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Original Article

Association Between Irritable Bowel Syndrome and Restless Legs Syndrome: A Comparative Study With Control Group

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Background/Aims
As a common gastrointestinal (GI) disorder, irritable bowel syndrome (IBS) has been reported to be associated with some psychological and neurological factors. This study aimed to evaluate the prevalence rate of restless legs syndrome (RLS) in a sample of IBS patients and to compare this prevalence with that of matched healthy controls.

Methods
This prospective comparative study was conducted in Tehran, Iran during 2010-2011. Based on the Rome III criteria, a total number of 225 definite IBS patients and 262 age- and sex-matched healthy controls were recruited in the final assessment to compare the prevalence rate of RLS between the 2 groups.

Results
RLS was significantly more frequent in IBS group (25.3% vs 6.5%, $P < 0.001$) which led to an odds ratio (OR) of 4.89 (95% CI, 2.75-8.70). IBS patients with co-morbid RLS significantly suffered more from stomach pain (96.5% vs 86.3%, OR = 4.36 [95% CI, 1.00-19.12]), nausea (40.4% vs 21.4%, OR = 2.48 [95% CI, 1.30-4.73]) and vomiting (10.5% vs 2.4%, OR = 4.82 [95% CI, 1.31-17.76]).

Conclusions
By enrolling a considerable number of IBS patients and healthy controls, our study showed a significantly higher prevalence of RLS in IBS patients. Surprisingly, a higher prevalence rate of RLS was also accompanied with a more severe discomfort and stomach pain in IBS patients. It seems that screening patients with IBS for RLS may lead to greater identification of RLS and improved treatment for both conditions.
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Key Words
Irritable bowel syndrome; Restless legs syndrome; Control groups

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Introduction

Irritable bowel syndrome (IBS) is a common gastrointestinal (GI) disorder defined by abdominal pain, discomfort, flatulence and visceral hypersensitivity leading to general reduction in health related quality of life. Its incidence rate is about 10%-20% in normal population, with a female predominance.[1] The etiology of IBS is unknown but alteration in motility, visceral sensitivity, intestinal barrier function and genetics have been implicated in its pathogenesis.[2-6] Considering the unknown underlying mechanism of IBS, it has been reported to be associated with psychological and neurological factors, too. Moreover, the disruption of enteric and central nervous system communication due to changes in inflammatory mediators triggered by small intestinal bacterial overgrowth (SIBO) infection, has been implicated in IBS patients.[7]

On the other hand, restless legs syndrome (RLS) - a neurological movement disorder - which is characterized by an urge for leg movement, often with abnormal leg sensations, has been also shown to be associated with SIBO.[8] Furthermore, SIBO may play an important role in mucosal inflammation, leading to increased cytokine activity and intestinal motility, and neurotransmitter release such as 5-hydroxytryptamine. This may highlight the association between IBS and SIBO.[9] Therefore, it is hypothesized that a relationship might exist between RLS, IBS and SIBO. More evidences also support this hypothesis when RLS has been reported to be associated with fibromyalgia in a single case series,[10] which is accepted as a common co-morbid condition with IBS, too.[11-13]

Uncovering the internal association between IBS and RLS may lead to some important information improving our knowledge about the pathophysiology of IBS as the most common functional bowel disorder and a neurogastroenterology phenomenon.[14] To date, there are few reports assessing the probable association between IBS and RLS and all of them lacks control group for comparison. Thus, we aimed to evaluate the prevalence rate of RLS in a sample of IBS patients and to compare this prevalence with that of matched normal population.

Materials and Methods

Patients and Controls Enrollment

This prospective study was performed in Gastroenterology Clinic of Imam Khomeini Hospital (affiliated to Tehran University of Medical Sciences) and one private Gastroenterology Clinic in Tehran, Iran from September 2010 to September 2011. The inclusion criteria for the patients of the case group were as follow: definite IBS diagnosis based on the Rome III criteria, according to which, recurrent abdominal pain or discomfort must be present for at least 3 days per month in the last 3 months with onset of symptoms at least 6 months prior to diagnosis.[14] Afterwards, the IBS patients were categorized in accordance with the Rome III IBS module[14] into diarrhea predominant IBS (IBS-D) if they had loose, mushy or watery stools in the last 3 months with no hard or lumpy stools; constipation predominant IBS (IBS-C) if they had hard or lumpy stools with no loose, watery mushy or watery stools in the past 3 months; mixed IBS (IBS-M) if they had both loose and hard stools in the past 3 months; and unsubtyped IBS if they did not report either loose or hard stools in the past 3 months. A total number of 300 IBS patients were diagnosed within a 1-year period in our setting.

