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ORIGINAL PAPER

Restless Legs Syndrome in Patients with Irritable Bowel Syndrome: Response to Small Intestinal Bacterial Overgrowth Therapy

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Abstract *Background* Small intestinal bacterial overgrowth (SIBO) occurs in irritable bowel syndrome (IBS) and fibromyalgia. Since restless legs syndrome (RLS) occurs with fibromyalgia, a link between IBS, SIBO, and RLS was studied. *Methods* BS patients with abnormal lactulose breath tests received rifaximin 1,200 mg day^{-1} for 10 days, followed by tegaserod 3 mg, long-term, and 1 month of zinc 220 mg day^{-1} and once-daily probiotic (N = 11) or rifaximin monotherapy (N = 2). IBS symptom improvement was assessed after rifaximin. RLS symptoms, IBS symptoms, and overall IBS global improvement were assessed at last posttreatment visit: 8/10 patients were followed long-term (mean, 139 days; range, 54–450 days). *Results* Ten of 13 patients exhibited ≥80% improvement from baseline in RLS symptoms. Five maintained complete resolution of RLS symptoms. Global gastrointestinal symptom improvement was great (n = 6), moderate (n = 5), or mild (n = 2). *Conclusion* This study suggests that SIBO associated with IBS may be a factor in some RLS patients and SIBO therapy provides long-term RLS improvement.

Keywords Antibiotic · Irritable bowel syndrome · Restless legs syndrome · Rifaximin

Introduction

Restless legs syndrome (RLS) is characterized by an urge for leg movement, often with abnormal leg sensations. Symptoms are triggered by rest, often at night, and improve temporarily with movement, especially walking. This syndrome has a prevalence ranging from 7% to 15% and significantly contributes to sleep disorders [1–3]. Most RLS cases are idiopathic, but contributing factors include iron deficiency and renal failure [4, 5]. Restless legs syndrome occurs frequently in patients with peripheral neuropathy, particularly in individuals with Charcot–Marie–Tooth disease [6, 7]. The prevalence of RLS has also been reported in a single case series of fibromyalgia (31% of 135 patients) [8] and scleroderma (22% of 27 patients) [9].

Fibromyalgia and irritable bowel syndrome (IBS) are accepted as common comorbid conditions [10–12]. In the past, central hypersensitivity had been considered a mutual problem [13]. However, evidence continues to gather suggesting that small intestinal bacterial overgrowth (SIBO), with systemic inflammation and visceral neurological changes, may be an alternative explanation for the development and persistence of IBS, fibromyalgia, and other hypersensitivity syndromes (e.g., interstitial cystitis and chronic fatigue syndrome) [14–19]. The occurrence of SIBO in patients with IBS has been suggested by direct evidence with small bowel culturing and by indirect evidence using breath testing [20–24]. One explanation for the occurrence of SIBO in patients with IBS and other conditions that involve SIBO is an abnormality of the phase 3 part of the migrating motor complex [15, 25, 26]. Increased intestinal permeability has been observed in patients with postinfectious IBS and diarrhea-predominant IBS [27] and may be a consequence of SIBO [15].

The propositus that led to the current study was a patient with a 14-year history of chronic postprandial abdominal pain and diarrhea that had immediately followed an episode of travelers' diarrhea, with subsequent development

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of RLS 2 months later. It was suspected that the patient might have postinfectious IBS and SIBO. Empiric treatment with the minimally absorbed (<0.4%), broad-spectrum antibiotic rifaximin resulted in a dramatic, rapid, and prolonged response for both RLS and IBS symptoms. In this open-label, observational pilot trial, the efficacy of rifaximin, followed by treatment for possible motility and permeability disturbance [28–30], was evaluated in IBS patients with RLS who showed indirect evidence of SIBO.

Methods

Patient population

Patients visiting a community-based adult gastroenterology clinic over a 4-month period were eligible for the study if they presented with functional bowel symptoms and had abnormal lactulose breath test (LBT) results. Patients were excluded if they had celiac disease, Crohn's disease, pancreatic insufficiency, ulcerative colitis, scleroderma, diabetes, chronic renal failure, or surgeries predisposing them to SIBO. A diagnosis of RLS was confirmed using the Johns Hopkins validated interview process [31].

Lactulose breath testing

Patients consumed a low carbohydrate dinner and fasted overnight. Breath samples were collected every 15 min for 180 min and were analyzed by gas chromatography (QuinTron DP Plus MicroLyzer™, QuinTron Instrument Company, Milwaukee, WI, USA) for levels of hydrogen and methane. After a baseline recording, patients consumed 10 g of lactulose powder (Kristalose®, Bertek Pharmaceuticals, Sugar Land, TX, USA) dissolved in 240 mL water. An abnormal LBT result was defined as an increase of >20 ppm above baseline levels for hydrogen and/or methane gas ≤180 min after ingesting lactulose. An abnormal flatline LBT result was defined as a lack of a >5-ppm increase above baseline levels for either hydrogen or methane during the 180-min test. The flatline response is suggestive of bacterial overgrowth by hydrogen sulfide-producing bacteria and which is not detectable by current gas chromatography technology (personal communication, Henry C. Lin, MD, USA; 2005).

