

# Celiac Disease Is Associated With Restless Legs Syndrome

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## INTRODUCTION

- Celiac disease is autoimmune disease that is triggered by gluten and that damages intestinal lining<sup>1</sup>
  - May be undiagnosed for years<sup>1</sup>
  - May be associated with neurological disorders (eg, ataxia, peripheral neuropathy, migraine, and epilepsy)<sup>2</sup>
- Restless legs syndrome (RLS) is common central nervous disorder with compelling urge to move legs often associated with discomfort and contributes to sleep disorders and poor quality of life<sup>3</sup>
  - Pathophysiology is unknown,<sup>3</sup> although central nervous system iron deficiency plays significant role<sup>4</sup>
  - May be idiopathic or secondary to gastrointestinal (GI) disorders<sup>5</sup>
  - In prospective clinical trial of 13 patients with irritable bowel syndrome (IBS) and RLS, 77% (10 of 13) of patients reported ≥80% remission of RLS symptoms after treatment for IBS<sup>5</sup>
  - Prospective multicenter study found that 43% (93 of 218) of patients with Crohn's disease had RLS (see poster P308 by Weinstock et al presented at this meeting)
- Both celiac disease and RLS may be associated with asymptomatic iron deficiency to varying degrees<sup>1,3</sup>
- No previous studies have investigated potential relationship between celiac disease and RLS

## OBJECTIVE

- To determine epidemiology, clinical characteristics, and risk factors for RLS in patients with celiac disease

## METHODS

### Inclusion criteria

- Patients with celiac disease were interviewed at community adult GI clinic during 6-month period from October 2007 to March 2008
- Additional patients were recruited from computerized search of patients with celiac disease who were seen at same clinic during past 5 years
- Patients had GI symptoms or idiopathic iron deficiency anemia that improved on gluten-free diet (GFD) and at least 1 of following:
  - Duodenal villous blunting or atrophy, increased intraepithelial lymphocytes, and elevated tissue transglutaminase immunoglobulin A antibody (tTG)
  - Duodenal villous blunting or atrophy and increased intraepithelial lymphocytes
  - Elevated tTG

### Assessments

- Patients who met inclusion criteria were evaluated for RLS according to criteria set by International Restless Legs Syndrome Study Group<sup>6</sup>
- Presence of RLS in spouses of patients with celiac disease was determined through patient query
- Past history of and current presence of iron deficiency or anemia were confirmed by review of laboratory data, with iron deficiency defined as serum ferritin <50 ng/dL and anemia defined as hemoglobin level lower than 12%

- Onset and duration of RLS symptoms
- Frequency and severity of RLS symptoms were measured using International RLS (IRLS) scale<sup>7</sup>
- Improvement of RLS symptoms while on GFD
- Statistical analysis using chi-square test, with  $P < 0.05$  considered significant

## RESULTS

### Demographics and patient characteristics

- Of patients screened for celiac disease, 9 had elevated tTG, 29 had duodenal villous blunting or atrophy and increased intraepithelial lymphocytes, and 47 had duodenal villous blunting or atrophy, increased intraepithelial lymphocytes, and elevated tTG
- 30 of 85 patients with celiac disease (35%) were determined to have had RLS based on history of symptoms meeting criteria set by International Restless Legs Syndrome Study Group<sup>6</sup> (Table 1)
  - 63% (19 of 30) of these patients had current RLS symptoms

