Movement Disorders
Vol. 25, No. 7, 2010, pp. 877–881

Restless Legs Syndrome is a Common Feature of Adult Celiac Disease

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Abstract: Restless legs syndrome (RLS) is a common neurological condition, frequently idiopathic, sometimes associated with specific disorders such as iron deficiency. We investigated RLS prevalence in celiac disease (CD), an autoimmune disease characterized by several features such as malabsorption-related iron deficiency anemia and peripheral neuropathy. We screened a population of 100 adult CD patients for CD features, iron metabolism, clinical and neurological conditions, and enrolled 100 age- and sex-matched controls in the general population. RLS was ascertained in CD patients and controls by both the presence of the four essential International RLS Study Group diagnostic criteria and neurological examination. The International RLS Study Group rating scale was used to measure RLS severity. We found a 31% prevalence of RLS in the CD population that was significantly higher than the prevalence in the control population (4%; $P < 0.001$). The average severity of RLS in CD population was moderate (17 ± 6.5). In the CD population, no significant correlation was found between RLS and either gluten-free diet or iron metabolism, despite hemoglobin levels were significantly lower in CD patients with RLS than without RLS ($P = 0.003$). We found no correlation between RLS and other possible causes of secondary RLS, including signs of peripheral neuropathy, pregnancy, end-stage renal disease, and pharmacological treatments.Our study broadens the spectrum of neurological disorders associated with CD and indicates that RLS should be sought for in all patients with CD. © 2010 Movement Disorder Society

Key words: restless legs syndrome; celiac disease; sleep disorders

Restless legs syndrome (RLS) is a common underdiagnosed sensory-motor disorder, characterized by paresthesias and intense urge to move the legs.[1] The disorder, idiopathic in most cases, is considered secondary when linked to end-stage renal disease, pregnancy, and iron deficiency.[2] Moreover, RLS is associated with polyneuropathy,[3] irritable bowel syndrome, and autoimmune disorders such as rheumatoid arthritis or Sjögren syndrome.[4,5]

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Potential conflict of interest: Nothing to report.

Received 17 September 2009; Revised 21 October 2009; Accepted 27 October 2009

Published online 13 April 2010 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.22903

Celiac disease (CD) is a chronic immune-mediated gluten-dependent enteropathy, induced by ingestion of gluten-containing products, characterized by intestinal malabsorption and subtotal or total atrophy of intestinal villi, which improves after gluten-free diet (GFD). The prevalence of CD is 0.5 to 1% in international population studies.[6] The clinical presentation of adult CD is characterized by nonspecific gastrointestinal features resembling irritable bowel syndrome and extraintestinal disorders including rheumatoid arthritis, Sjögren syndrome, and other autoimmune diseases.[7] Several neurological disorders, such as peripheral neuropathy (PN),[8,9] cerebellar ataxia, and epilepsy, have been associated with CD.[10,11] Frequently reported symptoms of adult CD are burning and throbbing sensations in limbs.[8] Iron deficiency has been associated with CD.[7] The consideration that sensory symptoms and iron deficiency are common features of both RLS and CD

prompted us to investigate the prevalence and characteristics of RLS in CD.

METHODS

One hundred twenty patients with CD were consecutively referred to us by the Gastroenterology Unit of "Federico II" University Hospital between December 2007 and November 2008. The study was approved by the Ethical Committee of University "Federico II" and participants gave informed consent according to the Declaration of Helsinki. CD diagnosis was based on the evidence of specific intestinal damage at duodenal biopsy and on the presence of specific antibodies in serum.[12] Intestinal mucosa was evaluated at duodenal biopsy according to Marsh by the method of Oberhuber et al.[13,14] The search of specific antibodies in serum focused on antigliadin IgA-IgG in patients who were diagnosed in the years 1975 to 1991 and on antiendomysium and antitissue-transglutaminase IgA in patients who were diagnosed after 1992. Data collection at time of CD diagnosis included weight and height for calculation of body mass index (BMI = $weight_{kg}/height_{m^2}$), presence of diarrhoea (three or more liquid voids/d in the last month), presence of dyspepsia (chronic or recurrent pain in the upper abdomen, upper abdominal fullness, or feeling full earlier than expected with eating), and the measurement of laboratory indices for assessment of absorptive status (serum concentration of iron, albumin, and cholesterol). Clinical workup at CD diagnosis included the search of all immune-mediated diseases associated with CD (e.g., Hashimoto thyroiditis, autoimmune hepatitis, biliary cirrhosis, Sjogren syndrome, sclerosing cholangitis, etc). Patients were investigated for family history of CD and GFD adherence.

