

Dopa responsive irritable bowel syndrome: restless bowel syndrome or a gastrointestinal variant of restless legs syndrome?

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SUMMARY

In addition to the legs, restless legs syndrome (RLS) affects various other parts of the body, including the arms, abdomen, face, head-neck, oral cavity, genital area and bladder. RLS is also associated with several comorbid conditions, including irritable bowel syndrome (IBS). We are reporting two cases of RLS who also had IBS, fulfilling the Rome IV criteria. The administration of levodopa and dopamine agonists provided a complete improvement in both IBS and RLS. Review of the literature suggest that the clinical semiology and clinical pattern of IBS (urge to defaecate, abdominal pain, abdominal distension, bloating, disturbed sleep and circadian rhythm) simulate the semiology and pattern of RLS. Similarities are also noted in the associated comorbid conditions, effective drugs and proposed hypotheses for both clinical syndromes. We hypothesise that RLS may affect intestine, and IBS-like symptoms in a subset of patients with RLS may be the part of RLS symptoms complex.

BACKGROUND

Restless legs syndrome (RLS) and irritable bowel syndrome (IBS) are both very high in the general population. The pooled global prevalence of IBS is about 10%, and it is the most common reason for referral to gastroenterologists.^{1,2} The prevalence of RLS is 5%–15% in the general population and is considered the most common movement disorder.³ There are a number of comorbidities for both RLS and IBS. A few recent studies have demonstrated a high prevalence of RLS in patients with IBS.⁴ However, the inter-relations between the two have not been discovered in the literature. Herein, we describe two patients of RLS with IBS. The symptom complex of both RLS and IBS responded to dopamine or dopamine agonists.

CASE PRESENTATION

Case 1

A 37-year-old man had a history of variable abdominal discomfort since his childhood. The symptoms included abdominal cramping, bloating, abdominal distension and excessive flatulence. These symptoms were associated with increased bowel movements (five to six times daily), faecal urgency and a feeling of incomplete evacuation. These symptoms were predominantly in the morning, and he was often awakened from sleep by abdominal cramps. Abdominal symptoms have woken him up many times even at 02:00 to 03:00. Bowel movements

used to relieve his abdominal problems, and there have been typically minimal or no symptoms after the morning hours. The gastrointestinal symptoms were initially infrequent with a frequency of two to three attacks in a week. However, the frequency gradually increased, and the patient noted these symptoms almost daily for the last several years. He denied any nausea, vomiting, haematemesis and bleeding per rectum. The patient consulted several physicians and gastroenterologists over 20 years. He had been subjected to a number of investigations by gastroenterologists and, all were normal. The investigations included complete blood count, erythrocyte sedimentation rate, blood glucose, kidney function tests, liver function tests, thyroid profiles, stool studies, ultrasound of the gallbladder, abdominal and pelvic CT scan and upper and lower gastrointestinal endoscopy. A diagnosis of IBS was first made about 20 years ago by a general physician and later confirmed by several gastroenterologists. The patient received an array of management regimes over the course of his illness, including psychopharmacological treatments, and lifestyle and food modifications. However, he got only little and transient improvement with these approaches. He got fed up with these all treatments and left all medications and had not been on any drugs for the last 3–4 years. Although the abdominal symptoms were almost daily.

The patient visited the neurology outpatient department for his increasing unpleasant sensations in both legs. The symptoms had been infrequent, 2–4 days in a month, about 3–4 years ago. However, the discomforts in the legs gradually increased, and the patient felt unpleasant sensations about 20–25 days in a month for the last 6–7 months. He described the unpleasant sensation as a combination of burning sensation, stretching feelings and pain in both legs. The patient noted symptoms typically in the evening and during the night, especially while relaxing. The discomforts of the legs were relieved by walking and the movement of the legs. The patient felt the urge to move both legs to get relief from the unpleasant sensation. The unpleasant sensation in the legs interfered with his sleep, and it was accompanied by frequent wake up at night. His wife confirmed the presence of restlessness while sleeping. His sleep was not refreshing and used to take several naps during the daytime.

The patient fulfilled the International Restless Legs Syndrome Study Group (IRLSSG) criteria



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for RLS.⁵ The patient was subjected to various investigations to identify the secondary cause of RLS.

