International Journal of Colorectal Disease (2018) 33:955–962
https://doi.org/10.1007/s00384-018-3032-8

ORIGINAL ARTICLE

Restless legs syndrome is a relevant comorbidity in patients with inflammatory bowel disease

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Accepted: 19 March 2018 / Published online: 3 April 2018

Abstract

Background and aims In patients with inflammatory bowel disease (IBD), restless legs syndrome (RLS) may occur as an extraintestinal disease manifestation. Iron deficiency (ID) or folate deficiency/vitamin B_{12} deficiency (FD/VB_{12}D) has previously been described to cause RLS. Here, we determined the prevalence and severity of RLS in IBD patients and evaluated the effect of iron and/or folic acid/vitamin B_{12} supplementation.

Methods Patients were screened for ID and RLS by a gastroenterologist. If RLS was suspected, a neurologist was consulted for definitive diagnosis and severity. Patients with RLS and ID, FD, or VB_{12}D received supplementation and were followed-up at weeks 4 and 11 after starting supplementation.

Results A total of 353 IBD patients were included. Prevalence for RLS was 9.4% in Crohn's disease (CD) and 8% in ulcerative colitis (UC). Prevalence for the subgroup of clinically relevant RLS (symptoms ≥ twice/week with at least moderate distress) was 7.1% ($n = 16$) for CD and 4.8% ($n = 6$) for UC. 38.7% of RLS patients presented with ID, FD, and/or VB_{12}D. Most frequently ID was seen (25.8%; $n = 8$). Iron supplementation resulted in RLS improvement ($p = 0.029$) at week 4 in seven out of eight patients.

Conclusion Although the overall prevalence of RLS in IBD did not differ to the general population, clinically relevant RLS was more frequent in IBD patients and, therefore, it is important for clinicians to be aware of RLS symptoms. Though for definite diagnosis and proper treatment of RLS, a neurologist must be consulted. Additionally, iron supplementation of IBD patients with ID can improve RLS symptoms.

Trial registration ClinicalTrials.gov No. NCT03457571

Keywords Restless legs syndrome · Inflammatory bowel disease · Iron deficiency · Crohn's disease · Ulcerative colitis

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00384-018-3032-8) contains supplementary material, which is available to authorized users.

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Introduction

Patients with inflammatory bowel disease (IBD) such as Crohns's disease (CD), ulcerative colitis (UC), or IBD unclassified (IBD-U) develop in about 30% extraintestinal manifestations mostly including joints, skin, and the hepatobiliary system [1]. Although less frequent, neurological manifestations such as peripheral neuropathy, cranial neuropathies, or multiple sclerosis can occur [2]. Neurological symptoms may also occur secondary due to deficiencies including iron deficiency (ID), folate (folic acid) deficiency (FD), or vitamin B_{12} deficiency (VB_{12}D). Especially, ID is a common complication in IBD patients and is often underdiagnosed [3]. Besides anemia, ID can also result in restless legs syndrome (RLS) [4].

In a previous study in North America, a prevalence of 30% for RLS in patients with CD was shown and it was hypothesized that RLS should be considered as an extraintestinal

manifestation of CD [5]. Data for the prevalence of RLS in UC are lacking so far in Europe and North America. One recent study in Japan showed a prevalence of 21% in UC [6]. RLS is a common neurological disease that is characterized by a substantial urge to move legs or other parts of the body and is accompanied by unpleasant sensations. Furthermore, symptoms are typically aggravated during rest or inactivity and can be relieved by movement. The symptoms either deteriorate or occur exclusively during nighttime [7]. RLS may be categorized as primary early-onset and secondary late-onset [8, 9]. In idiopathic RLS, it is hypothesized that there is a hereditary component [9, 10]. In the last years, genome-wide association studies revealed a strong association between RLS, homeobox genes, and others that are possibly associated with iron metabolism [9, 11]. Secondary RLS has been associated with a various number of conditions such as peripheral polyneuropathy or end-stage renal disease [12]. Of note, ID has been described as a factor for clinically relevant RLS and it has been reported that patients with ID anemia suffer more severe symptoms [13].