Control participants were recruited through medical staffs of Imam Khomeini University Hospital and were required to be matched with the patients group with respect to the mean age and gender distribution, also not to be pregnant, and deny chronic, widespread pain and chronic fatigue. The research coordinator also screened controls not to have any symptoms in favor of IBS and 300 matched controls were primarily selected. Exclusion criteria for both of the study groups were age under 18 years old, dopaminergic or antidopaminergic (neuroleptics) drugs, specific diseases known to be related to RLS including anemia, hypothyroidism, varicose, rheumatoid arthritis and any other neuropathies and history of alcohol or drug abuse at the time of enrollment. After the exclusion of any patient or control with the mentioned criteria, especially hypothyroidism and/or anemia, a total number of 225 definite IBS patients and 262 healthy controls were recruited in the final assessment of our study.

The Local Ethics Committee of Tehran University of Medical Sciences approved the study and verbal informed consent was obtained from all subjects.

Assessment of Restless Legs Syndrome

Presence of RLS was assessed in all of the IBS patients and healthy controls. RLS was ascertained when the individual met the four standard diagnostic criteria developed by the International RLS Study Group which were asked during an interview by a single resident of internal medicine.[15] These criteria were as follows:

(1) An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs.
(2) Beginning or worsening of the urge to move or unpleasant sensations during periods of rest or inactivity such as lying or sitting.
(3) Partially or totally relieving of the urge to move or unpleasant sensations by movement, such as walking or stretching, at least as long as the activity continues.
(4) Worsening of the urge to move or unpleasant sensations in the evening or night than during the day or only occur in the evening or night.

Only participants endorsing either at least 3 or all of the 4 questions were considered to have RLS. A total number of 57 IBS patients and 17 healthy controls fulfilled RLS criteria.

In addition to the main variables (IBS module and RLS criteria), some other baseline and laboratory characteristics were also recorded in all of the recruited subjects in this study consisting of height, weight, body mass index (BMI), family history of RLS, history of smoking, hypertension, diabetes mellitus, hemoglobin, hematocrit, ferritin and fasting blood sugar. A complete list of GI and IBS related symptoms were also asked in IBS patients including any existence of stomach pain, fullness, heart burn, anorexia, belching, bloating, fatigue, weight loss, nausea and vomiting.

Statistical Methods

While preparing the study protocol, a minimum sample size of 201 individuals in each study group was calculated to be enrolled in order to show an estimated difference of 10% in the prevalence of RLS between the IBS and control groups with the maximum type I error of 5% and minimum statistical power of 80%. After data collection, all recorded variables were assessed using Statistical Programme for Social Sciences (SPSS software version 16.0; SPSS Inc., Chicago, IL, USA). Description of cat-

Table 1. Baseline and Clinical Characteristics of the Irritable Bowel Syndrome Patients and Healthy Controls

Variables	Study Groups		*P*-value
	IBS (n = 225)	Control (n = 262)	
Age (yr [SD])	37.48 (12.53)	37.03 (11.36)	0.702
Sex (n [%])			
Male	96 (42.7)	96 (36.6)	0.175
Female	129 (57.3)	166 (63.4)	
BMI (kg/m^2 [SD])	25.02 (3.69)	23.26 (2.91)	< 0.001[a]
Hemoglobin (mg/dL [SD])	14.28 (1.58)	13.65 (1.27)	< 0.001[a]
Hematocrit (% [SD])	42.57 (3.72)	41.40 (5.29)	0.008[a]
Ferritin (mg/dL [SD])	114.63 (228.05)	64.18 (48.46)	0.003[a]
FBS (mg/dL [SD])	95.06 (53.66)	90.13 (9.90)	0.145
Smoking (n [%])	14 (6.2)	13 (5.0)	0.545
Diabetes mellitus (n [%])	6 (2.7)	7 (2.7)	0.997
Hypertension (n [%])	14 (6.2)	4 (1.5)	0.007[a]
Family history of RLS (n [%])	20 (8.9)	12 (4.6)	0.056
Symptoms (n [%])			
Stomach pain	200 (88.9)	-	-
Nausea	59 (26.2)	-	-
Vomiting	10 (4.4)	-	-
Anorexia	54 (24.0)	-	-
Weight loss	40 (17.8)	-	-
Fatigue	126 (56.0)	-	-
Heart burn	66 (29.3)	-	-
Belching	57 (25.3)	-	-
Bloating	190 (84.4)	-	-
Fullness	25 (11.1)	-	-
RLS (n [%])	57 (25.3)	17 (6.5)	< 0.001[a]

