Celiac Disease Is Associated With Restless Legs Syndrome

L Weinstock,1,2 A Walters,1 G Mullen,1 S Duntley2

1Specialists in Gastroenterology, LLC, St Louis, MO; Washington University School of Medicine, St Louis, MO; New Jersey Neuroscience Institute at JFK Medical Center, Edison, NJ; Seton Hall University School of Graduate Medical Education, South Orange, NJ; Johns Hopkins Medical School, Baltimore, MD

INTRODUCTION

• Celiac disease is an autoimmune disease that is triggered by gluten and that damages intestinal lining
  • May be unnoticed for years
  • May be associated with neurological disorders (eg, ataxia, peripheral neuropathy, migraines, and epilepsy)
• 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
  • Pathophysiology is unknown, although central nervous system iron deficiency plays significant role
  • May be idiopathic or secondary to gastrointestinal (GI) disorders
• Persistent clinical trial of 13 patients with irritable bowel syndrome (IBS) and RLS, 77% (10 of 13) of patients reported ≥50% improvement in IBS symptoms while on GI treatment for IBS
• 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)
• To determine epidemiology, clinical characteristics, and risk factors for RLS in patients with celiac disease

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 computed search of patients with celiac disease who were seen at same GI clinic over past 5 years
• Patients had GI symptoms or idiopathic iron deficiency anemia that improved on gluten-free diet (GFD) and at least 1 of the following:
  • Duodenal villous blunting or atrophy and increased intraepithelial lymphocytes, and elevated tissue iron stores in duodenal biopsy specimens
  • Duodenal villous blunting or atrophy and increased intraepithelial lymphocytes
• Patients had GI symptoms or idiopathic iron deficiency anemia that improved on gluten-free diet (GFD) and at least 1 of the following:
  • Duodenal villous blunting or atrophy and increased intraepithelial lymphocytes, and elevated tissue iron stores in duodenal biopsy specimens
  • Duodenal villous blunting or atrophy and increased intraepithelial lymphocytes

Assessments

• Patients who met inclusion criteria were evaluated for RLS according to criteria set by International Restless Legs Syndrome Study Group
• Presence of RLS in spouses of patients with celiac disease was determined through
  • Review of laboratory data, with iron deficiency defined as serum ferritin <50 ng/dL and anemia defined as hemoglobin level lower than 12%

RESULTS

Demographics and patient characteristics

• Of patients screened for celiac disease, 9 had elevated tTG, 29 had duodenal villous atrophy and increased intraepithelial lymphocytes, and 47 had duodenal villous blunting or atrophy, increased intraepithelial lymphocytes, and elevated IRLS scale 17% (35 of 218) of patients had RLS symptoms after treatment for IBD
  • 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
• No previous studies have investigated potential relationship between celiac disease and RLS

• Objective

  • RLS was significantly more prevalent in patients with celiac disease (21 of 85 [25%]) than in their spouses (5 of 20 [25%]; P<0.02; Figure 1)
  • Presence of RLS in spouses of patients with celiac disease was significantly more likely to have RLS than their spouses (P<0.02; Figure 1)
• Improvement of RLS symptoms while on GFD
  • Mean maximum improvement of 78%, as estimated by patients
  • 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 an average of 5.7 months on GFD, with mean-maximum improvement of 78%, as estimated by patients

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

• Mean IRLS severity score for patients with celiac disease and RLS was 16 ± 7
• Substantial percentage of patients with celiac disease and active RLS symptoms displayed current iron deficiency (31 of 62 [50%]) 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>
<thead>
<tr>
<th>Parameter</th>
<th>Patients with RLS (n=55)</th>
<th>Patients without RLS (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD, y</td>
<td>50 ± 16</td>
<td>51 ± 19</td>
</tr>
<tr>
<td>Male:Female, n</td>
<td>2:28</td>
<td>14:41</td>
</tr>
<tr>
<td>Mean duration of disease ± SD, y</td>
<td>14 ± 17</td>
<td>10 ± 13</td>
</tr>
<tr>
<td>Mean time since celiac diagnosis ± SD, y</td>
<td>6 ± 10</td>
<td>6 ± 12</td>
</tr>
<tr>
<td>Current iron supplementation, n (%)</td>
<td>6 (20%)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Mean IRLS severity score ± SD</td>
<td>19.6 ± 3.3</td>
<td>8 ± 2</td>
</tr>
<tr>
<td>Improvement of symptoms while on GFD, n (%)</td>
<td>29 (52.7%)</td>
<td>8 (26.7%)</td>
</tr>
</tbody>
</table>

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

Discussion

• 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

Figure 2. Percentage of patients in Celiac Disease and RLS subgroup with RLS symptoms before and during GFD. In the Celiac Disease and RLS subgroup (n=20), 75% (15 of 20) of patients had RLS symptoms before GFD. During GFD, 35% (7 of 20) of patients had RLS symptoms. In this subgroup, RLS symptoms were significantly more prevalent in patients with celiac disease (15 of 20 [75%]) than in their spouses (5 of 20 [25%]; P<0.02; Table 1). Figure 1.

Figure 1. Presence of restless legs syndrome (RLS) 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).

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients with RLS (n=30)</th>
<th>Patients without RLS (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency or anemia</td>
<td>Current iron deficiency</td>
<td>Prior iron deficiency</td>
</tr>
<tr>
<td>Patients with active RLS (n=22)</td>
<td>11 (50)</td>
<td>12 (55)</td>
</tr>
<tr>
<td>Patients with RLS (n=10)</td>
<td>1 (10)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Patients without RLS</td>
<td>3 (6)</td>
<td>24 (44)</td>
</tr>
</tbody>
</table>

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 an average of 5.7 months on GFD, with mean-maximum improvement of 78%, as estimated by patients

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients with RLS (n=30)</th>
<th>Patients without RLS (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency or anemia</td>
<td>Current iron deficiency</td>
<td>Prior iron deficiency</td>
</tr>
<tr>
<td>Patients with active RLS (n=22)</td>
<td>11 (50)</td>
<td>12 (55)</td>
</tr>
<tr>
<td>Patients with RLS (n=10)</td>
<td>1 (10)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Patients without RLS</td>
<td>3 (6)</td>
<td>24 (44)</td>
</tr>
</tbody>
</table>

RLS, restless legs syndrome.

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

Presented at American College of Gastroenterology Annual Scientific Meeting • October 3-8, 2008; Orlando, FL