**Table 1.** Demographics and Baseline Characteristics of Patients With Celiac Disease

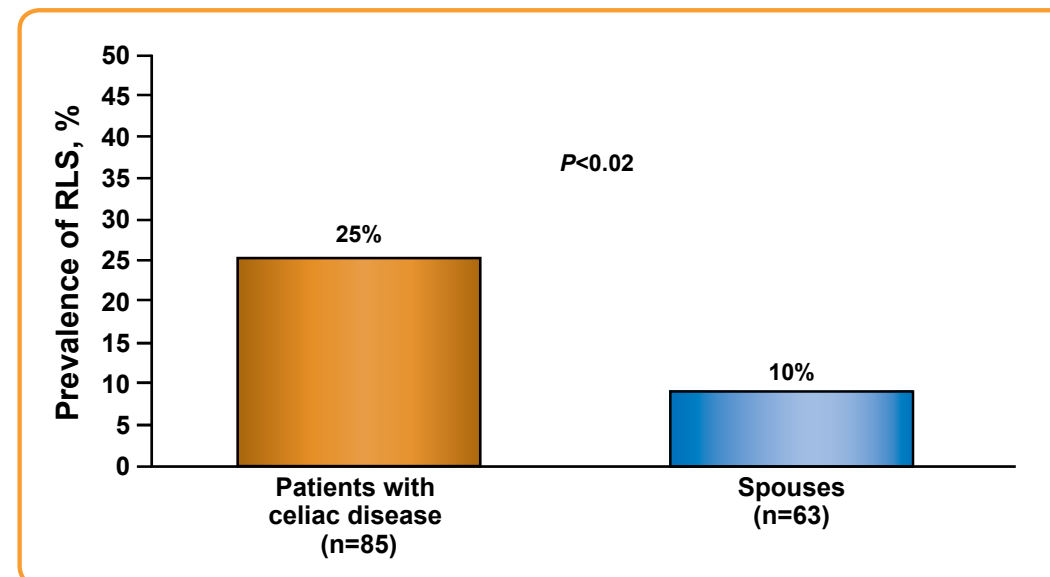
Parameter	Patients with RLS (n=30)	Patients without RLS (n=55)
Mean age ± SD, y	50 ± 16	51 ± 19
Male:Female, n	2:28	14:41
Mean duration of disease ± SD, y	14 ± 17	10 ± 13
Mean time since celiac diagnosis ± SD, y	6 ± 10	6 ± 12
Current iron supplementation, n (%)	6 (20)	5 (9)
Current RLS, n (%)	19 (63)	0 (0)
Mean IRLS severity score <sup>a</sup> ± SD	16 ± 7	0 ± 0
Interviewed for improvement of RLS symptoms while on GFD, n (%)	28 (93)	0 (0)

GFD, gluten-free diet; IRLS, International RLS; RLS, restless legs syndrome; SD, standard deviation. <sup>a</sup>IRLS scale minimum and maximum values range from 0 to 40.

- No patients were ever diagnosed or treated for RLS by physician
- 73% (22 of 30) of patients with celiac disease and RLS were married
- Twenty-eight patients were interviewed to determine correlation between GFD and RLS symptom improvement (Table 1)