IBS, irritable bowel syndrome; BMI, body mass index; FBS, fasting blood sugar; RLS, restless legs syndrome.
[a]Statistical significant difference ($P < 0.05$).

egorical and continuous measures was performed reporting frequency percentages and mean (SD), respectively. In analytical procedures, unpaired Student's *t* test was used to compare the mean of continuous baseline and laboratory variables between IBS and control groups. Chi-square and Fisher's exact tests were also used to compare the prevalence of qualitative variables (including RLS) between 2 study groups. In order to assess the factors associated with the prevalence of RLS in IBS patients, more intra-group analysis was performed and odds ratio (OR) statistics were calculated and reported with the 95% confidence interval (CI) of each estimation. Multivariate analysis was also used to adjust the relationship between IBS and RLS with regard to some other qualitative confounders by means of Mantel-Haenszel statistical test. A *P*-value of less than 0.05 was considered to be statistically significant.

Results

Baseline Characteristics

After the exclusion of any patient or control with hypothyroidism and/or anemia, a final number of 225 definite IBS patients and 262 healthy controls were recruited in this study. The mean age and gender distribution were matched between 2 groups of study. As shown in Table 1, the patients' group was consisted of 96 (42.7%) male and 129 (57.3%) female with the mean age of 37.48 (SD = 12.53) year, and the control group included 96 (36.6%) male and 166 (63.4%) female with the mean age of 37.03 (SD = 11.36) year which was not significantly different from the case group ($P = 0.175$ and 0.702, respectively). Other baseline characteristics are summarized in Table 1. According to the laboratory data, the IBS patients have significantly higher BMI (25.02 [SD = 3.69] kg/m^2 vs 23.26 [SD = 2.91] kg/m^2, $P < 0.001$), serum hemoglobin (14.28 [SD = 1.58] mg/dL vs 13.65 [SD = 1.27] mg/dL, $P < 0.001$) and serum ferritin level (114.63 [SD = 228.05] mg/dL vs 64.18 [SD = 48.46] mg/dL, $P = 0.003$). In addition to the co-morbidities listed in Table 1, it must be noted that neither the IBS patients nor the control cases had fibromyalgia. Regarding the symptoms of IBS patients, stomach pain (88.9%) and bloating (84.4%) were the most common complaints.

Assessment of Restless Legs Syndrome

A total number of 57 IBS patients and 17 healthy controls fulfilled RLS criteria. The results of Chi-square test showed that RLS was significantly more frequent in IBS group (25.3% vs 6.5%, Chi = 33.36, $P < 0.001$) which led to an OR of 4.89 (95% CI, 2.75-8.70). More analysis was performed to adjust the relationship between IBS and RLS with regard to the family history of RLS using Mantel-Haenszel statistics. Even after the adjustment of the probable confounding effect of positive family history, RLS occurred significantly more among IBS patients (OR = 4.41; 95% CI, 2.50-7.76; $P < 0.001$).

Prevalence rate of RLS was higher in female IBS patients compared with males; however, the difference was not statistically significant (28.7% vs 20.8%, $P = 0.181$). This gender difference was much lower among the controls (6.6% in females vs 6.3% in males, $P = 0.905$).

Table 2. Frequency Comparison of Irritable Bowel Syndrome Related Symptoms in Irritable Bowel Syndrome Patients With or Without Restless Legs Syndrome

Subgroup	RLS (+) (n = 57)	RLS (-) (n = 168)	OR (95% CI)	P-value
Stomach pain	55 (96.5%)	145 (86.3%)	4.36 (1.00-19.12)	0.048[a]
Fullness	8 (14.0%)	17 (10.1%)	1.45 (0.59-3.57)	0.416
Heart burn	20 (35.1%)	46 (27.4%)	1.43 (0.75-2.72)	0.269
Anorexia	15 (26.3%)	39 (23.2%)	1.18 (0.59-2.35)	0.636
Belching	14 (24.6%)	43 (25.6%)	0.95 (0.47-1.90)	0.877
Bloating	49 (86.0%)	141 (83.9%)	1.17 (0.5-2.75)	0.714
Fatigue	32 (56.1%)	94 (56.0%)	1.01 (0.55-1.85)	0.980
Weight loss	10 (17.5%)	30 (17.9%)	0.98 (0.44-2.15)	0.957
Nausea	23 (40.4%)	36 (21.4%)	2.48 (1.30-4.73)	0.005[a]
Vomiting	6 (10.5%)	4 (2.4%)	4.82 (1.31-17.76)	0.019[a]

RLS, restless legs syndrome.
[a]Statistical significant difference (P < 0.05).

