Linear regression analysis was utilized to identify predictors of RLSSS and regression coefficients (Coef.) with 95% CI were generated. A *p*-value of <0.05 was set as statistically significant. Stata/IC 12.1 for software for Mac (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP.) was used for all analysis.

Results. *Baseline characteristics.* A total of 218 IBD patients and 211 healthy controls were included after excluding 6 patients with positional discomfort and 4 patients with habitual foot tapping. The mean age was 30.3±11.8 and 64.6% were females. Seventy-seven percent of the participants were non-smokers, and 91.8% did not have a family history of IBD (**Table 2**).

Study outcomes. The RLS was diagnosed in 16/218 (7.34%) and 17/211 (8.06%) of IBD cases and non-IBD controls, respectively; the prevalence ratio of prevalence ratio of 0.91 (95% CI=0.47-1.76, *p*=0.78) was not statistically significant. Responses to the RLS screening questionnaire are outlined in **Table 3**.

The likelihood of having IBD in patients with confirmed RLS relative to those that did not have RLS is expressed by the (OR=0.90, 95% CI=0.44-1.84, *p*=0.78), which is not statistically significant (**Table 4**).

Table 2 - Baseline characteristics of the study cohort.

Characteristics	IBD (N=218)	Controls (N=211)	*P*-value
Mean age in years+-SD	30.90±1200	29.70±11.58	0.29
Female gender (%)	112	165	<0.001
Smoking status:			0.001
Never	161	170	0.07
Current cigarette	27	19	0.15
X cigarette	3	20	0.001
Current water pipe	17	10	0.15
X water pipe	2	0	0.15
Family history of IBD	17	19	0.68
Comorbidities:			
No chronic illness	178	172	0.36
DM	6	6	0.99
Hypertension	7	7	0.97
Rheumatoid arthritis	4	4	0.97
Vitamin B12 deficiency	7	12	0.22
Varicose veins	7	1	0.04
COPD	5	1	0.11
Hypothyroidism	4	7	0.34
Durations of RLS in years	1.36+-0.69	1.45+-0.79	0.20

Based on the RLSQ severity score, 6/16 (37.5%), 4/16 (25%) and 1/16 (6.3%) of the IBD patients with RLS had mild, moderate and severe RLS, respectively (**Table 5**).

Predictors of RLS and severe RLS among IBD Patients. In a logistic regression analysis, only Vitamin B12 deficiency (OR=10.2, 95% CI=1.40-74.10, *p*=0.022) was associated with RLS diagnosis among patients with IBD (**Table 6**).

Table 3 - Results of the RLS screening questionnaire for the study cohort.

Questions	IBD (N=218)	No IBD (N=211)	P-value
Do you experience an urge to move your legs that is usually accompanied or caused by uncomfortable and unpleasant sensations in the legs?	47	51	0.52
Do you experience an urge to move or an unpleasant sensation that begins or worsens during periods of rest or inactivity such as lying or sitting?	34	53	0.01
Do you experience an urge to move or unpleasant sensations that are partially or totally relieved by movement, such as by walking or stretching, at least as long as the activity continues?	41	60	0.02
Do you experience an urge to move or unpleasant sensations that are worse in the evening or at night than during the day or only occur in the evening or at night?	25	27	0.67

Table 4 - The study outcome comparing the odds ratio of IBD in patients with and without RLS.

	IBD (Exposure) (N=218)	Controls (No exposure) (N=211)	Total Cohort (N=429)	Statistics
Restless leg syndrome (Case)	16	17	33	OR=0.90
No restless leg syndrome (Control)	202	194	396	95% CI=0.44 - 1.84
Total	218	211	429	*p*=0.78

Table 5- Responses to the restless leg syndrome questionnaire comparing IBD patients and controls and a comparison of severity scores between the 2 cohorts.

