Restless abdomen : A phenotypic variant of restless legs syndrome

Hernando Pérez-Díaz, Alex Iranzo, David B. Rye, et al.

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Restless abdomen

A phenotypic variant of restless legs syndrome

Hernando Pérez-Díaz, MD
Alex Iranzo, MD
David B. Rye, MD, PhD
Joan Santamaría, MD

Address correspondence and reprint requests to Dr. Alex Iranzo de Riquer, Neurology Service, Hospital Clinic de Barcelona, C/Villarroel 170, Barcelona 08036, Spain
airanzo@clinic.ub.es

ABSTRACT

Background and Objective: A diagnosis of restless legs syndrome (RLS) requires an urge to move the legs in combination with sensory leg discomfort. Localization of the symptoms to other body areas in the absence of leg involvement is not recognized as part of the phenotypic spectrum of RLS. We describe 3 patients who presented with sensorimotor symptoms confined to the abdominal wall and, with the exception of not involving the legs, satisfied the primary and secondary diagnostic criteria for RLS.

Methods: Patients underwent detailed clinical history, video-polysomnography, abdominal imaging, and serologic and genotyping assessment.

Results: Unpleasant abdominal symptoms emerged at night during periods of rest and were accompanied by an urge to move and temporized by movement. Patients reported sleep onset and sleep maintenance insomnia due to their abdominal symptomatology. Abdominal imaging was normal. Secondary features included periodic leg movements of sleep (PLMS), and dramatic symptom amelioration with the D_2-D_3 dopaminergic agonist pramipexole. Two subjects were anemic. Conventional RLS emerged in one subject and resolved after dose escalation. Each subject was homozygous for the most common RLS/PLMS–associated risk allele in the *BTBD9* gene.

Conclusions: Our observations indicate that the restricted abdominal symptomatology manifest in our subjects represents a phenotypic variant of RLS. Physicians should be vigilant to the existence of this unique phenotype when encountering subjects who present with insomnia and abnormal abdominal sensations. Our experience emphasizes the importance of supportive clinical features in rendering a correct diagnosis such that the most cost-effective workups and treatment can be realized. **Neurology® 2011;77:1283–1286**

GLOSSARY

OR = odds ratio; **PLMS** = periodic leg movements of sleep; **RLS** = restless leg syndrome; **SNP** = single nucleotide polymorphism.

Restless legs syndrome (RLS) is characterized by an urge to move the legs accompanied by uncomfortable sensations during periods of rest, improves with movement, and exhibits a diurnal preference for the evening or night.[1] Anecdotal reports of sensory disturbances isolated to the arms, mouth, trunk, and perineum, but in the absence of leg involvement, have been interpreted as RLS equivalents.[2,3] It remains unclear whether these cases represent genuine RLS variants because most RLS-associated features such as diurnal preference, periodic limb movements of sleep (PLMS), family histories, iron deficiency, and sleep disruption were absent. We encountered 3 patients in whom RLS symptoms were confined to the abdomen and satisfied the primary and secondary diagnostic criteria for RLS.

METHODS Subjects were identified from among 2,496 new patients and 362 patients diagnosed with RLS seen at the Hospital Clinic of Barcelona Sleep Center between July 2004 and June 2009.

For genotyping for RLS/PLMS risk alleles, a pair of PCR primers was designed to amplify the flanking region of 5 single nucleotide polymorphisms (SNPs) in the *MEIS1*, *BTBD9*, *PTPRD*, and *MAP2K5* genes.[4] A SNP assay was performed on a 7900 HT Fast Real-Time PCR System (Applied Biosystems). After PCR, the intensities of the 2 reporters were used to compute the relative

CME

From the Neurology Service (H.P.-D., A.I., J.S.), Hospital Clinic Universitari, Centro Investigación Biomédica en Red Enfermedades Neurodegenerativas, IDIBAPS, Universidad de Barcelona, Barcelona, Spain; and Department of Neurology and Program in Sleep (D.B.R.), Emory University School of Medicine, Atlanta, GA.