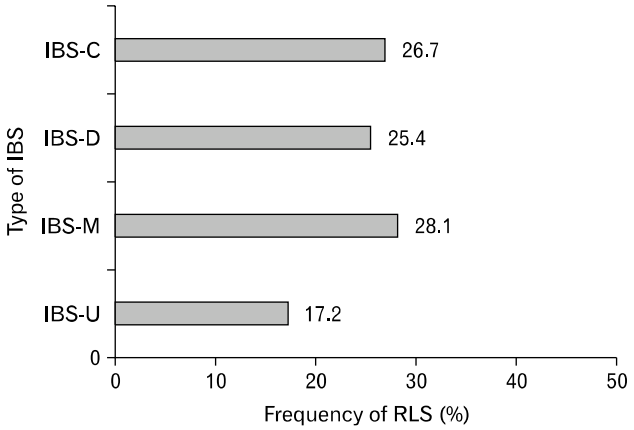

Figure 1. Co-existence of different types of irritable bowel syndrome with restless legs syndrome ($P = 0.745$). IBS, irritable bowel syndrome; IBS-C, constipation predominant IBS; IBS-D, diarrhea predominant IBS; IBS-M, mixed IBS; IBS-U, unsubtyped IBS; RLS, restless legs syndrome.

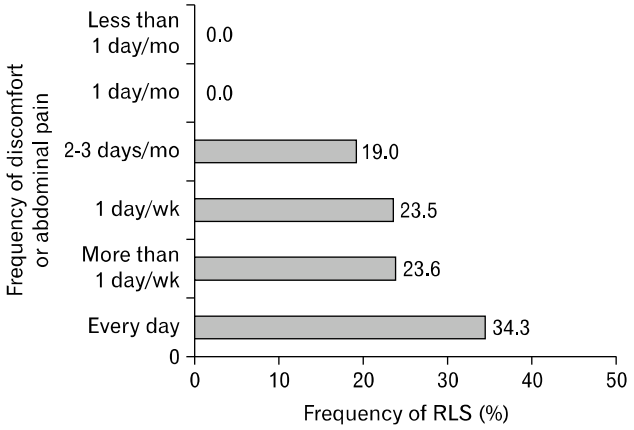

Figure 2. Association of intensity of discomfort and abdominal pain in irritable bowel syndrome patients within last 3 months of study with restless legs syndrome (Kendall's tau $P = 0.027$). RLS, restless legs syndrome.

Relationship Between Irritable Bowel Syndrome Module and Restless Legs Syndrome

In order to assess the factors associated with the prevalence of RLS in IBS patients, more intra-group analysis was performed. As shown in Table 2, IBS patients with co-morbid RLS suffered significantly more from stomach pain (96.5% vs 86.3%; OR = 4.36; 95% CI, 1.00-19.12; $P = 0.048$), nausea (40.4% vs 21.4%; OR = 2.48; 95% CI, 1.30-4.73; $P = 0.005$) and vomiting (10.5% vs 2.4%; OR = 4.82; 95% CI, 1.31-17.76; $P = 0.019$). Figure 1 illustrates the frequency of RLS within different types of IBS modules. Although the observed difference was not statistically significant ($P = 0.745$), the highest prevalence of RLS was reported in IBS-M (28.1%) and IBS-C (26.7%) patients, respectively. Further analysis was performed to evaluate the association between pain and discomfort intensity with RLS. Interestingly, Kendall's tau analysis showed that the more frequent abdominal pain and discomfort existed, the significantly higher prevalence of RLS was reported ($P = 0.027$, Fig. 2). While up to 34.3% of IBS patients with an everyday complaint of abdominal pain suffered from RLS, no patient with equal or less than one day per month of pain had RLS (Fig. 2).