Questionnaire items	IBD N=218	No IBD N=211	P-value
	Mean±SD		
Overall, how would you rate The RLS discomfort in your legs or arms?	0.34±0.55	0.34±0.78	0.98
How would you rate the need to move around because of your RLS symptoms?	0.31±0.74	0.36±0.84	0.53
How severe was your sleep disturbance due to your RLS symptoms?	0.22±0.73	0.21±0.68	0.92
How severe was your tiredness or sleepiness during the day due to your RLS symptoms?	0.21±0.69	0.16±0.56	0.41
Overall, how severe was the impact of your RLS symptoms on your ability to carry out your daily affairs, for example carrying out a satisfactory family, home, social, school or work obligation?	0.27±0.96	0.16±0.52	0.14
How severe was your mood disturbance due to your RLS symptoms, for example feeling angry, depressed, sad, anxious or irritable?	0.28±0.79	0.26±0.74	0.75
Overall, how much relief of your RLS arm or leg discomfort did you get from moving around?	0.31±0.76	0.28±0.71	0.70
How often do you get RLS symptoms?	0.43±1.01	0.42±0.86	0.88
When you had RLS symptoms, how severe were they on average?	0.32±0.74	0.27±0.64	0.41
Total RLS severity score (RLSSS)	2.69±6.04	2.45±5.39	0.67
Severity category according to RLSSS	n (%)		P-value
Mild RLS (Total RLSSS=1-10)	6	6	0.94
Moderate RLS (Total RLSSS=11-20)	6	7	0.80
Severe RLS (Total RLSSS=21-30)	4	3	0.82
Very severe RLS (Total RLSSS=31-40)	0	1	-----
Pearson chi2 (3)=1.1906			0.76
Total number of RLS cases	16	17	33

Linear regression analysis identified male gender to be negatively associated with RLS severity (Coef.= -2.73, 95% CI=-4.47 - -0.98, *p*=0.002), and DM (Coef.=5.74, 95%=0.61 – 10.87, *p*=0.029) and hypothyroidism (Coef.=5.92, 95% CI=0.86 – 10.99, *p*=0.022) to be positively associated with more severe forms of RLS (**Table 6**).

Discussion. The RLS etiology is poorly understood, but a high prevalence of RLS has been linked with several

Table 6 - Predictors of restless leg syndrome and severe restless leg syndrome among IBD patients according to multiple logistic and linear regression analysis, respectively.

???	Odds ratio	*P*-value	95% CI
RLS			
Age in years	1.05	0.09	0.99-1.09
Sex	1.06	0.94	0.26-4.27
Cigarette smoker	0.50	0.56	0.05-5.10
X-cigarette smoker	0.81	0.86	0.08-7.92
DM	3.20	0.30	0.35-29.08
Rheumatoid Arthritis	7.72	0.12	0.60-99.95
Vitamin B12 deficiency	10.20	0.02	1.40-74.08
Varicose veins	5.01	0.11	0.68-36.92
COPD	5.47	0.16	0.51-59.00
RLSSS	**Coef**	***P*-value**	**95% CI**
Age in years	0.05	0.21	-0.03-0.12
Male gender	-2.73	0.002	-4.47--0.98
Cigarette smoker	-0.51	0.69	-3.02-2.01
X-cigarette smoker	-0.47	0.74	-3.29-2.34
Water pipe smoker	-1.61	0.39	-5.29-2.07
DM	5.74	0.03	0.60-10.87
Hypertension	0.83	0.73	-3.86-5.51
Rheumatoid Arthritis	5.48	0.06	-0.23-11.20
Vitamin B12 deficiency	3.46	0.12	-0.94-7.85
Varicose veins	0.96	0.66	-3.44-5.53
COPD	5.92	0.02	0.86-10.99
Hypothyroidism	0.64	0.83	-5.08-6
COPD - Chronic obstructive pulmonary disease			

diseases, such as kidney disease, cardiovascular disease, hypertension, obesity, respiratory disease, insomnia, mental illness[7,8,16-18] arthritis, anemia, and DM.[19-23] Moreover, literature that links RLS with IBD is often contradictory. Therefore, our study aimed to assess the prevalence of RLS in IBD patients in comparison with controls who did not have IBD. Our results suggest that RLS is less likely to occur in IBD patients relative to controls (OR=0.90, 95% CI=0.44-1.84, *p*=0.78) with a prevalence ratio of 0.91 (95% CI=0.47-1.76, *p*=0.78). By contrast, a number of other studies have suggested that RLS occurred more frequently in patients with IBD than the general population, with a reported prevalence rate of between 20% and 30%,[2,9,10,22] although our prevalence rate was similar to that of one other study (8.8%).[24]