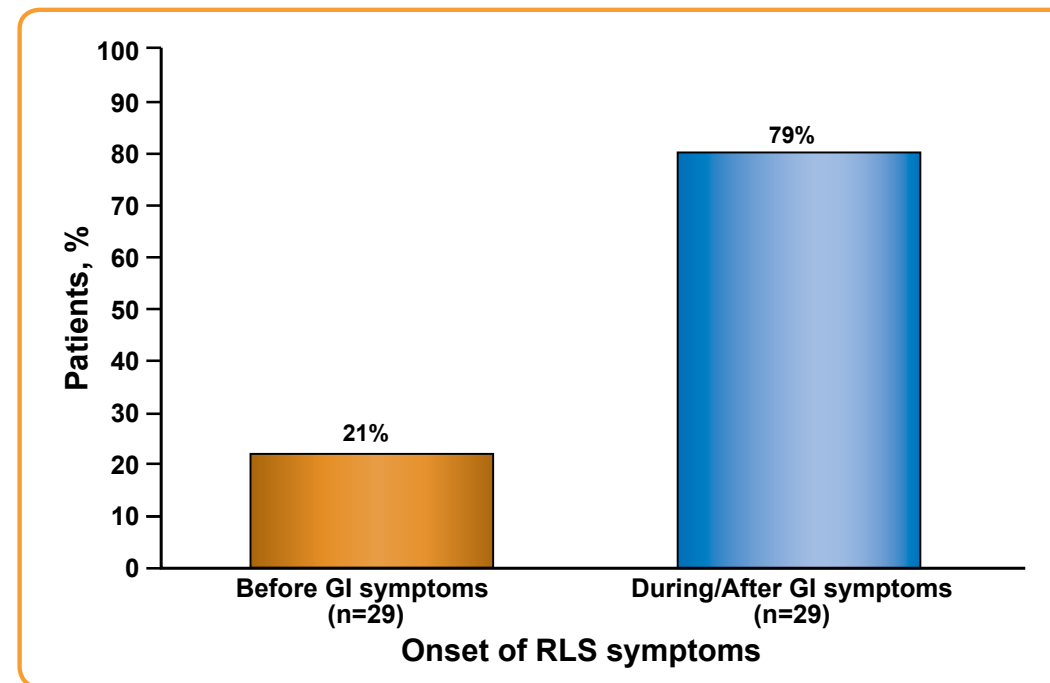
### Prevalence, severity, and iron deficiency in patients with celiac disease and RLS

- RLS was significantly more prevalent in patients with celiac disease (21 of 85 [25%]) than in their spouses (6 of 63 [10%];  $P < 0.02$ ; Figure 1)



**Figure 1.** Restless legs syndrome (RLS) prevalence in patients with celiac disease and their spouses. Patients with celiac disease were significantly more likely to have RLS than their spouses ( $P < 0.02$ ).

- Symptoms of RLS starting during or after onset of GI symptoms were described in 23 of 29 patients (79%) who reported GI symptom onset (Figure 2)



**Figure 2.** Percentage of patients (n=29) with celiac disease describing onset of RLS symptoms before and during/after initiation of GI symptoms. Substantially greater percentage of patients with celiac disease reported initiation of RLS symptoms during or after GI disturbance than before GI symptoms. RLS may precede GI symptoms and diagnosis of celiac disease. GI, gastrointestinal; RLS, restless legs syndrome.

- Mean IRLS severity score for patients with celiac disease and RLS was  $16 \pm 7$
- Substantial percentage of patients with celiac disease and active RLS symptoms displayed current iron deficiency (11 of 20 [55%]) compared with patients with celiac disease having prior history of RLS or with patients with celiac disease who had never displayed RLS (Table 2)

**Table 2.** Association Between RLS and Iron Deficiency and Anemia in Patients With Celiac Disease

Iron deficiency or anemia	Patients, n (%)		
	Current iron deficiency	Prior iron deficiency	Current anemia
Patients with active RLS (n=20)	11 (55)	12 (60)	4 (20)
Patients with prior RLS (n=8)	1 (13)	5 (63)	0 (0)
Patients without RLS (n=54)	3 (6)	24 (44)	3 (6)

RLS, restless legs syndrome.

### Improvement of RLS symptoms on GFD

- 50% of patients with celiac disease and RLS reported improvement of RLS symptoms while on GFD (14 of 28 patients)
- Greatest improvement of RLS severity occurred after mean of 5.7 months on GFD, with mean maximum improvement of 78%, as estimated by patients

## DISCUSSION AND CONCLUSIONS

- In this prospective evaluation of RLS in patients with celiac disease, RLS occurred frequently and was associated with iron deficiency
- RLS may precede GI symptoms and diagnosis of celiac disease
- Initiation of GFD improved RLS symptoms in 50% of patients with celiac disease
- Celiac disease may be underlying and correctable factor for some patients diagnosed with idiopathic RLS
- Screening for celiac disease in patients with RLS is important to consider because celiac disease often remains overlooked, and treatment of this disease may improve RLS symptoms

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