Discussion

As an undesired urge for leg movement, RLS symptoms are triggered by rest, often at night, and improve temporarily with movement, especially while walking. In normal population, the syndrome has a prevalence ranging from 7% to 15% and significantly contributes to sleep disorders.[16-18] To date, the most commonly associated medical condition is iron deficiency,[19] which accounts for just over 20% of all cases of RLS. Other conditions associated with RLS include varicose vein or venous reflux, folate and magnesium deficiency, fibromyalgia, sleep apnea, diabetes, thyroid disease, peripheral neuropathy, celiac disease and rheumatoid arthritis.[20]

Having enrolled a considerable number of IBS patients and healthy controls, our study showed a significantly higher prevalence of RLS in IBS patients. It seems that screening patients with IBS for RLS may lead to greater identification of RLS and improved treatment for both conditions. In a recent single-group, community-based study, Basu et al[21] have shown that 29% of IBS patients based on Rome III criteria also suffered from RLS. Similarly, our findings also suggest that RLS symptom is more common in IBS patients. In this study, we revealed that RLS could be a co-morbid condition with IBS in 57 of 226 patients (25.3%), in comparison with 6.5% of control population. This study contributes to the available consensus suggesting screening patients with IBS for RLS, leading to greater identification of RLS which may enhance treatment options for patients and medications may provide relief for both entities.[7] Furthermore, Basu et al[21] showed 62% of patients with both RLS and IBS had IBS-D, while 4% had IBS-C and 33% had IBS-M, suggesting that the specific pathophysiology of IBS-D may contribute to or relate to RLS. Our findings of IBS patients with co-morbid RLS revealed they suffered more from stomach pain, nausea and

vomiting. Although, not statistically significant, the highest prevalence of RLS was reported in IBS-M (28.1%) and IBS-C (26.7%) patients, respectively, which was not in line with Basu's report.[21] Even though SIBO is not evaluated in our study, this difference between Basu's findings[21] and our investigation may reflect different portion of SIBO subtypes such as hydrogen-producer or methane-producer; where methane-producer has been reported to be more associated with constipation.[22]

Interestingly, our results showed that more severe IBS symptoms also occurred in patients suffering from both IBS and RLS. This could be in line with some recent evidences demonstrating more severe IBS symptoms as well as negative impacts on patients' quality of life in cases with other neurologic and/or psychologic co-morbidities such as anxiety and depression.[23,24] All of these findings are supporting the neurologic-related identity of IBS and more specifically the association between RLS and symptom severity in IBS patients, which could be linked to serotonin transmission shown to be involved in both conditions of IBS[25] and RLS.[26]

In our study, the prevalence rate of RLS was higher in female IBS patients compared with male (28.7% vs 20.8%). Although the difference failed to demonstrate a statistically significant level, it was considerably more prominent than the gender difference observed among the controls with RLS (6.6% vs 6.3%). This may add another aspect to the previously demonstrated gender-related differences in IBS patients.[27,28] Moreover, while some significant differences were observed in baseline characteristics between 2 study groups, it must be noted that the mean of hemoglobin, hematocrit and ferritin in both groups was within the normal range. Additionally, the difference between RLS prevalence between 2 study groups is to some extent underestimated as the lower hemoglobin and ferritin which have been previously demonstrated to associate with higher incidence of RLS,[29,30] are more likely observed in control group and not the IBS patients (where the prevalence of RLS is shown to be significantly higher). With respect to the reported significant difference in BMI between 2 study groups, it could be considered to have insignificant effect on the final association between IBS and RLS. Although BMI seems to influence symptoms in IBS patients (where higher BMI is associated with more IBS-D and looser stools),[31] there is an evidence confirming no association between BMI and RLS.[32]

Previous research has identified an association between SIBO, a possible contributing factor to IBS, and several sensory disorders including fibromyalgia and RLS. Basu et al[21] proposed the diagnosis of simultaneous IBS and RLS might provide enhanced therapeutic efficacy for these patients, as some medications like rifaximin, might provide symptom relief for both conditions. Nineteen out of 26 patients with both IBS and RLS were treated with the antibiotic rifaximin, with 9 reporting relief of RLS symptoms. The study was powered by the fact that the diagnosis of RLS was made based on a standard questionnaire formulated by the International Restless Legs Syndrome Study Group and was confirmed by polysomnography, which in our cases was not utilized. It might permit more accurate diagnosis if more non-invasive diagnostic approaches were implied. However, our study is privileged by the large number of study population and control group. To date this is the first study worldwide to be designed as such.

