Restless Legs Syndrome (Willis-Ekbom Disease) and Gastrointestinal Diseases

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Abstract

Over 50 diseases, disorders and conditions have been reported to be associated and/or contribute to restless legs syndrome (RLS) (recently renamed Willis-Ekbom disease). In many of these diseases, disorders and conditions is the potential to have systemic inflammation or immune disorders. In addition, in some of the idiopathic syndromes and diseases, there is an underlying gut dysfunction with subsequent dysbiosis and/or small intestinal bacterial overgrowth (SIBO). Recently, idiopathic or primary RLS has been shown to be associated with SIBO and preliminary evidence suggests that treating the underlying gastrointestinal disorder can improve RLS severity. In this chapter, all gastrointestinal diseases and disorders that are associated with RLS are reviewed and potential mechanisms to explain the relationship are discussed. Potential food triggers and mechanisms of action for the food triggers are discussed with respect to these gastrointestinal diseases.

Key words: *(*
Restless legs syndrome; RLS; Celiac; Crohn's; Liver; Bacterial overgrowth; SIBO; Dysbiosis; Lactulose breath test

Introduction

Over 50 diseases, disorders and conditions have been reported to be associated and/or contribute to restless legs syndrome (RLS) (recently renamed Willis-Ekbom disease) (Weinstock-2012). Most of these states have the potential to have systemic inflammation or immune disorders (Weinstock-2012). In addition, in many of these idiopathic syndromes and diseases, there is an underlying gut dysfunction with subsequent dysbiosis and/or small intestinal bacterial overgrowth (SIBO) (Weinstock-2011-A). Recently, idiopathic or primary RLS has been shown to be associated with SIBO and preliminary evidence suggests that treating the underlying gastrointestinal disorder can improve RLS severity (Weinstock-2010-C).

Gastrointestinal (GI) dysfunction is the presence of abnormal metabolic function, motility, structure, infection or inflammation. Several GI diseases have systemic symptoms and extra-intestinal manifestations that may be an expression of such dysfunction. Systemic inflammation resulting from asymptomatic gut dysfunction including autoimmune phenomenon and increased intestinal permeability (Weinstock-2011-A) can lead to extra-intestinal disorders.

Examples of extra-intestinal manifestations of celiac disease include thyroid disease, liver disease and osteoporosis (Reilly-2012). Neurological disorders associated with celiac disease include restless legs syndrome, peripheral neuropathy, ataxia, migraines, seizure, peripheral neuropathy, cerebellar ataxia, autonomic dysfunction, myopathy, infantile hypotonia, developmental delay, learning disorders, attention deficit hyperactivity disorder, occipital calcifications, seizures and migraines (Weinstock-2010-A). Examples of extra-intestinal manifestations of inflammatory bowel disease (including Crohn's disease and ulcerative colitis) primarily consist of arthralgias, erythema nodosum, iritis and hepatobiliary diseases (Hou-2009). Neurological disorders associated with Crohn's disease include restless legs syndrome and peripheral neuropathy (Weinstock-2010-B).

In this chapter, all GI diseases and disorders that are associated with RLS are reviewed (Table 1) and potential mechanisms to explain the relationship is discussed. In the setting of these gastrointestinal diseases and in primary RLS the hypothesis for potential food triggers and mechanisms of action of these triggers is proposed. In addition to the GI disorders, ten other secondary RLS disorders have been linked to SIBO, immune and inflammatory processes (Weinstock-2012). These conditions include Parkinson's disease, diabetes, end stage renal disease, rheumatoid arthritis, fibromyalgia, scleroderma, pregnancy, hypothyroidism, acromegaly and advanced age.

TABLE

Table 1. Iron Deficiency, Small Intestinal Bacterial Overgrowth (SIBO), Inflammation and/or Immunological Alterations, and Peripheral Neuropathy in Gastrointestinal Conditions Highly-Associated with Restless Legs Syndrome.

Name and Reference for Conditions Highly Associated with RLS	Iron Deficiency [a]	SIBO	Inflammation and/or Immune Alterations [b]	Peripheral Neuropathy [c]

Gastric resection	Yes	Yes	NS	Yes
Chronic liver disease	Yes	Yes	Yes	Yes
Irritable bowel syndrome	No	Yes	Yes	NS
Celiac disease	Yes	Yes	Yes	Yes
Crohn's disease	Yes	Yes	Yes	Yes

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[a] Includes alterations in iron and ferritin levels. [b] Includes alterations in inflammation. (changes in interleukins 1, 6, 8, 12, and 17 and TNF-α) and overall immune function. [c] This denotes references to case reports of peripheral neuropathy in conditions where neuropathy is not well known to occur. Abbreviations: NS: not studied; RLS: restless legs syndrome; SIBO: small intestinal bacterial overgrowth. References as per Table 1 in Weinstock-2012.