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Table 1 Clinical features of the 3 patients

	Case 1	Case 2	Case 3
Age at presentation, y	62	62	62
Sex	M	M	F
Symptom duration, y	14	6	1
Essential criteria			
Urge to move	+	+	+
Emergence during periods of rest	+	+	+
Relief with movement	+	+	+
Nocturnal preponderance	+	+	+
Supportive criteria			
Family history	–	–	–
Response to dopaminergic therapy	+	+	+
Periodic leg movements of sleep	+	+	+
Associated features			
Sleep onset insomnia	+	+	+
Sleep maintenance insomnia	+	+	+
Serum hemoglobin, g/dL	16.4	11.5	12.9
Serum iron, μg/dL	100	48	66
Serum ferritin, ng/mL	441	9	79
Additional workup			
Physical examination	Normal	Normal	Normal
Abdominal ultrasonography	Normal	Normal	Normal
Spinal MRI	Normal	Normal	Normal

abundance and allelic composition of the relevant SNP. Odds ratios (ORs) for RLS/PLMS with respect to the average person were calculated by using the ORs and SNP frequencies for each at-risk allele with respect to noncarriers in the Icelandic population, which are similar to those in other European populations. The OR in the population was calculated on the basis of the following formula (illustrative example for rs3923809 in *BTBD9*) = $1 \times (1 - 0.669) \times (1 - 0.669) + 1.7 \times 2 \times (1 - 0.669) \times 0.669 + 1.7 \times 1.7 \times 0.669 \times 0.669 = 2.41$. By assuming a multiplicative model, the normalized OR for the GG genotype is 0.59 (1/1.7), for the AG genotype is 0.71 (1.7/2.41), and for the AA genotype is 1.20 ($1.7 \times 1.7/2.41$). The overall OR for RLS was derived by multiplying the normalized OR for each marker.

RESULTS Subjects were self-referred because of insomnia and uncomfortable sensorimotor abdominal symptoms. Each patient denied gastrointestinal disorders and abdominal surgery. Family histories of similar abdominal symptomatology and RLS were denied. Physical and neurologic examinations and abdominal imagining were normal. Two subjects were anemic. Video-polysomnography or accelerometry[5] documented PLMS and sleep fragmentation (tables 1 and 2).

Case 1. A 62-year-old man complained of 14 years of nocturnal awakenings due to a "nervous twitchy feeling" in his abdomen. Discomfort occurred nightly, 2–3 hours after sleep onset, persisted for 30–120 minutes, and was relieved by sitting up and walking.

Video-polysomnography documented 6 episodes of rhythmic (2 Hz) abdominal rocking, each persisting for 15–20 minutes at wake-sleep transitions. Pramipexole (0.18 mg) brought immediate relief. Dose titration to 0.65 mg was necessary after 1 year, and he has remained asymptomatic for 4 years.

Case 2. A 62-year-old man described 6 years of an unpleasant "abnormal tickling" in his abdomen that awakened him about 20 minutes after lying down for sleep and that partially improved when he moved, arose from bed, or walked. Treatment with the neuroleptic levomepromazine (15 drops of a 4% solution), which might be expected to worsen RLS, and 5 mg diazepam, was ineffective. Iron deficiency anemia due to Barrett esophagus was discovered. Video-polysomnography documented leg pedaling movements and repeated compression of his abdominal wall with his hands coincident with waking sensory symptoms that culminated in his arising from bed to gain relief. Pramipexole (0.18 mg) brought immediate relief. Dose titration to 0.70 mg was necessary after 1 month in addition to supplementation with oral iron for persistent anemia and pregabalin (150 mg) to maintain symptomatic relief.

Case 3. A 62-year-old woman with 15 years of sleep onset and maintenance insomnia complained of 1-year worsening coincident with anemia related to interferon and ribavirin therapy for a hepatitis C infection and the start of nocturnal abdominal discomfort mainly involving the epigastric area. Abdominal discomfort, which she described as "electric currents, shocks, or sparks deep in my belly," awakened her about 10 minutes after falling asleep. They forced her to either arise or to get out of bed and interfered with her resuming sleep.

Video-polysomnography revealed a PLMS index of 35 that included the arms and trunk. Pramipexole (0.18 mg) eliminated her discomfort within 1 week. Six months later, conventional RLS symptomatology that was indistinguishable from that previously experienced in her abdomen (which, otherwise, remained free of symptoms) emerged. Measurements of iron and hematologic parameters showed normal values. A second video-polysomnography with extended EMG revealed a PLMS index of 8 and no periodic movements in the rectus femoris and rectus abdominis. RLS disappeared after the pramipexole dose was increased to 0.36 mg. She has remained asymptomatic for 8 months.