Treatment

Patients received rifaximin (Xifaxan®, Salix Pharmaceuticals, Morrisville, NC, USA) 400 mg, 3 times daily, for 10 days. This was followed by long-term administration of the prokinetic medicine tegaserod (Zelnorm®, Novartis Pharmaceuticals, East Hanover, NJ, USA) 3 mg nightly plus short-term treatment with zinc 220 mg day^{-1} for 1 month for increased small intestinal permeability and a bifidobacteria-based probiotic (Flora-Q®, Kenwood Therapeutics, Fairfield, NJ, USA) once daily for 1 month. Patients may have also received rifaximin alone (n = 2).

Patient evaluation and follow-up

Each patient completed a questionnaire identifying the occurrence and rating the severity of six IBS symptoms experienced during the week before the LBT was conducted (baseline): abdominal pain, bloating, constipation, diarrhea, flatulence, and postprandial fullness. A history consistent with RLS and fibromyalgia was sought. Serum ferritin levels were measured at baseline. The ferritin was measured owing to the frequent occurrence of peripheral and central iron deficiency in RLS [1, 4].

Each patient received a follow-up questionnaire by mail and was asked to report on each of the gastrointestinal (GI) symptoms originally reported to be present at baseline and the percentage of improvement immediately after completing rifaximin treatment (day 11) and at the end of follow-up. Patients rated overall GI symptom improvement at the last follow-up visit as greatly improved, moderately improved, mildly improved, or no improvement. The percentage of RLS symptom improvement was assessed at the end of follow-up.

Results

Thirteen IBS patients with confirmed RLS were included in the study. Eleven of these 13 patients were originally included in a SIBO study of IBS [24]: nineteen of 161 patients with an abnormal LBT result thought they had RLS. A diagnosis of RLS was confirmed in eleven of these nineteen patients by the Johns Hopkins validated interview process. The remaining two of the thirteen patients (one was the propositus and one was referred from the neurology clinic) had been previously evaluated and treated for RLS by a neurologist.

All twelve patients who were tested for SIBO had an abnormal LBT result (Table 1). The propositus was treated empirically. Most of these twelve patients (75%) were diagnosed with high-hydrogen levels. One of these patients had a flatline LBT result. This result suggested the possibility of overgrowth of hydrogen sulfide-producing bacteria in the small intestine, which is not detectable by current LBT technology (Henry C. Lin, MD, USA; October 9, 2006, personal communication). The most common GI

Table 1 Patient demographics and baseline characteristics (n = 13)

Male:female, *n*	2:11
Mean age, year (range)	50 (35–63)
RLS, *n*	13
Fibromyalgia, *n*	6
Serum iron status	
Iron deficiency, n	1
Borderline iron deficiency, *n*	2
Meeting IBS Rome II criteria, *n*	13
Baseline GI symptoms, *n*	
Abdominal pain	13
Bloating	13
Constipation	9
Diarrhea	11
Excessive flatulence	10
Postprandial fullness	11
LBT result	
High hydrogen	9
High methane	2
Flatline	1
Not performed[a]	1

RLS, restless legs syndrome; IBS, irritable bowel syndrome; GI, gastrointestinal; LBT, lactulose breath test

[a] Propositus patient

symptoms at baseline included abdominal pain (n = 13), bloating (n = 13), diarrhea (n = 11), and constipation (n = 9) (Table 1).

Eleven patients were treated with rifaximin 1,200 mg day^{-1} for 10 days, followed by treatment with a prokinetic, zinc for intestinal permeability, and probiotic therapy. The remaining two patients (neurology clinic patient and propositus) received a modified treatment regimen. The neurology patient was treated with rifaximin 400 mg, 3 times daily, for 10 days. The propositus was treated empirically (prior to LBT availability at the clinic) and received rifaximin 400 mg, 3 times daily, for 10 days and a second course of the same regimen 2 months posttreatment. Two months after completion of the second course, the patient was prescribed rifaximin 800 mg day^{-1} for 12 months.

Only three of thirteen patients were diagnosed with possible iron deficiency at baseline. The neurology patient had borderline iron deficiency (ferritin level, 12 ng dL^{-1}; normal, <10 ng dL^{-1}) and received concomitant long-term iron supplementation (ferrous sulfate 325 mg, 3 times daily). One additional patient with borderline normal levels of ferritin and one patient with low ferritin levels did not receive iron supplementation during SIBO therapy.