Exclusion criteria were uncertain CD diagnosis, age younger than 18 years or older than 49 years, history of neuroleptic exposure or neuroleptic-induced akathisia, dementia or any reason that could interfere with interview. Among the 120 referred CD patients, twenty were excluded because of the age range.

As a control group, a sex- and age-matched population of 100 individuals was enrolled among the general population. Exclusion criteria were current presence of cancer, serious medical illness, presence of neurological or psychiatric disorder, and history of alcohol or drug abuse.

Clinical records and characteristics were collected including weight, height, presence of CD-related disorders such as type 1 diabetes, arthritis, or thyroid pathologies, and any pharmacological treatment. Iron metabolism was investigated in all CD patients by evaluation of blood levels of iron, ferritin, hemoglobin, and mean corpuscular volume (MCV). With regard to diet, patients were classified in two groups: GFD patients were on strict GFD as they referred and according to serum tissue transglutaminase antibodies under the normality value; unrestricted diet patients referred not to be on GFD or had serum tissue transglutaminase antibodies over the normality value because of low compliance to GFD.

A structured interview was administered to all subjects to explore RLS. According to International RLS Study Group (IRLSSG) diagnostic criteria,[1] RLS was investigated by asking the following four questions: "(1) do you ever feel an urge to move the legs, usually accompanied or caused by uncomfortable or unpleasant sensations? (2) does the urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting? (3) are the urge to move or unpleasant sensations partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues? and (4) are the urge to move or unpleasant sensations worse in the evening or night than during the day or only occur in the evening or night?" Subjects answering "yes" to all questions were diagnosed as having RLS and were evaluated by a sleep disorder expert according to IRLSSG rating scale.[15] Both subjects and partners were asked for presence of sudden and repetitive nocturnal limb movements, which might resemble periodic limb movements (PLMS). The occurrence of RLS symptoms during pregnancy and the presence of RLS-like symptoms in the relatives were also investigated. All subjects underwent a complete neurological examination. Definition of clinical significant PN was made according to consensus recommendations for case definition[16]: patients were screened for neuropathic symptoms (numbness, altered sensation, or pain in the feet), ankle reflexes, distal sensation (pin sensation and vibration), distal muscle weakness, and atrophy. Patients with neuropathic symptoms, or with decreased or absent ankle reflexes, or with both neuropathic symptoms and decreased distal sensation, were considered as having a PN likelihood of +. Patients with contemporary presence of neuropathic symptoms, decreased or absent ankle reflexes, decreased distal sensation with or without distal muscle weakness or atrophy, were considered as having a PN likelihood of ++. According to the consensus recommendations for case definition in epidemiologic studies, only patients with a likelihood of ++ were considered as possibly affected by PN and, therefore, addressed to electro-

TABLE 1. *Demographics of CD and control populations*

	CD patients (n = 100)	Controls (n = 100)	*P*
Men/women	20/80	20/80	NS
Age, yr (range)	32 ± 8.4 (18–49)	32 ± 8.3 (18–49)	NS
Body mass index (kg/m^2)	21.9 ± 3	23.2 ± 2.2	0.001

NS, not significant.

diagnostic studies.[17] Moreover, RLS patients were investigated for all conditions whose symptoms mimic those of RLS such as leg cramps, arthritic pains, positional discomfort, and pronounced or frequent unconscious foot or leg movements (e.g., hypnic jerks, habitual foot tapping, leg shaking, general nervous movements).[18]

Statistical comparisons between CD patients and healthy controls and between CD patients with RLS (CD+RLS) and CD patients without RLS (CD−RLS) were performed using χ^2 test or *t*-test when appropriate. Correlations between RLS presence and severity and other clinical features were assessed using Spearman's rank test. Significance was set at 5%. Results are reported as mean ± SD.

RESULTS

Demographic features of CD patients and controls are listed in Table 1. There was no significant difference in either age or sex between patients and controls. BMI was significantly higher in healthy controls than in CD patients ($P = 0.001$; Table 1).

The prevalence of RLS was significantly higher in CD patients than in controls ($P < 0.001$; Table 2). The average severity of RLS was lower in CD patients than in controls ($P < 0.001$; Table 2).

None of CD patients or controls presented a pattern of neuropathic symptoms and signs supporting high likelihood of PN according to England et al. (Table 3).[17] Consequently, no subject underwent electroneurographic studies.