General discussion of small intestinal bacterial overgrowth

The colon is accustomed to having contact with 100 trillion bacteria yet the small intestine has very few by comparison. Complications arise when the coliform count increases in the small intestine or there is an imbalance of bacteria in the colon with harmful bacteria (dysbiosis). The natural protective mechanisms that keep the small bowel bacteria colony counts suppressed include the presence of stomach acid, normal gastrointestinal motility, digestive enzymes, mucosal immunity and the integrity of the ileocecal valve. The balance in the colon is generally kept in check by the background of healthy bacteria, mucosal integrity and normal motility (Weinstock-2011-A).

Small intestinal bacterial overgrowth (SIBO) is defined as the presence of more than 10^5 colony forming units per milliliter in the jejunum with a symptoms or signs of bacterial overgrowth or malabsorption. Non-invasive diagnostic testing to determine the presence of SIBO are lactulose or glucose breath tests that determine excess products of fermentation (hydrogen or methane) from the proximal small intestine which pass into the respiratory system. This condition can result in gas, bloating, flatulence, altered bowel function and/or malabsorption of nutrients. Bloating, diarrhea, and nutrient deficiencies are induced by excess intraluminal small intestinal bacteria, which results from: (1) fermentation of nutrients producing gas, and (2) bile salt deconjugation by bacteria, leading to fat malabsorption and subsequent steatorrhea and secretory effects, causing diarrhea. Bacterial overgrowth is associated with many complex syndromes including irritable bowel syndrome, fibromyalgia syndrome, rosacea, interstitial cystitis and type III chronic prostatitis (Weinstock-2012). Furthermore, SIBO occurs in the setting of many diseases and treatment with antibiotic therapy is beneficial including RLS (Weintock-2011-A, Weinstock-2008, Weinstock-2009, Weinstock-2010-C).

Chronic SIBO can result in systemic inflammation (Lin-2004). Circulating levels of cytokines, such as TNF-α and pro-inflammatory interleukins and immune complexes are elevated in both SIBO and irritable bowel syndrome (Hughes-2013). Net effects of damaged tight junctions of intestinal mucosal cells include stimulation

of the inflammatory network and activation of lymphocytes and mast cells locally and systemically. With increased intestinal permeability there is translocation of lipopolysaccharides (the outer covering of Gram-negative bacteria) into the damaged mucosal lining can this increase hepcidin production by the liver (Ganz-2003) which may play a role in RLS.

Gastrointestinal diseases associated with RLS

Gastric resection

In 1960 Ekbom reported an increased incidence of RLS in patients who had gastric surgery which was confirmed by a study amongst 106 patients with "malabsorption syndrome" after gastric surgery (Banerji-1970). The incidence of RLS was 11% in this case series compared to others who had RLS (17% with diabetes, 17% with uremia and 2% of otherwise healthy individuals). In the 12 post-gastric surgery RLS patients, only 3 had additional neurologic disorders. There was not an apparent correlation of having low iron levels in those affected by RLS vs. those without RLS in the total group. Reduced acid production and intrinsic factor production by loss of the antrum and its parietal cells result in decreased iron and vitamin B12 absorption (Koike-2001). Lower levels of ferritin could have been present in this cohort that can precipitate RLS (Sun-1998) but this particular measurement was not performed. In addition, gastric resection with subsequent achlorhydria and gastroparesis occur and they promote small intestinal bacterial overgrowth which may have factored into RLS in this group (Paik-2011).

Ulcer surgery has been uncommonly employed with the advent of proton pump inhibitors and treatment for Helicobacter pylori. We are now faced patients who undergo bariatric surgery and studies for RLS may prove to be interesting since outcome of surgery has similar malabsorption potential. (Vargas-Ruiz-2001).

Chronic liver disease

One of the first published reports of liver disease and RLS is a cohort of patient with hepatitis C (Gemignani-1997). The proposed theory to explain this association was that peripheral neuropathy from cryglobulinemia caused RLS in these patients.

