

Crohn's Disease is Associated with Restless Legs Syndrome

LEONARD WEINSTOCK, ARTHUR WALTERS, ELLEN LI, GERARD MULLIN,
MELISSA MUNSELL, UGONNA IROKU, BRIAN BOSWORTH, ELLEN SCHERL

Leonard B. Weinstock, MD, Associate Professor of Clinical Medicine and Surgery,
Washington University School of Medicine, MO; Director, Specialists in
Gastroenterology, LLC

Arthur S. Walters, MD, Professor of Neurology, Vanderbilt University School of
Medicine, Nashville, TN

Ellen Li, MD, Professor of Medicine, Washington University School of Medicine

Gerard E. Mullin, MD, Assistant Professor of Medicine, Johns Hopkins School of
Medicine, Baltimore, MD

Melissa A. Munsell, MD, Gastroenterology Fellow, Johns Hopkins School of Medicine,
Baltimore, MD

Ugonna Iroku, MD MHS, Gastroenterology Fellow, Columbia University Medical
Center, NYC, NY

Brian P. Bosworth, MD, Assistant Professor of Medicine, Weill Cornell Medical Center,
NYC, NY

Ellen J. Scherl, MD, Associate Professor of Medicine, Weill Cornell Medical Center,
NYC, NY

Short title: Crohn's Disease and RLS

Abbreviations used in this manuscript: CI, confidence intervals; F, Female; IRLS
scale, international restless legs syndrome scale; M, Male; N, number; OR, odds ratio;
RLS, restless legs syndrome

Word count:

Full title = 57 characters with spaces; Short title = 24 with spaces

Abstract = 172 (including subtitles); maximum = 175

Manuscript = 1350 (introduction, methods, discussion, acknowledgment, and references); maximum = 1500; References: 20; maximum = 20

Disclosures:

Dr. Weinstock is on the speaker's bureau for Salix

Dr. Walters has received research funding from the National Institutes of Health, Xenoport, Schwarz-Pharma, and Kyowa. Dr. Walters has received research funding and is on the speaker's bureau of Glaxo Smith Kline and Boehringer-Ingelheim

Dr. Li: none; Dr. Mullin: none; Dr. Munsell: none; Dr. Iroku: none; Dr. Bosworth: none

Dr. Scherl is on the speaker's bureau for Salix

Partial funding: Washington University Digestive Diseases Research Core Center P30 DK52574.

Manuscript writing: Dr. Weinstock; **Revisions:** Drs. Mullen, Walters

Potential conflicts to study candidates: None

Address correspondence to:

Leonard Weinstock, MD

11525 Olde Cabin Road

St. Louis, MO 63141; Tel: 314-997-0554; Fax: 314-997-5086

E-mail: lw@gidoctor.net

ABSTRACT

Backgrounds and Aims: Restless legs syndrome (RLS) is the compelling urge to move the legs and can be secondary to many diseases. We determined if Crohn's disease was associated with RLS since both are associated with iron deficiency.

Methods: 272 Crohn's disease outpatients (F-151, M-121; age 43.6 ± 15.2 years) were prospectively surveyed at a community practice and 3 tertiary care university referral centers. Four international RLS-diagnostic criteria were required. Prevalence was compared to spouses. One IRB allowed query of prevalence but not incidence in 54 patients.

Results: RLS incidence was 42.7% (93/218). RLS prevalence was 30.2% (82/272; CI 29.9-30.3%) vs. 8.4% (17/202; CI 8.6-8.8%) of spouses ($p < 0.0001$; OR=4.5; CI 2.54-7.87%). RLS started during/after onset Crohn's disease in 91.8%. Relationship of RLS severity to gastrointestinal activity was noted in 44.5%. RLS(+) and RLS(-) patients had: age 46.8 ± 13.1 vs. 42.6 ± 15.7 years and prior iron deficiency in 49.3% vs. 33.1%.

Conclusion: RLS occurs frequently in Crohn's disease. Further studies are warranted to determine the cause of RLS and its effect on the quality of life in Crohn's patients.