Thus, the aim of this study was to determine the prevalence and severity of RLS in patients with CD and UC in a tertiary IBD outpatient referral center in Germany. For this, a collaborative approach between gastroenterologists and neurologists was chosen. Furthermore, the effect of iron and folic acid supplementation in IBD patients with RLS and a respective deficiency was evaluated.

Methods

Study design and assessment

IBD patients (age ≥ 18 years) presenting at our IBD outpatient clinic (tertiary referral center) between February 2014 and February 2015 were prospectively recruited for the study after written consent. The study was approved (16 January 2014) by the ethics committee of the Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin (reference EA4/132/13). The study is registered at clinicaltrials.gov with the identifier NCT03457571.

Assuming a prevalence of 30% in Crohn's disease patients [5] and a desired confidence interval of ± 10% according to the modified Wald method, 80 patients had to be included. Since we wanted to estimate the prevalence in Crohn's disease and ulcerative colitis patients separately, a total of 160 patients were deemed to be necessary. Patients were screened for symptoms of ID and RLS by a self-developed questionnaire (see Supplementary data) and explored for RLS symptoms by a gastroenterologist. When at least one symptom of RLS was present, patients were referred to a neurologist for RLS or differential diagnosis. RLS diagnosis was established on the basis of the diagnostic criteria of the International RLS Study Group [7]: (1) an urge to move the legs usually but not always accompanied by, or felt to be caused by, uncomfortable and unpleasant sensation in the legs; (2) the urge to move the legs and any accompanying unpleasant sensations, begin or worsening during periods of rest or inactivity; (3) the urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement; (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; and (5) the occurrence of the above features is not solely accounted for symptoms primary to another medical or behavioral condition. A complete neurological examination was performed in all patients to rule out potential differential diagnosis. For severity of RLS symptoms, the International RLS Severity Scale (IRLS) was applied [14]. The scale has a range from 1 to 40 and is graduated in mild (1–10), moderate (11–20), severe (21–30), and very severe (31–40) symptoms. In two prior epidemiological studies, a consensus expert definition for patients with clinically relevant RLS ("RLS sufferers") served to define a patient subgroup who likely required medical treatment [15, 16]: symptoms have to occur at least twice per week with at least moderate severity. The IRLS questionnaire items were used in order to define these criteria [14].

Deficiencies for iron, folic acid, or vitamin B_{12} were diagnosed with transferrin saturation below 15% in serum for ID, serum folic acid levels below 4.6 μg/dl for FD, and cyanocobalamin levels below 191 ng/l and methylmalonate levels above 32 μg/l in serum for $VB_{12}D$, respectively.

Folic acid was supplemented by an oral intake of 5 mg per day. Patients' iron substitution requirement was estimated according to Ganzoni formula (total iron deficiency (mg) = [reference Hb − actual patient Hb (g/dl)] × actual body weight (kg) × 2.4 + 500 (mg)) [17], and Fe^{3+} complexes were administered intravenously.

In patients with deficiencies, follow-up visits were scheduled at weeks 4 and 11 after starting supplementation. Follow-up visits were conducted by the neurologist, and the IRLS was performed in all patients at each visit.

Data collection

Data were collected from all participating patients by using a self-developed data registry for IBD patients ("Charité IBD data registry"). Primary IBD diagnosis, disease duration, disease localization, and progression were categorized using the Montreal classification [18].