Two studies subsequently examined the prevalence of RLS in chronic liver disease patients in liver clinics in Chicago and Japan. The problem interpreting this data includes that there was a mixed group of liver conditions in both studies, one study lacked control of other underlying secondary RLS factors and both did not have age- and gender-matched controls.

In the Chicago tertiary hepatology clinic, investigators used a survey of RLS symptoms based on the International RLS Study Group and its 5 key questions to determine prevalence of RLS (Franco-2008). Of 141 surveys, 88 (62%) were positive for RLS in this population. RLS risk factors were further assessed through a chart review. Most of the RLS patients had secondary risk factors including kidney disease, anemia, iron deficiency, RLS-associated medications and self-reported neuropathy. Idiopathic or unexplained RLS symptoms had a prevalence of 16.3% (CI: 10.6-23.5). Severity of the liver dysfunction including the presence of cirrhosis did not correlate with the prevalence of RLS. The presence of RLS in the affected patients resulted in significantly diminished quality of life. These authors suggested that an increase in CNS serotonin precursors in liver disease patients results in dysfunction of the corticospinal tracts which leads to RLS.

In the Japanese liver disease clinic study, investigators examined the influence on sleep and quality of life and the prevalence of RLS in 149 consecutive

patients with chronic liver disease (Matsuzaki-2012). The same questionnaire was used as the Chicago study for a diagnosis of RLS. All cases with any sleep disturbance were evaluated using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI) and health-related quality of life was evaluated by the Japanese SF-36 Health Survey. Twenty-five of 149 patients (16.8%) fulfilled diagnostic criteria for RLS. The median global PSQI score of the RLS group was significantly higher than the non-RLS group (9 vs. 5, $P<0.01$). Patients deemed poor sleepers (global PSQI score, >5) in the RLS group was significantly higher than in the non-RLS group ($P<0.05$). The mental component summary score of the RLS group was significantly lower than the non-RSL group.

Neither of the above publications tested for neuropathy and SIBO. Peripheral neuropathy is common in chronic liver disease patients and this may account for a significant number of cases of RLS – in a recent study of patients on a liver transplantation waiting list, 65% had peripheral neuropathy (Cocito-2010). Other mechanisms of actions that could explain RLS in liver disease is SIBO and/or systemic inflammation including increased levels of IL-6, TNF-α, immune changes and increased hepcidin levels which occur in liver disease (Schnabl-2013).

Irritable bowel syndrome

Irritable bowel syndrome was first recognized to be associated with RLS in 2008 (Weinstock-2008). In 254 irritable bowel syndrome patients screened at a community gastroenterology practice for bacterial overgrowth and RLS, 54% had SIBO and of these 13 patients with RLS were identified. Some of these patients had a history of antecedent gastroenteritis prior to developing both irritable bowel syndrome and RLS. Using a non-absorbed gut-specific antibiotic (rifaximin) followed by prokinetic drug therapy for the small intestine, 10/13 (77%) of patients had ≥80% long-lasting improvement of RLS.

In an epidemiological study, 30 patients with diarrhea-predominant IBS, 30 with constipation-predominant IBS and 30 with mixed-symptom IBS were evaluated for the prevalence of RLS (Basu-2011). The diagnosis of RLS was assessed via the International RLS questionnaire and polysomnography. Twenty-six patients with IBS of all bowel types (29%) were diagnosed with RLS using the RLS questionnaire. Twenty-four of the 26 patients (92%) underwent polysomnography and all had RLS confirmed. Patients with RLS were more apt to have diarrhea-predominant IBS (62%) compared to constipation-predominant IBS (4%) or mixed-symptom IBS (33%). In other IBS studies when diarrhea prone IBS groups are compared to other groups there is more inflammation diagnosed in the setting of diarrhea.