TABLE 2. *RLS features in CD and control populations*

	CD patients (n = 100)	Controls (n = 100)	*P*
RLS diagnosis (n)	31	4	<0.001
RLS rating (n)			
Mild	7	0	NS
Moderate	11	1	NS
Severe	13	3	NS
Very severe	0	0	NS
Mean (±SD) IRLSSG-RS score	17 ± 6.5	22.7 ± 3.3	<0.001

NS, not significant.

TABLE 3. *PN likelihood in CD patients and controls*

	Likelihood +, n (%)	Likelihood ++, n (%)
CD+RLS (n = 31)	31 (100)	0 (0)
CD−RLS (n = 69)	22 (31.9)	0 (0)
Controls+RLS (n = 4)	3 (75)	0 (0)
Controls−RLS (n = 96)	22 (22.9)	0 (0)

+, Presence of neuropathic symptoms (numbness, altered sensation, or pain in the feet), or of decreased or absent ankle reflexes, or of both neuropathic symptoms and decreased distal sensation. ++, Contemporary presence of neuropathic symptoms (numbness, altered sensation, or pain in the feet), decreased distal sensation and decreased or absent ankle reflexes, with or without distal muscle weakness or atrophy.

No significant differences were found between CD+RLS and CD−RLS patients with regard to sex, age, and BMI (Table 4). No significant difference was found in RLS prevalence among GFD patients and unrestricted diet patients (Table 4).

In the CD population, 19 women and 2 men reported other relevant diseases. Prevalence of these concomitant disorders was not significantly different in CD+RLS and CD−RLS patients.

Nine patients were on medication, but none was treated for RLS. No relation was found between RLS and pharmacological treatments with thyroxine, non steroidal antiinflammatory drugs, oral contraceptives, H1-antagonists, benzodiazepines, corticosteroids, selective serotonin reuptake inhibitors, ACE inhibitors, and proton pump inhibitors.

Blood levels of iron, ferritin, and MCV were not statistically different between CD+RLS and CD−RLS

TABLE 4. *Clinical features in CD+RLS and CD−RLS patients*

	CD+RLS (n = 31)	CD−RLS (n = 69)	*P*
Men/women (n)	3/28	17/52	NS
Age (yr)	34 ± 9	31 ± 7.9	NS
BMI (kg/m^2)	22 ± 3	21.8 ± 3.2	NS
Diet			
GFD, strict	15	40	NS
GFD mean time (months)	62.2 ± 69.2	44.9 ± 55.8	NS
Unrestricted diet	16	29	NS
Blood parameters			
Iron (μg/dl)	63.6 ± 35	73.8 ± 29.2	NS
Ferritin (ng/ml)	30.3 ± 48.2	35.8 ± 41.8	NS
Hemoglobin (g/dl)	11.8 ± 1.8	13 ± 1.8	0.003
Mean corpuscular volume (fl)	81.9 ± 8	84.1 ± 8.2	NS

NS, not significant.

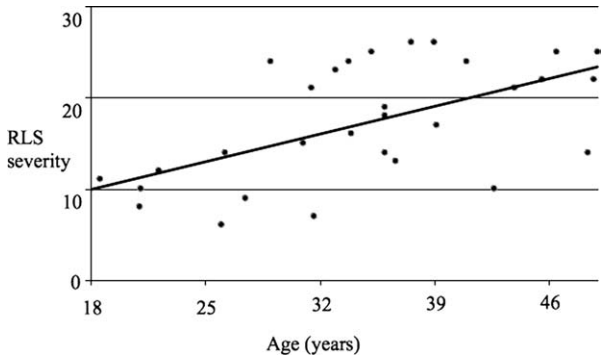

FIG. 1. Scatter plot showing correlation between RLS severity and age in CD patients.

patients, whereas hemoglobin levels were significantly lower in CD+RLS than CD−RLS patients ($P = 0.003$; Table 3).

Prevalence of sudden and repetitive nocturnal limb movements during sleep was higher in CD+RLS (38.7%) than CD−RLS patients (1.5%; $P = 0025$).

RLS severity did not relate with sex, BMI, GFD, and blood levels of iron, ferritin, hemoglobin, and MCV. RLS severity was positively correlated with age ($\rho = 0.6$; $P < 0.001$; Figure 1). None CD+RLS patient reported the occurrence of RLS symptoms during a pregnancy. A family history of RLS was reported by 25.8% of the CD patients affected by RLS.