Statistical analysis

Statistical analysis was performed using SPSS software package (IBM SPSS Statistics for Windows V. 23). For categorical data, chi-square test or Fisher's test was used. For not normally distributed data, the non-parametric Mann-Whitney,

Kruskal-Wallis, and Wilcoxon tests were applied, where appropriate. Linear regression analysis was performed for the dependent variable IRLS score with possibly associated characteristics, defined as independent variables. Parameters, which showed an association with the IRLS score in the univariable analysis, were included then in the multivariable analysis. Non-standardized regression coefficients (B) with a 95% confidence interval (95% CI), p values, as well as adjusted R^2 for the multivariate model are reported. Results of all tests were considered statistically significant if $p \leq 0.05$.

Results

Prevalence of RLS in IBD

A total number of 353 IBD patients were included in the study (224 CD, 125 UC, 4 IBD-U). There were 57.6% ($n = 129$) of female and 42.4% ($n = 95$) of male CD patients and 47.2% ($n = 59$) of female and 52.8% ($n = 66$) of male UC patients, respectively.

RLS was suspected in 13% ($n = 46$) of all patients by a gastroenterologist based on the questionnaire and clinical assessment. The majority of RLS patients were female (71%; $n = 22$). For CD, RLS was suspected in 12.9% ($n = 29$) of patients and confirmed by a neurologist in 72.4% ($n = 21$) of cases. For UC, in 13.6% ($n = 17$) of patients, RLS was suspected and confirmed by a neurologist in 58.8% ($n = 10$) of cases. The most common differential diagnosis established by the neurologist was polyneuropathy ($n = 5$). In all other cases, RLS was excluded but no further differential diagnosis could be established. Overall prevalence for RLS in IBD was 8.8% (CD 9.4%, UC 8%; Fig. 1). Data about concomitant diseases (malignoma, autoimmune disease, depression, coronary heart disease, osteoporosis, arterial hypertension, diabetes) were collected but showed no significant findings (see supplementary data Table 4).

The prevalence for the subgroup RLS sufferers (symptoms ≥ twice per week and with at least moderate distress) was 7.1% ($n = 16$) for CD and 4.8% ($n = 6$) for UC.

Deficiencies and follow-up after substitution

Of all RLS patients ($n = 31$), a total of 12 patients had at least one deficiency (ID, FD, $VB_{12}D$). Most frequently ID was seen in 25.8% ($n = 8$) of all RLS patients. FD was seen in 16.1% ($n = 5$) and $VB_{12}D$ in 3.2% ($n = 1$) of all RLS patients. However, one patient had concomitant ID and FD, and another patient had ID and $VB_{12}D$. Eleven patients were substituted. Nine patients could be followed up to week 11 after

