

Crohn's Disease Is Associated With Restless Legs Syndrome: a New Extraintestinal Manifestation

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INTRODUCTION

- Crohn's disease (CD) is chronic gastrointestinal (GI) disease primarily affecting small intestine and colon¹⁻³
 - Intestinal blood loss and other mechanisms may cause iron deficiency^{1,4}
 - CD is associated with bacterial overgrowth⁵ and increased, chronic inflammation^{3,6}
- Iron deficiency may cause fatigue and sleep disorders¹
- Patients at risk for iron deficiency are also at risk for development of restless legs syndrome (RLS)⁷
- RLS is central nervous system disorder that elicits compelling urge to move legs at rest and contributes to sleep disturbances and poor quality of life^{7,8}
 - Idiopathic or secondary to many disorders⁹
 - In prospective clinical trial of 13 patients with irritable bowel syndrome (IBS) and RLS, 77% of patients (10 of 13) reported ≥80% improvement from baseline of RLS symptoms after rifaximin treatment for IBS⁹

OBJECTIVE

- To determine if CD is associated with RLS because both conditions may display iron deficiency

METHODS

Study design

- Prospective evaluation of RLS in patients with CD seen in 3 academic outpatient GI clinics from either August 2007 or February 2008 to March 2008 and in 1 community GI clinic from August 2007 to March 2008

Assessments

- Diagnosis of RLS according to criteria set by International Restless Legs Syndrome (IRLS) Study Group¹⁰
- Incidence (presence of RLS during any period of life) and prevalence (display of RLS symptoms at time of survey) of RLS in patients with CD
- Prevalence of RLS in spouses of patients with CD, as determined by patient query
- Past and current reported history of iron deficiency or anemia
- Onset and duration of RLS symptoms
- Statistical analysis via chi-square test with $P < 0.05$ considered significant

RESULTS

- 272 patients were included in analysis
- RLS symptoms at any point during lifetime were reported in 93 of 218 patients^a with CD (43%) queried for RLS incidence (Table)

Table. Demographics and Baseline Characteristics of Patients With CD

Parameter	Patients with RLS ^a (n=93)	Patients without RLS (n=179)
Mean age ± SD, y	42 ± 16	47 ± 13
Male:Female, n	40:53	81:98
CD location, n ^a (%)		
Small intestine	53/68 (78)	78/117 (67)
Colon	27/68 (40)	74/117 (63)
Currently taking iron supplementation, n ^b (%)	10/67 (15)	14/118 (12)
Currently reporting iron deficiency, n ^b (%)	3/65 (5)	5/106 (5)

CD, Crohn's disease; RLS, restless legs syndrome; SD, standard deviation. ^aPatients with RLS at any point in lifetime. ^bReduction in total due to nonqueried data in questionnaires from 1 study site.

- RLS was significantly more prevalent in patients with CD (82 of 272; 30%) than in spouse control group (17 of 202 spouses, 8%; $P < 0.0001$; Figure 1)

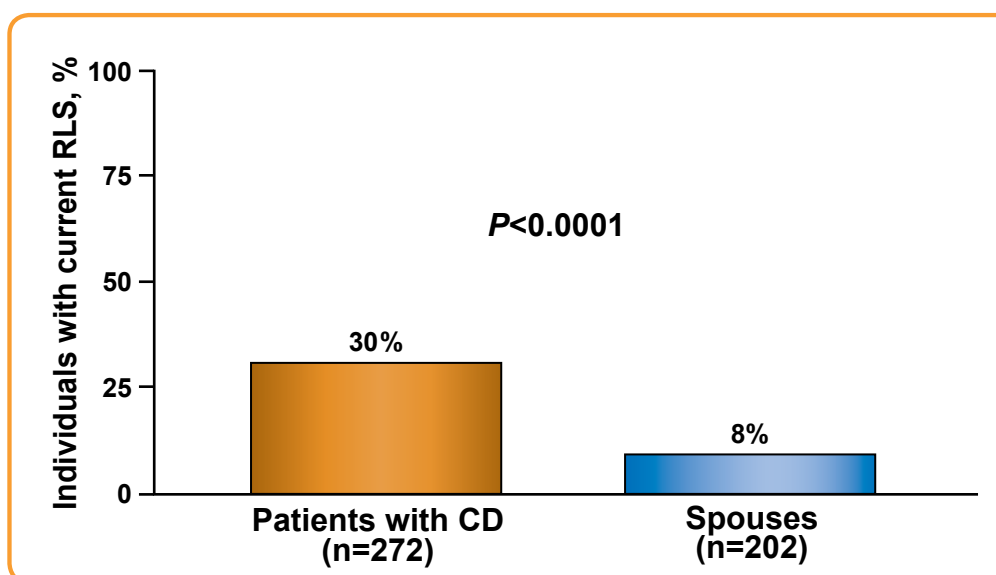


Figure 1. Restless legs syndrome (RLS) prevalence in patients with Crohn's disease (CD) and their spouses. Patients with CD were more likely to have current RLS (82 of 272 patients; 30%) than their spouses (17 of 202 spouses, 8%; $P < 0.0001$).