Case 2

A 26-year-old man consulted for an uncomfortable sensation in the legs for a 15-month duration. He described the sensation as a tight feeling, deeply situated and painful. It was perceived more by the end of the afternoon and during the night-time. The discomfort used to occur after a period of inactivity or rest, while seated or supine. The symptoms had increased recently, and he felt discomfort almost daily for the last 6 months. The unpleasant sensation interfered with his sleep, and sometimes caused him to wake up at night and had pacing activities to relieve his symptoms. Prior treatments with various medications did not provide any benefit.

On direct questioning, he admitted the presence of abdominal cramping, abdominal distension, excessive flatulence, increased bowel movements (five to seven times in the morning), faecal urgency and a feeling of incomplete evacuation. Bowel movements used to relieve his abdominal reports, and most of these symptoms were present mainly in the morning. The gastrointestinal symptoms had been present for 7–8 years. He received a diagnosis of IBS about 5–6 years ago by gastroenterologists. All diagnostic investigations for gastrointestinal problems, including upper and lower gastrointestinal tract endoscopy, abdominal CT and stool studies were normal. The patient received a number of therapeutic regimens for IBS. Although there had been some relief with medications, he was non-compliant and could not continue any drug for a prolonged period. The gastrointestinal symptoms were almost daily for the last 1 year, and he considered it a part of his life.

INVESTIGATIONS

Case 1

All his investigations for RLS, including kidney function tests, liver function tests, iron studies, vitamin B₁₂ levels, serum vitamin D and nerve conduction studies, were normal. The patient was extensively investigated for gastrointestinal problems over 20 years by several gastroenterologists, and no abnormality was detected.

Case 2

The investigations to rule out secondary RLS did not reveal any abnormalities and it included kidney function test, iron studies, vitamin B₁₂ levels, serum vitamin D and nerve conduction studies. The previous investigations for his gastrointestinal problems were largely normal.

TREATMENT

Case 1

A combination of levodopa plus carbidopa (110/10 mg) was prescribed at bedtime.

Case 2

Pramipexole (0.25 mg) was started at bedtime.

OUTCOME AND FOLLOW-UP

Case 1

The unpleasant sensation of the legs started to improve from the first day of treatment, and there had been a complete response in the 'lower legs' symptoms in about 2 weeks. Surprisingly, his gastrointestinal symptoms also improved markedly in 2 weeks with a levodopa and carbidopa combination. There had been

no increased bowel movement, faecal urgency, bloating, abdominal distension and excessive flatulence. He felt only occasional mild abdominal cramping. The patient never had such relief with any drug in the past. In the follow-up, we switched dopamine to pramipexole (0.50 mg at night) as he developed mild hypertension (144/90 mm Hg). There had been almost a complete response even with this drug. We followed the patient for 2–3 years. We tried to withdraw the drug at least four to five times over 2 years. However, withdrawal of the drug led to reappearance of both gastrointestinal and lower leg symptoms in 7–10 days. The reinstatement of the drug provided a complete response in both IBS and RLS on each occasion.

Case 2

His lower limb symptoms fulfilled the IRLSSG criteria for RLS. The patient noted relief in both IBS and RLS by pramipexole. The improvement started within 2–3 days, and there had been an almost complete improvement in RLS in a 3-week duration. The improvement in IBS was noted with markedly reduced abdominal cramping (one to two times in 3 weeks), reduced bowel movement (one to two times in the morning) and no faecal urgency. The patient never got such a response in IBS by any drug in the past. We followed the patient for 13 months. He was non-compliant for the medication. Skipping of the drug led to the reappearance of symptoms related to both IBS and RLS within 5–7 days. The reinstatement of pramipexole provided a significant response in both IBS and RLS on each occasion.

DISCUSSION

Both patients visited the neurology clinic for the evaluation of the unpleasant sensations in the legs, and they met the IRLSSG criteria for RLS.⁵ In parallel, both patients fulfilled the Rome III and Rome IV criteria of IBS.⁶ They were extensively investigated over the years to rule out secondary causes of gastrointestinal reports. Dopamine or dopamine agonists provided an almost complete response in both symptom complexes in each patient. A possibility of a placebo response was less likely as there was a temporal relation in the administration of the drug and the disappearance of the symptom complex. A withdrawal of the drug led to the re-emergence of the symptoms (both IBS and RLS). The reinstatement of the drug always provided a marked improvement in the symptoms. Such temporal relations, the disappearance of symptoms by drug and reappearance of symptoms by skipping the drugs, were noted on several occasions in the follow-up. So, dopamine or dopamine agonist was pivotal in the improvement of both syndromes.