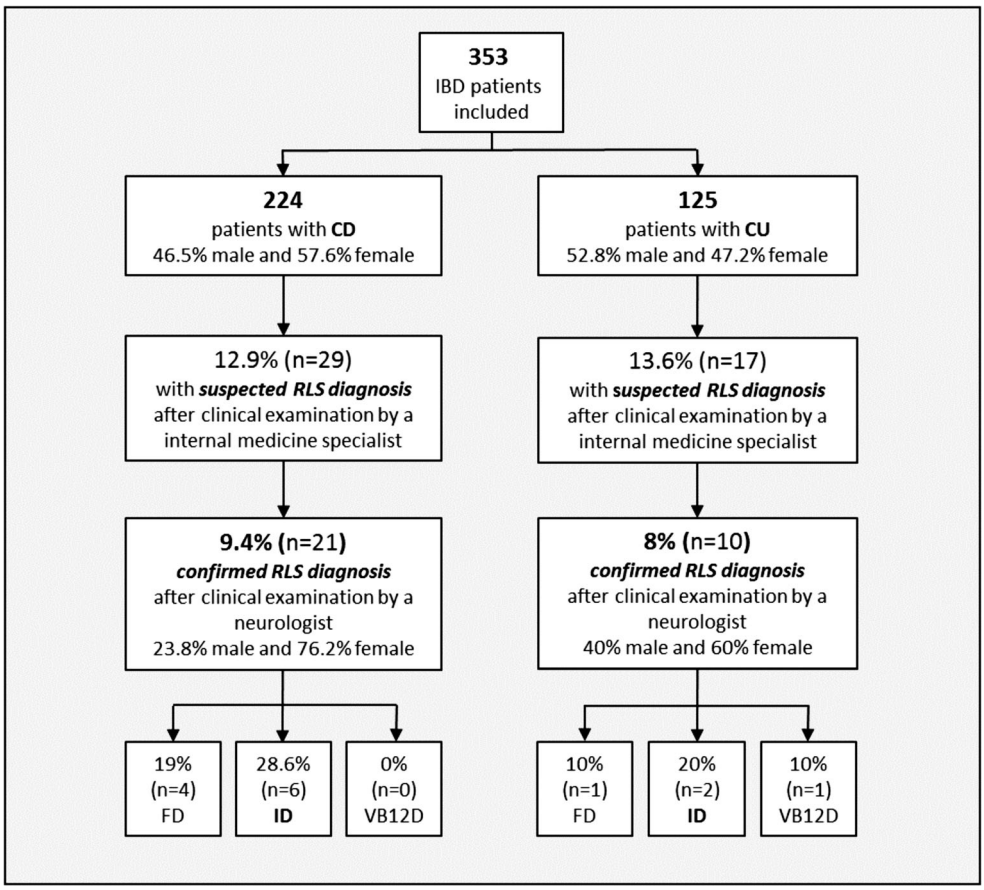


Fig. 1 Three hundred fifty-three patients were screened by a questionnaire and examined by a gastroenterologist for RLS symptoms. Patients suspected for RLS were consecutively examined by a neurologist to confirm RLS diagnosis and were subsequently screened for deficiencies of iron, folate, or vitamin B_{12}. Not shown are four patients with indeterminate colitis with no suspicion for RLS. FD folic acid deficiency, ID iron deficiency, $VB_{12}D$ vitamin B_{12} deficiency

starting substitution (Table 1). Eight patients underwent iron substitution (Fig. 2). There were significantly lower IRLS scores at week 4 after iron substitution ($p = 0.029$), though at week 11, at least a trend in changes of IRLS scores (albeit not significant) ($p = 0.058$) was seen when compared to baseline. Seven out of eight patients had decreased IRLS score after substitution. Six out of eight patients developed a decrease of at least one IRLS category. Two patients showed no RLS symptoms at all after substitution. At week 11 after substitution, five patients presented with a recurrent increase of IRLS score. One patient was still without any RLS symptoms.

Three patients with FD were treated, and a follow-up was performed. Two patients showed a decreased and one patient an increased IRLS score by one IRLS category in week 4 after starting substitution.

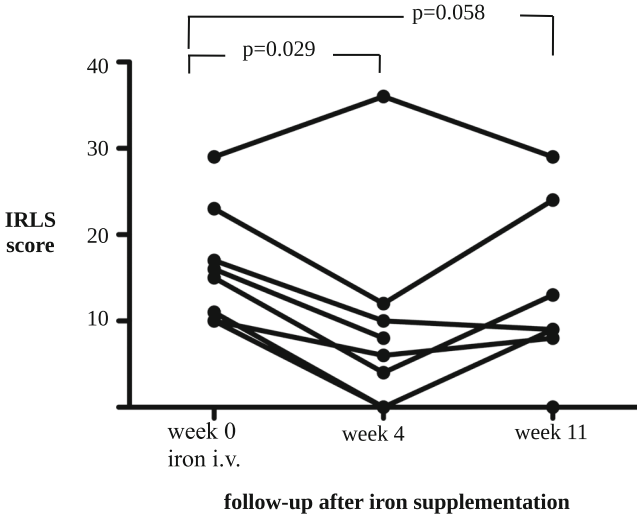


Fig. 2 Follow-up after iron supplementation and IRLS score. Change of IRLS score after iron supplementation of IBD patients with RLS and ID is shown. Eight IBD patients received parenteral iron supplementation at week 0 and were followed-up at weeks 4 and 11, and IRLS score was determined. IRLS score: mild (1–10), moderate (11–20), severe (21–30), and very severe (31–40)

Factors affecting RLS severity in IBD

Severity of RLS in relation to the type of IBD, disease duration, location, behavior, and extend as well as ID, FD, or $VB_{12}D$; sex; and age was assessed (Table 2).