INTRODUCTION

Crohn's disease is directly and indirectly associated with many extraintestinal diseases and disorders by several mechanisms (1). Sleep disturbance in inflammatory bowel disease is common (2). There are no previous investigations of the relationship of Crohn's disease and restless legs syndrome (RLS). This central nervous system disorder is the compelling urge for leg movement usually with abnormal leg

sensations (3). The prevalence of RLS is 10% and contributes significantly to sleep disorders and poor quality of life (4,5). RLS may be a primary (idiopathic and familial) or a secondary syndrome and is associated with central nervous iron deficiency (6,7). We determined if Crohn's disease was associated with RLS since both are associated with iron deficiency.

METHODS

All consecutive CD outpatients (151 females, 121 males; mean age 43.8 ±15.0 years) were prospectively surveyed by gastroenterologists at Specialists in Gastroenterology, a community GI practice (N=135), Weill Cornell Medical Center (N=71), Washington University School of Medicine (N=54), and Johns Hopkins School of Medicine (N=12). No patients were excluded or refused the survey.

All four international criteria were required to be positive for RLS: 1) urge to move legs often with discomfort, 2) worse at rest, 3) worsening at night, and 4) relief with activity. Incidence (having RLS at any point in time), prevalence (having RLS at time of survey), clinical characteristics, RLS risk factors, and potential qualitative relationship to gastrointestinal symptoms were queried. The patients were asked whether they thought their spouse or their first degree relatives presently had RLS. The study was approved by human study committees at each institution. One committee limited the RLS frequency question to prevalence and did not allow RLS risk factor questions to be asked in 54 of the 272 total surveys. Statistics were performed using t-test for continuous variables and chi-square tests for categorical variables. A p-value of <0.05 was considered as statistically significant.

RESULTS

RLS incidence in Crohn's disease was 42.7% (93/218). Prevalence of RLS was 30.2% (82/272; CI 29.9-30.3%) vs. 8.4% (17/202; CI 8.6-8.8%) of spouses ($p < 0.0001$; odds ratio = 4.5; CI 2.54-7.87%). The controls were the spouses of the patients: 79.5% of all of patients were married; 86.8% of the RLS(+) patients and 77.2% of the RLS(-) patients were married.

RLS started during or after the onset of Crohn's disease in 91.8% of patients and before the onset of Crohn's disease in 8.2% of patients. Among 72 RLS(+) patient respondents, 44.5% stated there was correlation between qualitative RLS symptom improvement and overall gastrointestinal symptom improvement.

Comparisons between RLS(+) and RLS(-) Crohn's disease patients are shown in Table 1. Patients with RLS were a mean of 5 years older than those without RLS ($p = 0.01$). A clinical history of iron deficiency anemia in the past was more common in RLS patients (49.3% vs. 33.1%; $p = 0.031$). If patients had Crohn's limited to their colon they were less likely to have RLS ($p = 0.002$). There was no difference between the Crohn's patient groups with respect to: gender ratio, current iron deficiency (4.6%), distribution of Crohn's disease, RLS family history (12%), or the rare prevalence of concomitant RLS disorders.

DISCUSSION

Sleep disorders and fatigue are common in Crohn's disease but no one has previously examined the role of RLS. The present study demonstrated that RLS is common in patients with Crohn's disease. The incidence of RLS was 42.7% in a large number of Crohn's disease patients from three academic centers and one large community practice. The prevalence of RLS in Crohn's disease was 30.2% compared to a

prevalence of 8.4% in the sexed-matched spouse control group (similar to the prevalence of RLS in the general population) (6). RLS is a vexing sensory and motor disorder which can have a significant impact on the quality of life.

Iron deficiency was originally suspected as a possible link for the presence of RLS in Crohn's disease since it commonly occurs in both conditions. Central nervous system iron deficiency is present in all forms of RLS (8). The prevalence of anemia in Crohn's disease ranges from 6% -70% and is often multi-factorial (9,10). Most of the patients who currently had RLS in this study did not presently have anemia or iron deficiency. Evidence for peripheral iron deficiency in RLS is variable (11). The quality of this pilot study was diminished by the fact that serum ferritin levels were not measured on each patient and there is evidence that levels lower than 50 ng/dL are clinically significant (12).

Bacterial overgrowth as a co-factor for RLS in Crohn's disease is a consideration to explain the association in light of recent reports of the association of RLS in small intestinal bacterial overgrowth (13,14) and three other gastrointestinal conditions that are associated with RLS which not infrequently have bacterial overgrowth (15-17). The inflammatory state from small intestinal bacterial overgrowth (18) or from Crohn's disease could be related to RLS possibly by direct or indirect stimulation of hepcidin with subsequent decreased central nervous system iron transportation (19).