A study of primary RLS patients addressed the incidence of IBS and SIBO compared to controls (Weinstock-2011-B). RLS subjects were recruited from unbiased ads that did not mention gastrointestinal symptoms. General population controls (GPC) were spouses of patients who came to a GI clinic and they were excluded for RLS. Completely healthy controls (CHC) were excluded for RLS, gastrointestinal symptoms and any other disease. The study included 32 RLS subjects (23F/9M; 57 y.o.), 25 GPC (13F/12M; 58 y.o.), and 30 CHC (19F/11M; 44 y.o.). Twenty nine of the RLS subjects had RLS unassociated with other GI diseases, one had celiac disease and two had gastric resections. IBS was diagnosed in 28% RLS subjects compared to 4% GPC ($P=0.0317$). SIBO was diagnosed in 69% RLS subjects compared to 28% GCP ($P=0.0033$) and 10% CHC. Using a false positive rate of 10%, 59% of positive LBT results are associated with RLS. Four of these patients had IBS that began before onset of RLS symptoms (range, 2-13 years

before RLS). In addition, 3 patients had concurrent onset of RLS and IBS symptoms, and 1 patient developed IBS 20 years after the beginning of RLS. There seemed to be no relationship between dopaminergic use and IBS. There was no association between RLS severity or duration and the presence of IBS, and neither age nor sex played a role in the distribution of IBS. Thus in this small study it appeared that primary RLS patients had an increased incidence of both SIBO and IBS.

Immunological disorders associated with excess gut bacteria (Rubio-Tapia-2009, Rutgeerts-1981) and immunity and inflammation (Mahida-1991) may hypothetically predispose patients to RLS because of effects on central or peripheral nerves. An alternate explanation may be that inflammation leads to iron deficiency with increased hepcidin levels as an intermediary as has been documented in the literature (Ganz-2003). Establishing the link between RLS and SIBO may provide a new approach to the treatment of RLS. Current treatments for SIBO, including antibiotic and probiotic therapies, low carbohydrate diet, and stimulation of small intestinal activity may be beneficial for patients with RLS. Therapy with the non-systemic antibiotic rifaximin is emerging as a promising therapy for SIBO and IBS and may be a useful as primary or adjunctive therapy in patients with RLS (Weinstock-2009, Weinstock-2010-C). A study is currently underway looking for specific antibodies against invasive bacteria and examining the presence of these antibodies in brain and peripheral nerve tissue in healthy individuals and patients with RLS in order to solidify the association between inflammation and RLS.

Celiac disease

Celiac disease is a common autoimmune disease (1/133 people in USA) and is associated with many neurologic disorders by different mechanisms (Green-2005).

Celiac disease was investigated as a potential cause for iron deficiency in four consecutive patients with RLS and a ferritin < 25 ng/mL (Manchanda-2009). Mild anemia was present in only 1 of these 4 patients. All were confirmed to have celiac disease by duodenal biopsy and they responded to a gluten free diet. Marked improvement in RLS symptoms occurred in all and the two patients who were on medications were able to stop therapy. In 2 cases response to gluten was independent of the iron level: one had rapid improvement on the gluten free diet prior to seeing the ferritin rise and the other had relapses in RLS with dietary noncompliance. A survey study of celiac patients were compared to the spouse controls to determine the incidence and prevalence of RLS (Weinstock-2010-A). The incidence of RLS among 85 patients with celiac disease was 35%, with a prevalence of 25% compared with 10% of spouses ($P<0.02$). In 79% of the patients with RLS and celiac disease, RLS symptoms began during or after onset of the gastrointestinal symptoms. Prospective evaluation of iron deficiency was determined in those with active RLS. Iron deficiency was present in 40% of the celiac patients with active RLS compared with 6% of patients who never had RLS ($P<0.001$). After 6 months of a gluten-free diet, RLS symptoms improved in 50% of 28 patients. Secondary RLS conditions other than iron deficiency were uncommon in the patients with and without RLS. A review of family histories revealed prevalence of RLS in a first-degree relative of approximately 20% in both patient groups. One patient with RLS had a first-degree relative with both celiac disease and RLS. A similar proportion of patients with RLS took SSRIs (7%) compared with patients without RLS (9%), and use of SSRIs did not appear to have an effect on RLS symptoms. One patient without RLS who also had Parkinson's disease took dopaminergic medication. Restless legs syndrome