16.1% ($n = 5$) of patients showed mild, 54.8% moderate ($n = 17$), 25.8% severe ($n = 8$), and 3.2% ($n = 1$) very severe symptoms of RLS. Severity of RLS symptoms based on plain IRLS score did not differ significantly between CD and UC; however, when IRLS score-dependent graduation was considered, the majority of CD patients (61.9%, $n = 3$) presented with moderate symptoms whereas the majority of UC patients (40%, $n = 4$) had severe to very severe symptoms (Fig. 3a).

Female patients suffered significantly more often from at least severe RLS symptoms than male patients (40.9% ($n = 9$) female vs. 0% ($n = 0$) male; $p = 0.001$) and had significantly higher IRLS scores than male patients ($p = 0.001$, Fig. 3b).

To characterize the impact of patient age on RLS symptoms, two groups with patients over 45 years of age ($n = 16$) and patients below 45 years of age ($n = 15$) were created based on a previous study which divided into early-onset RLS (with age < 45, likely hereditary cause) and late-onset RLS (with

Table 1 Follow-up of RLS patients with iron, folate, or vitamin B_{12} deficiency

	IRLS score before substitution	IRLS score at week 4	IRLS score at week 11	Iron deficiency	Folic acid deficiency	Vitamin B_{12} deficiency
Patients with iron deficiency						
1	29	36	29	+	−	−
2	16	8	−	+	−	+
3	11	0	0	+	−	−
4	15	4	13	+	−	−
5	10	0	9	+	−	−
6	10	6	8	+	+	−
7	17	10	9	+	−	−
8	23	12	24	+	−	−
p value		*0.029*	*0.058*			
Patients with folic acid deficiency						
9	29	15	−	−	+	−
10	9	19	7	−	+	−
11	26	20	25	−	+	−

IRLS scores of patients before substitution and at weeks 4 and 11 after starting substitution of iron and/or folic acid, respectively, are shown. *p* values are calculated, comparing IRLS scores of patients 1–8 before substitution with IRLS scores at week 4 or 11 after starting substitution (Wilcoxon test)

Table 2 IRLS scores in relation to clinical characteristics of IBD patients

	No. of patients (%)	IRLS score, means (SD)	*p* value
Crohn's disease	21 (67.7)	15.8 (± 7.2)	ns
Ulcerative colitis	10 (32.3)	17.9 (± 9.2)	
Sex			
Male	9 (29.0)	9.9 (± 4.4)	*0.001*
Female	22 (71.0)	19.1 (± 7.3)	
Age			
< 45	15 (48.4)	12.9 (± 5.7)	*0.024*
≥ 45	16 (51.6)	19.7 (± 8.2)	
Iron deficiency			
EM+	8 (25.8)	14 (± 8.3)	ns
EM−	23 (74.2)	15.5 (± 6.7)	
Folate deficiency			
FD+	5 (19.3)	17.6 (± 9.3)	ns
FD−	26 (80.7)	16.2 (± 7.7)	
Vitamin B_{12} deficiency			
$VB_{12}D$+	1 (3.2)	N.S	
$VB_{12}D$−	30 (96.8)	N.S	
CD location			
L1 (ileal)	5 (23.8)	10.6 (± 6.4)	ns*
L2 (colonic)	4 (19.1)	19.2 (± 8.7)	
L3 (ileocolonic)	8 (38.1)	17 (± 6.6)	
L4 (upper gastrointestinal)	4 (19.1)	16.3 (± 7.1)	
CD behavior			
B1 (non-stricturing/non-penetrating)	9 (37.5)	18.2 (± 5.4)	ns*
B2 (stricturing)	7 (29.2)	14.3 (± 6.9)	
B3 (penetrating)	3 (12.5)	9.3 (± 8.3)	
p (perianal disease)	5 (20.8)	16.6 (± 7.3)	
UC extent			
E1 (ulcerative proctitis)	4 (40.0)	13.5 (± 6.4)	ns*
E2 (left-sided UC)	2 (20.0)	15 (± 1.4)	
E3 (extensive UC)	4 (40.0)	20 (± 10.8)	