RLS with IBS: any correlation?

IRLSSG consensus diagnostic criteria for RLS mention that arms (restless arms syndrome) and other body parts may be involved in addition to the legs. The abnormal unpleasant sensation may be noted in the abdomen (restless abdomen), genital area (restless genital syndrome), oral cavity (restless mouth syndrome), face, chest and back, and neck and head.^{7–12} The unpleasant sensation in different parts of the body may mimic several other diseases. The abnormal painful sensation in the lower legs mimics growing pains in the children, and a few authors suggest a causal association between both.¹³ An abnormal sensation in the oral cavity (restless mouth syndrome) may mimic burning mouth syndrome.⁹ Pain and unpleasant sensation in the head and neck may mimic as headache.¹² A few authors have reported restless bladder mimicking overactive bladder syndrome. Restlessness in atypical body parts usually coincides with the classical

Table 1 Similarities between restless legs syndrome (RLS) and irritable bowel syndrome (IBS)

Parameters	RLS	IBS
Prevalence	High (5%–15%). ³	High (5%–15%). ⁶
Age group	Usually 30–50 years. ³	Usually 20–50 years of age. ²
Sex	F>M (twofold). ³	F>M (twofold). ¹⁶
Type of pain	Diffuse lower limb pain. ⁵	Abdominal pain, abdominal distension. ⁶
Urge to move	Present. ⁵	Urge to defaecate. ^{18,19}
Circadian variation of symptoms	Typically in evening and during night. ⁵	Mainly during night-time and in the early morning. ^{22,23}
Worsening after rest / inactivity	Yes	Worsening in the night and early morning may be because of 'inactivity' of GIT.
Relieving factors	Walking.	Regular meal and frequent water intake. ²⁴
Disturb sleep	Common (up to 60%). ⁵	Common (30%–45%). ²²
Relation with Parkinson's disease (PD)	Increased prevalence of IBS in patients with PD. ²⁵	Increased prevalence of RLS in patients with PD. ²⁸
Dopaminergic dysfunctions	Well established hypothesis.	Low urinary dopamine. ²⁶ Low plasma dopamine. ²⁷
Small intestinal bacterial overgrowth	Noted in a few studies. ³⁴	An important association in IBS. ⁶
Neuroimaging abnormalities	Anterior cingulate, insula, prefrontal, thalamus, hippocampus.	Anterior cingulate, insula, prefrontal, thalamus, hippocampus.
Treatment overlap	Pregabalin, gabapentin, rifaximin. ^{25,34}	Pregabalin, gabapentin, rifaximin. ⁶

GIT, Gastrointestinal tract.

RLS of lower limbs.¹¹ Besides these, a significant association between RLS and pain of different origins have been reported in the literature.¹³ There is a higher prevalence of RLS in patients with fibromyalgia.¹⁴ Similarly, a high prevalence of RLS has been reported in patients presenting with IBS. Borji and colleagues noted a fivefold increased risk of RLS in the IBS study population. The inter-relation between RLS and IBS is not very clear.¹⁵