went undiagnosed and untreated in patients for an average of 6 years. Patients with RLS had their celiac disease diagnosed for a mean of 6 years but recalled having GI symptoms for an average of 14 years before a formal diagnosis. This study suggests that celiac disease is frequently associated with RLS and that treatment with a gluten-free diet, aggressive replacement of iron, or antibiotic treatment of bacterial overgrowth may improve the quality of life in patients with celiac disease who have RLS. Thus, celiac disease may be an underlying correctable factor for some patients diagnosed with idiopathic RLS. Another investigation of the prevalence of RLS in celiac disease included a population of 100 adult celiac patients and compared them to 100 age- and sex-matched controls in the general population (Moccia-2010). The patients came from a GI clinic that referred them directly and consecutively to the neurology clinic. The authors found a 31% prevalence of RLS in the celiac population and this was significantly higher than the prevalence in the control population (4%; $P<0.001$). The severity of the patients with RLS was moderate (IRLS score was 17 +/- 6.5). In the celiac population, hemoglobin levels were significantly lower in celiac patients with RLS than without RLS (11.8 vs. 13.0; $P=0.003$). In celiac patients with RLS, 16 of the 31 were compliant with the gluten free diet which did not differ from the celiac patients without RLS. Similarly there was no difference in ferritin levels (30 vs. 36 ng/mL). They excluded correlations between RLS and other possible causes of secondary RLS, including signs of peripheral neuropathy, pregnancy, end-stage renal disease and pharmacological treatments.

Screening for celiac disease in patients with idiopathic RLS may have importance because celiac disease is a commonly overlooked silent disease. A larger controlled study attempted to answer the question whether or not celiac disease is more prevalent in patients with RLS. To determine this, 96 RLS patients and 97 healthy controls, both with or without iron deficiency were studied (Cikrikcioglu-2010). All secondary causes of RLS except iron deficiency were excluded. Tissue transglutaminase antibodies, endomysium antibodies and gliadin antibodies were tested. In RLS patients positivity rates of all celiac antibodies were similar to those in controls. However, the rate of iron deficiency anemia in RLS patients with at least one positive celiac antibody was significantly higher than that of RLS patients whose antibodies were all negative. Overall the prevalence of celiac antibodies in the RLS patients studied was not increased. These authors suggested that iron deficiency is the key mechanism for RLS in celiac patients.

In contrast, peripheral iron deficiency was not highly correlated with RLS in the two RLS prevalence studies of celiac patients (Weinstock-2010-A, Mochia-2010). Thus, more than one mechanism (e.g., inflammatory and/or immunological alterations) may be relevant causes of RLS in celiac disease.

Crohn's disease

Crohn's disease (CD) is a chronic, inflammatory disease of the gastrointestinal tract that primarily affects the small intestine and colon. The etiology of CD is not fully understood but most likely results from abnormal mucosal immune responses stimulated by intestinal bacteria in genetically susceptible individuals (Baumagard-2007). Both CD and RLS have been associated with inflammation and bacterial overgrowth in the GI tract (Sartor-2007, Biancone-2000). Extra-intestinal manifestations of CD have not previously included the central nervous system. Up to a fourth of CD patients get extra-intestinal manifestations.

In a prospective multicenter study, RLS was found to be a comorbid condition in 272 CD patients, with an incidence of 43% and a prevalence of 30% (Weinstock-2010-B). In this study, the 9% prevalence of RLS in the spouse control group was comparable to the prevalence in the general population. The symptoms of RLS occurred during or after the onset of CD symptoms in the majority of patients, suggesting a link between CD and RLS. There was no difference between the CD groups with respect to current iron deficiency or RLS family history. In 91.8% of patients with RLS and CD, RLS started during or after the onset of CD diagnosis. Among 73 patients with RLS, 67 (44.5%) stated there was a relationship between qualitative RLS symptom improvement with overall CD symptom improvement.

Patients with CD and RLS were significantly older and less likely to have CD of the colon versus patients with CD but not RLS. A primary risk factor of RLS, genetic predisposition, was assessed as the incidence of RLS in a first-degree relative and was not significantly different among patients with CD with or without RLS (12.0% for both groups). Although RLS symptoms in patients with CD were not associated with current history of iron deficiency (4.6% vs. 4.7% for patients with and without RLS symptoms, respectively), the percentage of individuals with iron deficiency in the past was significantly higher in patients with CD and RLS than in patients with CD without RLS symptoms (49.3% vs. 33.1%, respectively; P=0.031). Other secondary RLS risk factors were not significantly different between patients with CD with or without RLS symptoms. Pathophysiology of CD includes small intestinal bacterial overgrowth (SIBO) and systemic inflammation. The results in the current study suggest ileal involvement in patients with CD may be a risk factor for RLS.

In the study above, the incidence of RLS was greater than the incidence of many of the known extra-intestinal manifestations of CD including disorders of the skin, joints, eyes and liver. The inflammatory state associated with SIBO and CD stimulates pro-inflammatory cytokines. Pro-inflammatory cytokines such as interleukin-6 have been shown to increase production of a small peptide, hepcidin, which affects iron transport in in vitro models and in healthy human volunteers (Nemeth-2004). We hypothesize that inflammation in CD caused by bacterial overgrowth increases hepcidin levels. This could result in an iron deficiency in the CNS, causing RLS.