- 67 of 73 patients^a (92%) with CD reported symptoms of RLS beginning during or after onset of GI symptoms (Figure 2)

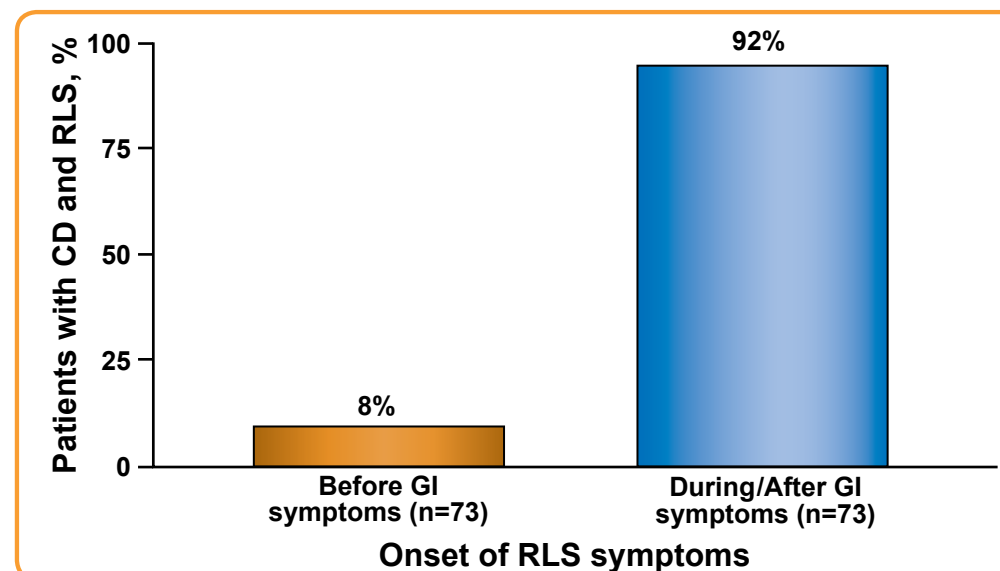


Figure 2. Percentage of patients with CD describing onset of RLS symptoms before or during/after onset of GI symptoms. Substantially more patients with CD reported onset of RLS symptoms during or after GI symptoms than before GI symptoms. CD, Crohn's disease; GI, gastrointestinal; RLS, restless legs syndrome.

- RLS symptoms in patients with CD did not correlate with iron deficiency

DISCUSSION AND CONCLUSIONS

- In this prospective multicenter study, RLS was found to be comorbid condition in patients with CD, with incidence of 43% and prevalence of 30%
- RLS symptoms occurred during or after onset of CD symptoms in majority of patients, suggesting link between CD and RLS
- Systemic iron deficiency was not associated with RLS in patients with CD, suggesting that other factors may be involved in RLS pathophysiology within this patient population; however, total body iron concentrations do not always correlate with central nervous system iron levels, which may be more relevant to RLS¹¹
- Pathophysiology may include small intestinal bacterial overgrowth and systemic inflammation. In vitro studies report that some proinflammatory cytokines, such as interleukin-6, increase production of hepcidin, which affects iron transportation¹²
- Further research on potential association and clinical impact of RLS in CD is warranted

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References: 1. Kulnigg S, Gasche C. *Aliment Pharmacol Ther.* 2006;24(11-12):1507-1523. 2. Loftus EV Jr, Schoenfeld P, Sandborn WJ. *Aliment Pharmacol Ther.* 2002;16(1):51-60. 3. Shanahan F. *Lancet.* 2002;359(9300):62-69. 4. Rockey DC. *N Engl J Med.* 1999;341(1):38-46. 5. Biancone L, Vernia P, Agostini D, Ferrieri A, Pallone F. *Curr Med Res Opin.* 2000;16(1):14-20. 6. Marks DJB, Segal AW. *J Pathol.* 2008;214(2):260-266. 7. Patrick L. *Altern Med Rev.* 2007;12(2):101-112. 8. Rama AN, Kushida CA. *Med Clin North Am.* 2004;88(3):653-667. 9. Weinstock LB, Fern SE, Duntley SP. *Dig Dis Sci.* 2008;53(5):1252-1256. 10. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J, and the participants in the Restless Legs Syndrome Diagnosis and Epidemiology workshop at the National Institutes of Health in collaboration with members of the International Restless Legs Syndrome Study Group. *Sleep Med.* 2003;4(2):101-119. 11. Allen R. *Sleep Med.* 2004;5(4):385-391. 12. Ganz T. *Blood.* 2003;102(3):783-788.

^aThese data not available for all patients.