We reviewed the literature to find out the overlap or similarities of RLS to IBS (table 1). The prevalence of both diseases is very high in the general population, up to 15%. Female preponderance is present in both conditions.^{3,16} Some overlaps are present in the age at onset (20–50 years for IBS and 30–50 years for RLS).^{2,3} The central feature of RLS is 'urge to move' the legs or the affected part. IRLSSG have described the following features associated with 'urge to move': (1) usually with uncomfortable and unpleasant sensations in the legs; (2) the symptoms begin or worsen during periods of rest or inactivity; (3) it partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues; (4) they are worse in the evening or night than during the day.⁵ The 'urge to move' has been described even in an atypical variant of RLS. In restless mouth syndrome, 'urge to move' has been described as parafunctional habits, like tongue thrusting or tongue nibbling or continuous rubbing of the teeth, lip and cheek.⁸ Urge to void has been described in patients with a restless bladder.¹¹ A restless bladder causes unpleasant sensations in the lower abdomen and perineum, which are relieved by urination. 'Urge to defaecate' (faecal urgency) is one of the common and bothersome symptoms in patients with IBS. A faecal urgency is commonly considered as a symptom of IBS with diarrhoea (IBS-D). It was noted in about 64% of women diagnosed with IBS with diarrhoea (IBS-D) in one survey.¹⁷ However, various recent studies have demonstrated a high prevalence of faecal urgency even in IBS with constipation (IBS-C). Mangel and colleagues noted faecal urgency in 45%–50% of patients with IBS-C.¹⁸ In a recent study on IBS-C, about 71% of patients reported faecal urgency. Like

urge to move of typical RLS, urge to defaecate is associated with the unpleasant sensation (pain or bloating) in the abdomen.¹⁹ Mangel *et al* define faecal urgency as 'unpleasant sensation that one needs to rush to the toilet or they may soil themselves'.

One of the points in the IRLSSG criteria for RLS is 'unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting'. As people are relatively less active or take rest in the evening or night, RLS symptoms are more prominent in the evening or night, and 'aggravation of symptoms in the evening or night' is one of the essential components in the RLS criteria. The gastrointestinal motility depends on food and water intake. Ingestion of food increases gastrointestinal activity.²⁰ The human eating pattern is usually restricted during the daytime and in the early part of the night. People take sleep and avoid food intake in the later part of the night. So, the gastrointestinal tract is relatively in 'inactive' state in the late night and in the early morning.²¹ So, we hypothesise that 'relative inactivity of the gut' during late night and early morning may produce symptoms in the same time frame (late night and early morning) in the susceptible person, just like unpleasant sensation and urge to move in typical RLS. Abdominal discomfort is very common during the night and in the early morning. In one study, about 57% of patients with all subtypes of IBS reported that their abdominal ache, pain or discomfort awaken them from sleep during the night.²² Frequent bowel movements in the morning (early morning rush) is the first thing in a significant proportion of patients with IBS.²³ Although intolerance to specific foods is common in IBS, regular meal and regular water intake may provide relief in a subset of patients. National Institute for Health and Care Excellence (NICE) guideline of IBS recommends avoid missing meals or leaving long gaps between eating, and drink at least eight cups of fluid per day. Regular meal and frequent water intake maintain gastrointestinal motility by keeping the gut active and thus avoid inactivity in the gut.²⁴

Sleep disturbances are the most common associated symptoms in both IBS and RLS. More than 75% of patients with RLS seeking treatment have sleep disturbances.⁵ Sleep disturbances may be the primary morbidity for seeking treatment in patients with RLS. Similarly, 50%–80% of patients with IBS may have sleep disturbances.²² An inability to fall asleep (prolonged latency) and repeated awakenings (sleep fragmentation) are common sleep problems in both diseases.

Pathophysiological correlation between RLS and IBS

The most widely accepted mechanisms of RLS include dopaminergic dysfunction, abnormal iron metabolisms and genetic factors.²⁵ The pathophysiology of IBS is not completely understood and appears to be multifactorial. The proposed hypothesis include altered gastrointestinal motility, small bowel bacterial overgrowth syndrome, visceral hypersensitivity, genetic factors, food hypersensitivities, gut–brain axis dysfunction, hypersensitivity of the intestine and psychosocial factor.⁶ A few recent studies have demonstrated an overlap between proposed mechanisms of RLS and IBS.

Dopaminergic dysfunction is the main mechanism for RLS, and a response by dopaminergic agent is one of the supporting features in the diagnostic criteria of RLS.⁵ Recently Keshteli and colleagues have demonstrated lower urinary dopamine in patients with IBS than healthy controls.²⁶ Chojnacki *et al* have also demonstrated low dopamine in plasma in patients with IBS.²⁷ So, a role of dopamine has been suggested in the pathogenesis of IBS as it modulates the interactions between the brain and the enteric nervous system. A high prevalence of Parkinson's disease