Dietary triggers for RLS and for RLS associated with celiac disease and SIBO

Studies on RLS food triggers are limited. There are many barriers and defensive mechanisms by which the intestinal tract mucosa can be exposed to antigens, bacteria and chemicals, yet still be selective about what is absorbed and secreted. Healthy commensal bacteria play a role in protecting the mucosal barrier by direct and indirectly by improving immune function. When this balance is disturbed, absorption of food antigens may be increased. When the bacterial load is increased in SIBO, carbohydrate consumption resulting in increased fermentation, increased bacterial colony counts and increased inflammation. Gluten sensitivity without celiac disease is a common condition but it is not known if it can directly affect RLS as it could in those with celiac disease (Jackson-2012).

According to a posting on the RLS Foundation website, many with RLS have found alcohol consumption, especially in the evening hours, can lead to an increase in RLS symptoms. Alcohol as a factor for poor sleep was not supported by one epidemiologic study of various sleep disorders including RLS (Vinson-2010). In contrast, the author (LW) has RLS patients who have RLS and concomitant SIBO

who have exacerbations of RLS symptoms by alcohol intake. This may relate to fructose consumption and this will be addressed later in this section. The effect of alcohol on periodic limb movements was evaluated in 40 alcohol dependent patients (Gann-2002). Alcohol dependent patients displayed a significantly enhanced PLMS-arousal index compared to age- and gender-matched healthy subjects. The PLMS-arousal index was significantly elevated in patients who relapsed during the next 6 months compared to abstinent patients. The study did not address RLS per se.

In another posting on the RLS Foundation website, it was stated that many with RLS have found that caffeine leads to an increase in RLS symptoms. A clinical, uncontrolled study of 62 RLS patients and associated anxious-depressed states suggested that caffeine worsened RLS symptoms (Lutz-1978).

Saccharin as an additive has been studied and was compared to cyclamate in randomized, double-blind, placebo-controlled trial with a crossover design (de Groot-2007). During a period of 48 days, the subjects took 4 capsules per day containing either 150 mg of cyclamate, 22.5 mg of saccharine, either sweeteners or placebo on two successive days. Between each of these 2-day periods there was a 2-day rest period during which no capsules were taken. The subjects had symptoms more often and more severe RLS while using saccharine or the combination of saccharine and cyclamate than when taking the placebo. The potential mechanism of action is unknown. In one of the antibiotic treatment studies for bacterial overgrowth in RLS, an observation was made that consumption of alcohol and fruit exacerbated RLS symptoms (Weinstock-2010-C) and other clinic patients have had similar problems. Foods high in carbohydrates or carbohydrates which are difficult to digest such as the “FODMAPs” should be examined. These foods are substrates for bacterial fermentation and hence could not only explain worsening symptoms in patients with IBS but also those with SIBO and possibly SIBO-associated RLS. The term FODMAPs stands for fermentable oligo-, di-, and mono-saccharides and polyls. These include lactose, fructose, fructans, galactans and sugar alcohols. Fructans are present in wheat, onions, garlic and other vegetables.

Conclusions

Common gastrointestinal diseases and disorders including IBS, celiac disease, Crohn’s disease and chronic liver disease have a relatively high prevalence of RLS. The prevalence of small intestinal bacterial overgrowth and of IBS appears to be increased in patients with restless legs syndrome but larger studies will be required to be definitive (Weinstock-2011-B). Although the prevalence of RLS is higher in celiac disease (Weinstock -2010-A; Moccia 2010) the reverse is not true, i.e. there is not an increased prevalence of celiac disease in RLS patients (Cikrikcioglu-2010). This is exactly what one would expect if the inflammatory/immunologic processes associated with celiac disease lead to RLS and not vice versa. In cases of other GI disorders where RLS is found to be increased such as in Crohn’s disease, it is suggested that these reverse prevalences, e.g. the prevalence of Crohn’s disease in RLS also be investigated. Findings similar to those found with celiac disease would similarly strengthen the immunological hypothesis for the pathogenesis of RLS. Overall and in summary, the pathophysiology of a subset of RLS may relate to underlying GI dysfunction, inflammation or immune mechanisms.

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