Percentages of RLS and IBS symptom improvement and global IBS symptom improvement were assessed at a mean of 107 days (range, 22–450 days). Ten of thirteen patients with RLS exhibited ≥80% improvement in RLS symptoms at the last follow-up visit. The ten patients who responded included the three patients who had borderline or low serum levels of iron at baseline. All ten patients indicated that the ≥80% improvement in RLS symptoms occurred during or at the end of rifaximin treatment. Eight of the ten patients with ≥80% improvement in RLS symptoms were followed long-term (mean, 139 days; range, 54–450 days), and five of the eight patients reported complete (100%) resolution of RLS symptoms at the last follow-up visit (Table 2).

After completion of 10 days of rifaximin therapy (day 11), GI symptom improvement was reported as follows: abdominal pain (74%), diarrhea (73%), bloating (70%), postprandial fullness (65%), constipation (64%), and flatulence (47%). At the end of follow-up, symptom improvement was maintained: abdominal pain (81%), diarrhea (68%), bloating (76%), postprandial fullness (67%), constipation (59%), and flatulence (55%). Global symptom improvement was rated as greatly improved for six patients, moderately improved for five patients, and mildly improved for two patients. Follow-up LBT was not available for the thirteen patients, with the exception of the neurology patient. This individual had a normal LBT result 2 months after completing rifaximin therapy.

Table 2 Percentage improvement in RlS symptoms after SIBO treatment[a]

RLS symptom improvement	Patients, *n* (%), *n = 13*
Improvement, %	
100	6 (46)
95	2 (15)
90	1 (8)
80	1 (8)
50	1 (8)
30	1 (8)
25	1 (8)
Mean overall improvement	82%
Mean overall improvement in eight patients with long-term follow-up	86%
Mean follow-up, days (range)	139 (54–450)

RLS, restless legs syndrome; SIBO, small intestinal bacterial overgrowth

[a] SIBO treatment: rifaximin 1,200 mg day^{-1} for 10 days followed by tegaserod 3 mg long-term and 1 month of zinc 220 mg and probiotic daily. Deviations from this regimen occurred in two patients: the propositus had two 10-day courses of 1,200 mg day^{-1} rifaximin followed by rifaximin 800 mg day^{-1} for 1 year; and one patient received rifaximin 1,200 mg day^{-1} for 10 days (these two patients reported 100% improvement)

Discussion

Substantial overlap exists between IBS and other hypersensitivity disorders [32]. Small intestinal bacterial overgrowth may be a common denominator for these disorders, which are characterized by visceral hypersensitivity, chronic inflammation, and neurochemical changes [15]. Altered genetic control of immune activation, production of proinflammatory cytokines, increased intestinal permeability, and immune responses triggered by bacterial endotoxins may lead to the development of intestinal and extraintestinal manifestations of IBS [15–17, 33–35]. Persistence of an underlying motility disorder of the migrating motor complex is thought to be responsible for SIBO and GI symptom relapse after antibiotic therapy [15, 25].

It was hypothesized that a relationship might exist between RLS, IBS, and SIBO because RLS may be a comorbid condition of fibromyalgia, [8] fibromyalgia is a known comorbid condition of IBS, [10–12] and fibromyalgia and IBS have been associated with SIBO [14]. Also, there was a dramatic response to rifaximin by the propositus who had postinfectious IBS, which is caused by SIBO. Evidence that SIBO plays a role in IBS continues to accumulate despite continued debate and controversy [14, 15, 21–24, 36, 37]. In a single case series, patients with scleroderma had an increased incidence of RLS, although they did not have end-stage small intestinal disease with the commonly accepted presentation of SIBO, such as malabsorption and steatorrhea [9]. Another possible mechanism to explain a role for SIBO in RLS is that a chronic inflammatory state directly [38] and indirectly (via increasing hepcidin levels) [39] plays a role in iron deficiency [4], which is sometimes associated with RLS. Iron deficiency can affect cell oxygenation by direct (e.g., reduced hemoglobin levels) and indirect mechanisms (e.g., functioning of mitochondrial iron-containing proteins required to process oxygen in cells) [40]. We theorize that the latter may be one mechanism to explain RLS muscle discomfort that is relieved by leg movement.

This pilot study provides preliminary data to support the novel hypotheses that SIBO associated with IBS may be an important factor in some patients with RLS and that comprehensive SIBO therapy may provide long-term improvement in both RLS and GI symptoms. The limitations of this study include the open-label study design, the multiple medication protocol, the lack of a placebo arm, posttreatment LBT performed in one patient only, and not using the International RLS Study Group Scale. A randomized, double-blind, placebo-controlled study of rifaximin is planned to determine the relationships among SIBO, RLS, and IBS by performing an LBT and measuring interleukin 6 levels, hepcidin levels, Likert scale GI scores, IBS quality of life scores, and ratings on the International RLS Study Group Scale, pretreatment and posttreatment. If SIBO is a potential trigger, then the treatment paradigm for RLS could radically change for this difficult-to-treat, common disorder.

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