IRLS scores according to the subtype of IBD, sex, age, type of deficiency syndrome, and extent, location, and behavior of inflammatory bowel disease according to the Montreal classification are indicated; *p* value was based on the Mann-Whitney *U* test

ns not statistically significant, *N.S* not stated, *SD* standard deviation, *EM+* iron deficiency, *EM−* no iron deficiency, *FD+* folate deficiency, *FD−* no folate deficiency, *$VB_{12}D$+* vitamin B_{12} deficiency, *$VB_{12}D$−* no vitamin B_{12} deficiency

*Based on the Kruskal-Wallis test

age ≥ 45, likely secondary cause) [19]. Patients aged 45 years or older presented with significantly higher IRLS scores than patients aged below 45 years ($p = 0.024$) (Fig. 3c).

A linear regression analysis was performed to further determine if and to what extent age, sex, and IBD duration may influence IRLS scores (Table 3). In the univariate model, age was a predictor for an increase of IRLS score. When the model was adjusted for disease duration and sex, the association of age and IRLS score remained stable. While disease duration of IBD revealed no significant effect, sex could prominently be associated with IRLS score in the univariate and multivariate models, indicating that males have lower IRLS scores than females. Deficiencies were not used as a predictor in the linear regression analysis due to a lack of data.

There were no significant correlations between IRLS score and ID, FD, and $VB_{12}D$, as well as no significant difference between IBD subgroups regarding location, behavior, or extent of disease.

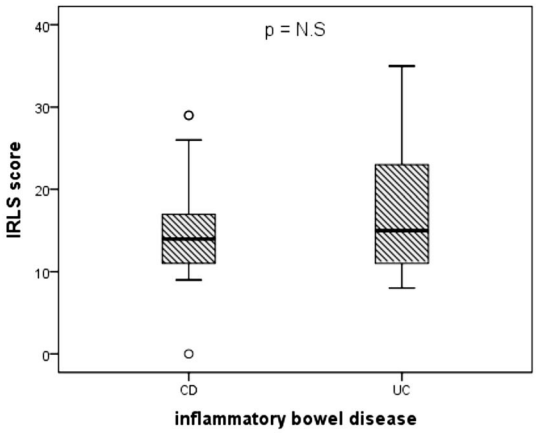
Discussion

In this study, the prevalence of RLS in IBD patients was determined and the effect of iron and/or folic acid supplementation on RLS severity was evaluated. Our data indicate that RLS prevalence in IBD patients in a tertiary IBD referral center is comparable to the general population (5–10 vs. 8.8% for IBD patients in our study) [15, 20, 21]. However, clinically relevant RLS was more frequent in our IBD cohort compared to the general population. Severity of RLS was associated with female sex and increasing age. Iron substitution in the presence of ID decreased RLS severity in IBD patients with ID.