(PD) in patients with RLS indicates an overlap of dopaminergic abnormalities in both conditions.²⁵ Similarly, a few studies have noted a high prevalence of PD in patients with IBS.²⁸ Mishima *et al* demonstrated a higher prevalence of IBS in patients with PD.²⁹ So, a bidirectional relationship between IBS and PD indicate some overlap in the pathophysiology between the two. Involvement of the brain–gut axis is an emerging concept in the pathogenesis of IBS.⁶ The gut–brain dopamine axis depends on the nutrients or foods. The direct stimulation of the gastrointestinal tract with foods stimulates the release of dopamine in brain circuits controlling various functions of the gastrointestinal tract.³⁰ So, a role of dopamine, just like RLS, can be speculated in IBS at the brain level. In the earlier years, domperidone (antidopaminergic drug) had been used in IBS. However, a few double-blind studies did not find any response. One study demonstrated a marked increase in the frequency of abdominal distension with domperidone.³¹ So, an aggravation of abdominal discomfort by dopamine antagonists indirectly hint a role of dopamine in IBS. Neuroimaging abnormalities are well defined in patients with RLS.³² A few recent neuroimaging studies have noted structural abnormalities even in IBS.³³ There are marked overlap among the structures involved in both diseases (table 1), indicating some overlap in the central mechanism of both diseases.

Several studies and hypotheses have suggested a role of small intestinal bacterial overgrowth (SIBO) in the pathogenesis of IBS.⁶ A few authors have also noted a high prevalence of SIBO even in patients with RLS.³⁴ Rifaximin, an antibiotic, is one of the Food and Drug Administration (FDA) approved drug for IBS, especially in patients with a possibility of SIBO. A positive effect of rifaximin has been demonstrated in RLS in a double-blind, placebo-controlled study.³⁵

Visceral hypersensitivity is one of the accepted pathophysiological mechanisms for IBS.⁶ Alpha 2 delta ($\alpha 2\delta$) ligands, gabapentin and pregabalin, are known to reduce visceral hypersensitivity and IBS-related abdominal discomfort.⁶ $\alpha 2\delta$ ligands are also useful in RLS, and a few authors consider it as a first-line treatment for restless legs syndrome.²⁵ Therefore, this overlap in the drug therapy also hints an overlap between both diseases.

So, the review of the literature suggests that besides legs, several parts of the body may be involved in RLS, including the oral cavity, bladder and genital organs. So, a possibility of gastrointestinal tract involvement exists. The clinical semiology and clinical pattern of IBS (urge to defecate, abdominal pain, abdominal distension, bloating, disturbed sleep and circadian rhythm) simulate the semiology and the pattern of RLS. Similarities are noted even with the associated comorbid conditions, effective drugs and proposed hypotheses for pathophysiology for both clinical syndromes.

A response by any drug in just two patients is not enough to make any statement regarding the inter-relation between two diseases or with drugs. It will be too early to link both diseases. Still, these two case reports and a review of the literature suggest that IBS-like symptoms in patients with RLS may be because of a common aetiology/pathophysiology, and gastrointestinal symptoms may be the part of the RLS spectrum in a subset of patients. A subset of patients with IBS may be a phenotypic variant of RLS, just like restless bladder syndrome, restless genital syndrome and restless mouth syndrome. IBS is considered as a heterogeneous multifactorial disorder, and several hypotheses and aetiology have been proposed for the symptom complex of IBS. No single hypothesis can explain the heterogeneous nature of IBS. Therefore, our hypothesis cannot explain all the heterogeneous features of IBS. Multicentric therapeutic trials with drugs effective in RLS are required in a subset of patients with

RLS having comorbid conditions of IBS. A therapeutic trial with dopaminergic drug can be conducted even in patients with IBS alone, especially in those who are refractory to typical therapies. We hope our observations and proposed hypotheses will act as a catalyst for further investigations to clarify the inter-relation between RLS and IBS.

Patient's perspective

Case 1: No one understood my abdominal problems. Thank you doctor for helping me out from my both problems by just a single drug.

Learning points

- ▶ Both disorders (irritable bowel syndrome (IBS) and restless legs syndrome (RLS)) improved with dopaminergic medication.
- ▶ IBS-like symptoms in patients with RLS may be the part of RLS symptoms complex.
- ▶ IBS in patients with RLS may respond to dopaminergic drugs.

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