Weinstock et al,[33] in a pilot study, provided 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. Supporting the mentioned hypothesis, in one study on 13 patients with IBS and positive lactulose breath test, an indicator of SIBO, rifaximin 1,200 mg/day for 10 days was associated with at least 80% improvement from baseline in RLS symptoms in 10 patients and a "great" or "moderate" global GI symptom improvement in 11 patients.[34] Five of the 10 patients followed for long-term (mean duration of 139 days) showed maintenance of complete resolution of their RLS symptoms. Thus, if SIBO is a potential trigger, the treatment paradigm for RLS could radically change for this difficult-to-treat, common disorder.

In conclusion, the results presented herein contribute to the available literature supporting an association between IBS and RLS. Although our study has some limitations including cross-sectional design and lack of data on SIBO evaluation and polysomnographic confirmatory results, it must be taken into account that this is the first to enroll such a high number of IBS patients with a matched group of healthy individuals for comparing the prevalence of RLS. Moreover, the criteria used for RLS diagnosis have been previously cited in many RLS studies as the sole confident diagnostic instrument for this purpose.[15] The other strength of our study refers to the wide criteria applied for the exclusion of other probable co-morbid conditions with RLS in order for more clear and purified assessment of the association between IBS and RLS. After the exclusion of all of the enrolled cases and controls with specific diseases known to be related to RLS including anemia, thyroid diseases and etc, a significantly higher prevalence of RLS was shown in IBS group compared with the

healthy controls. Interestingly, a higher prevalence rate of RLS was also accompanied with a more severe discomfort and stomach pain in IBS patients. It seems that screening IBS patients for RLS, or vice versa, may allow greater identification and subsequent treatment of RLS, which is thought to be under diagnosed, even in the general population. Further research is needed to determine the underlying mechanisms common in both disorders addressing the causality of this connection. Similar studies including the assessment of SIBO seem to be helpful for better understanding of the association between IBS and RLS. Also, concomitant diagnosis of these disorders may enhance treatment options for patients, given that some medications may provide relief for both conditions. Therefore, it could be worthwhile to design a randomized controlled clinical trial in order to evaluate the effects of RLS treatment on IBS symptoms in patients suffering from both disorders.