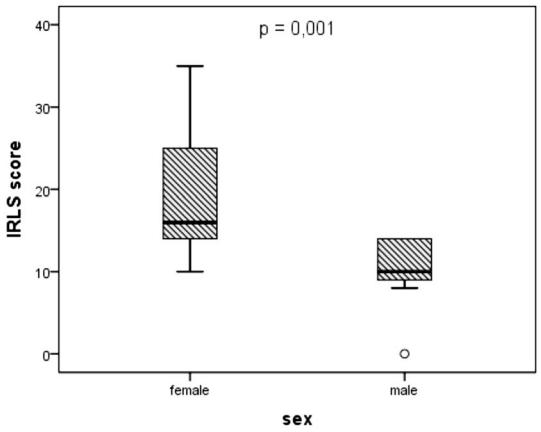
Prevalence of RLS in the general population ranges between 5 and 9% in males and between 9 and 14% in females [15, 20, 22, 23]. Our study confirmed that RLS is frequently seen in IBD patients, although the prevalence in IBD is much lower than it was previously reported (30, 25, and 20%, respectively, vs. 9% in our study) [5, 6, 24]. A reason for these divergent results with higher prevalence for IBD in the former studies may be due to the fact that in our study, diagnosis was established with complementary screening methods (questionnaire PLUS detailed medical history by an internal medicine specialist and, finally, a presentation to a neurologist for correct RLS diagnosis). In contrast, diagnosis of RLS in the previously reported studies relied solely on a questionnaire containing the four essential diagnostic criteria for RLS. In these studies, it has not been described if at least any physician had done a medical history examination. However, the diagnosis of RLS is challenging in clinical practice with regard to possible differential diagnosis. Since the diagnosis is solely based on clinical symptoms, we think that a detailed medical examination and anamnesis are crucial for RLS diagnosis. This difficulty is emphasized by our results where symptomatic patients who were merely seen by an internal medicine specialist/gastroenterologist were falsely suspected with RLS in 33% of the cases.

In the clinical relevant subgroup of RLS sufferers (patients with at least twice weekly and moderate to severe symptoms), a prevalence of 7.1% for CD and 4.8% for UC was found. RLS sufferers are patients who present more often with sleep problems, affected daytime performance, and negative quality of life and, therefore, are more likely in need for medical

A: *IRLS score in relation to type of IBD:*



B: *IRLS score in relation to sex:*



C: *IRLS score in relation to age:*

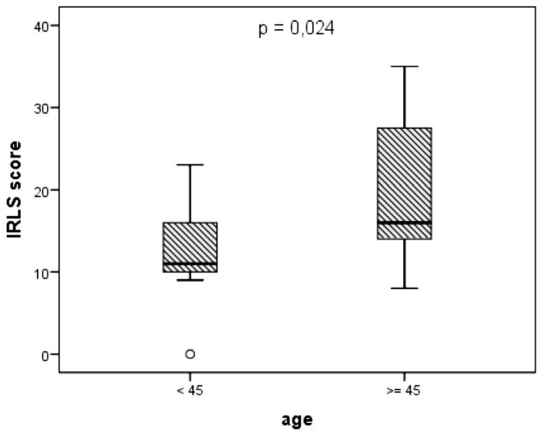


Fig. 3 Relation of IRLS score to characteristics of IBD patients. **a** IRLS score in relation to the type of IBD, showing no significant difference between the IRLS score and the type of IBD. **b** IRLS score in relation to sex. Females show significantly higher IRLS scores than males ($p = 0.001$). **c** IRLS score in relation to age. Patients with age ≥ 45 years (late-onset RLS) show significantly higher IRLS scores than patients with age ≤ 45 years (early-onset RLS) ($p = 0.024$). **a**–**c** The box extends from the 25th to the 75th percentile of each value. Horizontal bold lines in the box represent the median value. Top and bottom horizontal bars are the maximum and minimum values. p p values with significance cut-off ($p < 0.05$) and based on the Mann-Whitney U test; N.S not statistically significant

treatment [15, 16]. Therefore, the prevalence of RLS sufferers among IBD patients is doubled compared to the general population (2.1–3.5%) [15, 25].