Many studies have assessed the severity of RLS and reported the presence of moderate to very severe distressing manifestations in 55.2% to 97.2% of patients,[13,25-28] and very severe distressing manifestations in 2.3% to 5%.[13,26,27,29] By contrast, our study results revealed that the majority of IBD patients with RLS had mild (37.5%) or moderate (25%) RLS symptoms. Furthermore, most studies have shown that the prevalence of RLS is more common in females than males;[12,22,24-27,29] however, this inequality in gender is found mainly with respect to more severe manifestations.[12] Also, some studies have reported that moderate to severe manifestations are more predominant among females than males.[12,30] Results of our analysis are consistent with this finding as among our cohort of IBD patients, more severe forms of RLS were seen among females (-2.73, 95% CI=-4.47- -0.98, *p*=0.002). Other predictors of severity included DM (Coef.=5.74, 95%=0.61–10.87, *p*=0.029) and hypothyroidism (Coef.=5.92, 95% CI=0.86–10.99, *p*=0.022).

Multiple previous studies have reported a significant association between RLS and older age,[10,21,31] which is not supported by our results (OR=1.04, *p*=0.09), although there was an observed non-significant statistical trend. Results from a study that evaluated RLS in a cohort of Greek patients with IBD described an increased prevalence of RLS observed before 79 years, and a decreased prevalence above this age.[31] In a study of French adults, the prevalence of RLS appeared to increase with age up to 64 years, and then declined,[26] and a Turkish study reported an increase in RLS prevalence with increasing age up to 67 years followed by a drop thereafter.[21] In contrast, some other studies found no relationship between the prevalence of RLS and age.[18,27]

According to our analysis, having confirmed vitamin B12 deficiency is associated with RLS (OR=10.2, 95% CI=1.40-74.10, *p*=0.022). This finding is supported by previous studies[19,23,24] that have associated RLS with vitamin B12 and found that replacing vitamin B12 alleviated RLS symptoms.[23] By contrast, Tasdemir et al[21] have found no association between RLS and vitamin B12 deficiency. Previous studies have considered varicose veins and habitual foot tapping to be RLS mimickers, and excluded them from the diagnosis of RLS.[19] We therefore elected to exclude patients with symptoms consistent with habitual foot tapping or positional discomfort, both of which could be confused with RLS. Varicose veins has been previously associated with RLS but our study results did not support this notion as the association between RLS and varicose veins based on multiple regression analysis appeared to be non-significant statistically (OR=5.1, 95% CI=0.68-36.92, *p*=0.11).[20,32-34] Moreover, 2 of these studies note that an improvement in RLS symptoms often occurs after superficial venous insufficiency is treated surgically.[33,34] According to the RLSSS and based on our linear regression analysis, other predictors of severe RLS include male gender (Coef.=-2.73, 95% CI=

-4.47- -0.98, *p*=0.002), DM (Coef.=5.74, 95% = 0.61 – 10.87, *p*=0.029) and hypothyroidism (Coef.=5.92, 95% CI=0.86 – 10.99, *p*=0.022).

We acknowledge that our study is limited by its cross-sectional design and the use of a self-reported questionnaire to assess for RLS symptoms. Another limitation is the absence of data concerning hemoglobin levels for statistical adjustment. This was decided owing to the difficulty anticipated with the acquisition of such test samples from a large population of controls.

In conclusions, in this Saudi Arabian cohort, patients with IBD had no increase in the prevalence of RLS when compared to non-IBD controls. Vitamin B12 deficiency was associated with RLS diagnosis. Female gender, DM and hypothyroidism were associated with more severe forms of RLS.

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Statistics

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Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as the use of *P* values, which fails to convey important information about effect size. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the computer software used.