References

1. Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J. Harrison's principles of internal medicine. 17th ed. New York: McGraw-Hill 2011:2496.
2. Arebi N, Gurmany S, Bullas D, Hobson A, Stagg A, Kamm M. Review article: the psychoneuroimmunology of irritable bowel syndrome - an exploration of interactions between psychological, neurological and immunological observations. Aliment Pharmacol Ther 2008;28:830-840.
3. Latimer P, Sarna S, Campbell D, Latimer M, Waterfall W, Daniel EE. Colonic motor and myoelectrical activity: a comparative study of normal subjects, psychoneurotic patients, and patients with irritable bowel syndrome. Gastroenterology 1981;80:893-901.
4. Lawal A, Kern M, Sidhu H, Hofmann C, Shaker R. Novel evidence for hypersensitivity of visceral sensory neural circuitry in irritable bowel syndrome patients. Gastroenterology 2006;130:26-33.
5. Piche T, Barbara G, Aubert P, et al. Impaired intestinal barrier integrity in the colon of patients with irritable bowel syndrome: involvement of soluble mediators. Gut 2009;58:196-201.
6. Saito YA, Talley NJ. Genetics of irritable bowel syndrome. Am J Gastroenterol 2008;103:2100-2104.
7. Pimentel M, Wallace D, Hallegua D, et al. A link between irritable bowel syndrome and fibromyalgia may be related to findings on lactulose breath testing. Ann Rheum Dis 2004;63:450-452.
8. Weinstock LB, Walters AS. Restless legs syndrome is associated with irritable bowel syndrome and small intestinal bacterial overgrowth. Sleep Med 2011;12:610-613.
9. Ringel Y, Sperber AD, Drossman DA. Irritable bowel syndrome. Annu Rev Med 2001;52:319-338.
10. Yunus MB, Aldag JC. Restless legs syndrome and leg cramps in fibromyalgia syndrome: a controlled study. BMJ 1996;312:1339.
11. Veale D, Kavanagh G, Fielding JF, Fitzgerald O. Primary fibromyalgia and the irritable bowel syndrome: different expressions of a common pathogenetic process. Br J Rheumatol 1991;30:220-222.
12. Lubrano E, Iovino P, Tremolaterra F, Parsons WJ, Ciacci C, Mazzacca G. Fibromyalgia in patients with irritable bowel syndrome. An association with the severity of the intestinal disorder. Int J Colorectal Dis 2001;16:211-215.
13. Sperber AD, Atzmon Y, Neumann L, et al. Fibromyalgia in the irritable bowel syndrome: studies of prevalence and clinical implications. Am J Gastroenterol 1999;94:3541-3546.
14. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology 2006;130:1480-1491.
15. Allen RP, Picchietti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 2003;4:101-119.
16. Allen RP, Walters AS, Montplaisir J, et al. Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med 2005;165:1286-1292.
17. Berger K, Luedemann J, Trenkwalder C, John U, Kessler C. Sex and the risk of restless legs syndrome in the general population. Arch Intern Med 2004;164:196-202.
18. Lavigne GJ, Montplaisir JY. Restless legs syndrome and sleep bruxism: prevalence and association among Canadians. Sleep 1994;17:739-743.
19. Restless legs syndrome: detection and management in primary care. National Heart, Lung, and Blood Institute Working Group on Restless Legs Syndrome. Am Fam Physician 2000;62:108-114.
20. Pantaleo NP, Hening WA, Allen RP, Earley CJ. Pregnancy accounts for most of the gender difference in prevalence of familial RLS. Sleep Med 2009;11:310-313.
21. Basu PP, Shah NJ, Krishnaswamy N, Pacana T. Prevalence of restless legs syndrome in patients with irritable bowel syndrome. World J Gastroenterol 2011;17:4404-4407.
22. Pimentel M, Sheila L, Kimberly L. Methane production in IBS subjects is associated with a constellation of symptoms: not just constipation. Am J Gastroenterol 2007;102:S499-S500.
23. Tang YR, Yang WW, Wang YL, Lin L. Sex differences in the symptoms and psychological factors that influence quality of life in patients with irritable bowel syndrome. Eur J Gastroenterol Hepatol 2012;24:702-707.
24. Cho HS, Park JM, Lim CH, et al. Anxiety, depression and quality of life in patients with irritable bowel syndrome. Gut Liver 2011;5:29-36.
25. Kumar S, Ranjan P, Mittal B, Ghoshal UC. Serotonin transporter gene (SLC6A4) polymorphism in patients with irritable bowel syndrome and healthy controls. J Gastrointestin Liver Dis 2012;21:31-38.
26. Shioda K, Nisijima K, Yamauchi Y, Ohtuka K, Kato S. Use of a serotonin 1A receptor agonist to treat restless legs syndrome. J Clin Psychopharmacol 2006;26:673-675.
27. Anbardan SJ, Daryani NE, Fereshtehnejad SM, Taba Taba Vakili S, Keramati MR, Ajdarkosh H. Gender role in irritable bowel syndrome: a comparison of irritable bowel syndrome module (ROME III) between male and female patients. J Neurogastroenterol Motil 2012;18:70-77.

28. Chang FY. Why do irritable bowel syndrome women often have nausea symptom? J Neurogastroenterol Motil 2012;18:1-3.
29. Kim WH, Kim BS, Kim SK, et al. Restless legs syndrome in older people: a community-based study on its prevalence and association with major depressive disorder in older Korean adults. Int J Geriatr Psychiatry 2012;27:565-572.
30. Quinn C, Uzbeck M, Saleem I, et al. Iron status and chronic kidney disease predict restless legs syndrome in an older hospital population. Sleep Med 2011;12:295-301.
31. Sadik R, Björnsson E, Simrén M. The relationship between symptoms, body mass index, gastrointestinal transit and stool frequency in patients with irritable bowel syndrome. Eur J Gastroenterol Hepatol 2010;22:102-108.
32. Sarberg M, Josefsson A, Wiréhn AB, Svanborg E. Restless legs syndrome during and after pregnancy and its relation to snoring. Acta Obstet Gynecol Scand 2012;91:850-855.
33. Weinstock LB, Fern SE, Duntley SP. Restless legs syndrome in patients with irritable bowel syndrome: response to small intestinal bacterial overgrowth therapy. Dig Dis Sci 2008;53:1252-1256.
34. Weinstock LB, Klutke CG, Lin HC. Small intestinal bacterial overgrowth in patients with interstitial cystitis and gastrointestinal symptoms. Dig Dis Sci 2008;53:1246-1251.