In summary, the overall prevalence for RLS in IBD is not higher than in the general population. However, the clinical relevant subgroup of RLS sufferers occurs

Table 3 Univariable and multivariable linear regression for the dependent variable IRLS score

Predictor	Univariable analysis		Multivariable analysis	
	B (95% CI)	*p*	*B* (95% CI)	*p*
Age	0.215 (0.05 to 0.38)	0.01	0.472 (0.05 to 0.4)	0.014
Sex	9.25 (3.8 to 14.7)	0.002	7.60 (2.3 to 12.9)	0.007
IBD disease duration	0.028 (− 0.2 to 0.26)	0.80	− 0.193 (− 0.4 to 0.02)	0.075
Adjusted R^2			0.381	

Three univariable models (age, sex, IBD disease duration) of linear regression and one multivariable model are shown. Also shown are the following: *B* = unstandardized linear regression coefficient, confidence interval, and adjusted R^2 which shows the percentage of the response variable variation that is explained by the multivariable regression model

CI confidence interval

with a higher prevalence compared to the general population.

There were significantly higher IRLS scores in female than in male patients, and the regression model indicates that females had increased IRLS scores by 7.6 points compared to males. However, one has to recognize the limitation of this analysis, since the group of male patients with RLS was rather small compared to the group of female patients (9 vs. 22 patients). Nevertheless, females are known to develop more often ID than males and, hence, might be more prone for RLS [26]. Furthermore, a previous study indicated that RLS may be associated with parity and excretion of sex hormones following a circadian rhythm [20].

Our data indicate that increasing age contributes to RLS severity and, in the regression model, it was revealed that each additional year of age was associated with an increase of IRLS score by 0.47 points. Age as a factor for increased RLS severity was previously reported for early-onset RLS [27, 28]. One might hypothesize that with increasing age, the contributing factor for RLS of the accompanying IBD is more relevant than in younger patients. At this point, the mechanism triggering the age-dependent RLS progression in IBD requires further evaluation.

In our study cohort, one third of the patients presented with either ID, FD, or $VB_{12}D$, and ID was the most frequent. We hypothesized that the respective deficiencies represent a contributing factor for RLS in IBD patients. In fact, the improvement of the IRLS score after iron supplementation supports this hypothesis. Especially in the first 4 weeks after supplementation, patients seemed to benefit significantly from intravenous iron supplementation and, even after week 11, a trend towards decreasing IRLS scores was observed, though not statistically significant possible due to our small study cohort or an insufficient iron supplementation at that later time point. Since iron supplementation was not performed in a blinded manner, we cannot entirely exclude a placebo effect. In a recent Cochrane review [29], three double-blinded, placebo-controlled studies revealed a significant decrease of IRLS scores after either intravenous iron supplementation [30, 31] or oral supplementation [32]. However, the Cochrane report concluded that there is insufficient evidence to decide whether iron supplementation is beneficial for RLS patients or not due to a variety of reasons, e.g. selection bias, different subgroups of patients, or alternative formulation of iron supplementation. However, distinct subgroups of patients that remain to be defined might still benefit from iron therapy [29]. IBD patients may constitute such a subgroup.

Even though the overall prevalence does not differ between IBD patients and the general population, patients with clinically relevant RLS (RLS sufferers) are more frequently to have IBD. In addition, we have recently shown that RLS affects quality of life in IBD patients independent of the underlying IBD activity [33]. Therefore, clinicians and experts in the field of IBD should be alert and should recognize that RLS is an important syndrome not only for neurologists, although diagnosis and therapy should be closely elaborated with a neurologist. In case of ID, an iron supplementation as a supportive therapy to treat RLS should be considered. Further studies with a larger cohort of IBD patients with RLS and ID are required to provide conclusive evidence that iron supplementation can treat RLS symptoms in these patients.

Compliance with ethical standards

The study was approved (16 January 2014) by the ethics committee of the Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin (reference EA4/132/13).

Conflict of interest The authors declare that they have no conflict of interest.

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