DISCUSSION

Several neurological disorders have been extensively described in association with CD including PN,[18,19] epilepsy,[19] cerebellar ataxia,[10,20] chronic progressive leukoencephalopathy,[21] myopathy and dementia.[22,23] This is the first study to show a relevant association between RLS and CD, with a significantly higher prevalence of RLS in CD patients (31%) than in controls (4%). Interestingly, the prevalence of RLS in CD patients is comparable to that reported in association with uremia and pregnancy.[24] Although a low prevalence of RLS in controls might reflect the exclusion of control subjects with neurological or psychiatric disorders the value is consistent with those reported in the general population (form 3.2% to 11.1%).[24]

Recently, four patients with RLS and low serum ferritin levels have been diagnosed as having CD, suggesting that RLS was secondary to iron metabolism defect.[25] According to our results, it seems unlikely that RLS is related to nutritional status in CD patients. In fact, we found no significant difference in iron metabolism, BMI, and GFD adherence between CD+RLS and CD−RLS. The finding of a lower hemoglobin level in CD+RLS patients is difficult to explain and deserves further studies. As a possible explanation, a lower hemoglobin level might reflect a more severe CD in CD+RLS patients. However, our finding of no significant difference in GDF and BMI between CD−RLS and CD+RLS does not support the hypothesis of a more severe nutritional status in CD+RLS patients. Furthermore, other possible causes of secondary RLS were excluded in our CD population, including pregnancy, end-stage renal disease, and pharmacological treatments.[1,26,27] According to an expert consensus for clinical definition of PN,[16] we reasonably excluded an involvement of PN as a possible cause of RLS in our patients. Moreover, false-positive RLS due to PN are unlikely, since the specificity of the four question IRLSSG screening questionnaire has been recently reported to be 91% in patients with PN and 99% in controls.[28] On the other hand, the presence of RLS before the age of 45 years and the increase of RLS severity with age would support the primary nature of CD-related RLS.[29,30] It is possible that RLS may develop following to a still unknown provoking factor in genetically susceptible CD patients. Association studies could be helpful to identify genetic variants possibly associated to CD-related RLS.

The mean severity of RLS was lower in CD than in controls, but there was no significant difference in distribution among the different classes of severity. However, the reliability of this result may be impaired due to the small number of RLS among controls.

A great majority of patients with RLS also experience PLMS.[30] In our study, sudden and repetitive nocturnal limb movements were reported in approximately 40% of CD+RLS patients, suggesting possible PLMS. Because of the lack of polysomnography, however, we cannot draw conclusions about nature and frequency of these self-reported nocturnal limb movements.

The mechanisms leading to neurological disorders in CD are not yet understood. Two different mechanisms have been proposed: a) malabsorption-related deficiency of neurotrophic and/or neuroprotective factors; b) presence of antineuronal antibodies and/or infiltration of lymphocytes in the nervous system.[31–34] The latter hypothesis is supported by the evidence that neither GFD nor vitamin replacement therapy ameliorate symptoms of neurological disorders in CD.[31] Similarly, in our CD patients, neither RLS prevalence nor severity was related to iron status or GFD adherence.

In conclusion, our study broadens the spectrum of neurological disorders associated with CD and indicates that RLS should be sought for in all patients with CD. Further studies are needed to characterize mechanisms underlying CD-related RLS.

Acknowledgments: This study has received a partial financial support by NEURECA FONDAZIONE-Onlus, an Italian no-profit organization devoted to support research initiatives in movement disorders and sleep fields.

Author's Roles: 1) Research project: A. Conception, B. Organization, C. Execution; 2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3) Manuscript: A. Writing of the first draft, B. Review and Critique. Moccia Marcello: 1B, 1C, 2B, 3A. Pellecchia Maria Teresa: 1B, 2A, 2C, 3A. Erro Roberto 1C, 2C, 3A: Zingone Fabiana: 1B, 1C, 2C. Marelli Sara: 1B, 1C, 2C. Barone Damiano Giuseppe: 1B, 1C, 2B. Ciacci Carolina: 1B, 2C, 3B. Ferini Strambi Luigi: 1B, 2C, 3B. Barone Paolo: 1A, 1B, 2C, 3B.

Financial Disclosures: Professor Ferini-Strambi received honoraria from serving on the scientific advisory board of UCB-Pharma, Boehringer-Ingheleim, GSK, Sanofi-Aventis. Professor Barone has received compensation for consulting services and received research support from Boehringer Ingelheim; for consulting services from Novartis, Schwarz Pharma/UCB and Lundbeck. All the other authors have no financial disclosures to make.

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