RLS occurs frequently in Crohn's disease. Further studies are warranted to evaluate the potential impact that RLS has on the quality of life in Crohn's disease using the validated international RLS scale (20). This is important since fatigue is so common in Crohn's disease and RLS contributes to sleep disorders and poor quality of life.

Although peripheral iron deficiency is important in disorders that cause secondary RLS, systemic inflammation and small intestinal bacterial overgrowth may be additional factors in Crohn's disease. We propose a theory that inflammation associated with Crohn's disease increase hepcidin levels which results in central nervous system iron deficiency resulting in RLS.

Acknowledgements

We appreciate clerical assistance from Nicole Green, Data Control Coordinator, Jill Roberts IBD Center, Weill Cornell Medical Center, NYC, NY.

References

1. Juillerat P, Mottet C, Pittet V, et al. Extraintestinal manifestations of Crohn's disease. *Digestion* 2007;76:141-148.
2. Ranjbaran Z, Keefer L, Farhadi A, et al. Impact of sleep disturbances in inflammatory bowel disease. *J Gastroenterol Hepatol* 2007;22:1748-1753.
3. Walters AS. Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. *Mov Disord* 1995;10:634-642.
4. Berger K, Luedemann J, Trenkwalder C, et al. Sex and the risk of restless legs syndrome in the general population. *Arch Intern Med* 2004;164:196-202.
5. Happe S, Reese JP, Stiasny-Kolster K, et al. Assessing health-related quality of life in patients with restless legs syndrome. *Sleep Med* 2008 Mar 21. [Epub ahead of print]
6. Rama AN, Kushida CA. Restless legs syndrome and periodic limb movement disorder. *Med Clin North Am* 2004;88:653-667.
7. Allen R. Dopamine and iron in the pathophysiology of restless legs syndrome (RLS). *Sleep Med* 2004;5:385-391.

8. Earley CJ, Barker P, Horska A, Allen RP. MRI-determined regional brain iron concentrations in early- and late-onset restless legs syndrome. *Sleep Med* 2006;7:458-461.
9. Gasche C, Lomer MC, Cavill I, Weiss G. Iron, anaemia, and inflammatory bowel diseases. *Gut* 2004;53:1190-1197.
10. Kulnigg S, Gasche C. Systematic review: managing anaemia in Crohn's disease. *Aliment Pharmacol Ther* 2006;24:1507-1523.
11. Aul EA, Davis BJ, Rodnitzky RL. The importance of formal serum Fe studies in the assessment of RLS. *Neurology* 1998; 51:912.
12. Sun ER, Chen CA, Ho G, et al. Iron and the restless legs syndrome. *Sleep* 1998;21:371-377.
13. Weinstock LB, Fern SE, Duntley SP. Restless legs syndrome in patients with irritable bowel syndrome: response to small intestinal bacterial overgrowth therapy. *Dig Dis Sci* 2008;53:1252-1256.
14. Weinstock LB. Rifaximin improves restless legs syndrome associated with small intestinal bacterial overgrowth [Abstract]. *Am J Gastroenterol* 2008;103:P448.
15. Banerji NK, Hurwitz LJ. Restless legs syndrome; with particular reference to its occurrence after gastric surgery. *Br Med J* 1970;4:774-775.
16. Franco RA, Ashwathnarayan R, Deshpandee A, et al. The high prevalence of restless legs syndrome symptoms in liver disease in an academic-based hepatology practice. *J Clin Sleep Med* 2008;4:45-49.
17. Weinstock LB, Walters AS, Mullen GE. Celiac disease is associated with restless legs syndrome [Abstract]. *Am J Gastroenterol* 2008;103:P448.

18. Lin HC. Small intestinal bacterial overgrowth: a framework for understanding irritable bowel syndrome. *JAMA* 2004;292:852-858.
19. Raja KB, Latunde-Dada GO, Peters TJ, et al. Role of interleukin-6 in hypoxic regulation of intestinal iron absorption. *Br J Haematol* 2005;131:656–662.
20. The International Restless Legs Syndrome Study Group. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Med* 2003;4:121-132.