Each subject was homozygous for the most common RLS/PLMs–associated risk allele in the *BTBD9* gene. The overall lifetime risk of RLS/PLMS in pa-

Table 2 Polysomnographic features

	Case 1	Case 2	Case 3
Total sleep time, min	195	129	306
Sleep efficiency, %	41	31	70
Sleep onset latency, min	108	20	27
Wake time after sleep onset, min	175	274	104
N1 stage, %	26.6	25.9	8.7
N2 stage, %	56.3	74.1	55.6
N3 stage, %	4.6	0	22.5
REM sleep stage, %	12.5	0	13.2
REM sleep stages, n	2	0	2
REM sleep onset latency, min	94		145
Apnea-hypopnea index	0	3	6
Arousal index	15.7	3	21
PLM index	22[a]	25	35
Video analysis	Six episodes of abdominal rocking during wakefulness to relieve abdominal discomfort	Behavioral maneuvers during wakefulness to relieve abdominal discomfort	Periodic movements also involving the trunk and upper limbs

PLM index = periodic leg movements; PLMS = periodic leg movements of sleep.
[a] Absence of PLMS on a single night of polysomnography but ambulatory, bilateral accelerometry during 4 consecutive nights showed PLM indices of 20, 21, 23, and 23 (mean PLM index of 21.75).

tient 2 (OR = 1.02) was comparable to that of the population of Spain in whom the RLS prevalence is approximately 10%, whereas risk was more than 2½ times higher in patients 1 (OR 2.57), and 3 (OR 2.69) (table 3).

DISCUSSION We describe a clinical picture indistinguishable from RLS with the sole exception being that symptoms were confined to the abdominal wall. The essential and secondary criteria for RLS and associated features were observed save for the exception that family histories were absent. Symptoms could not be attributed to an alternate medical condition including propriospinal myoclonus. We conclude that the abdominal symptomatology of our patients represents a phenotypic variant of RLS. That conventional RLS emerged in one patient after elimination of abdominal symptomatology with pramipexole is supportive of our conclusion.

Arms, hips, trunk, or face may be involved in RLS in addition to the legs, particularly in severe cases[1] or during augmentation. To the best of our knowledge, there are no previous reports of RLS-like symptomatology confined to the abdomen. A single patient with idiopathic RLS had restlessness in the legs and lower abdomen in association with a "rhythmic movement disorder."[6] There are a few descriptions of patients with symptoms resembling RLS occurring exclusively in body areas other than the legs such as the mouth, arms, trunk, and perineum.[2,3] It is not certain whether these anecdotal cases represent phenotypic variants of RLS because they were not comprehensively assessed, and symptom reversal with dopaminomimetics is insufficient to render a diagnosis, given that supraspinal dopamine networks modulate sensory perception[7] and dopamine receptors are associated with placebo analgesic responses.

PLMS is an RLS endophenotype critical to defining the biology of RLS inclusive of the extent of the phenotypic spectrum as we show here.[8] The pattern of PLMS in RLS shows that the anterior tibialis is the first to be activated and also the most frequently involved but axial muscles such as the rectus abdominis can also be involved in 3%–6% of cases.[9] The pathophysiology of RLS remains unclear, although supraspinal hyperexcitability of the lumbosacral segments (L4–S1) of the spinal cord has been implicated. The pedaling movements seen in one patient may reflect the activation of a lumbosacral spinal pattern generator.[10] The substrate must also engage the T7–T12 thoracic spinal segments to account for the abdominal symptoms in our patients.

Patients reported here with restlessness restricted to the abdomen represent part of the RLS spectrum. Physicians should be vigilant to the existence of this phenotype when they encounter subjects who present with insomnia and abnormal abdominal sensations. This will avoid misdiagnoses and facilitate

Table 3 RLS/PLMs-associated genotypes and risk assessment[a]

Subject	*MEIS1* rs2300478	*BTBD9* rs3923809	*PTPRD* rs1975197	*PTPRD* rs4626664	*MAP2K5* rs3784709	OR RLS/PLMs
Case 1	GT	AA	CC	AG	CC	2.57
Case 2	GT	AA	CT	GG	TT	1.02
Case 3	GG	AA	CT	GG	CT	2.69

Abbreviations: OR = odds ratio; PLMS = periodic leg movements of sleep; RLS = restless leg syndrome.
[a] Genotypes at each of the individual single nucleotide polymorphisms within 4 genes (indicated) known to be associated with increased risk of RLS. At-risk alleles are indicated in boldface.

symptom management guided by RLS practice parameters.

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AUTHOR CONTRIBUTIONS

Dr. Pérez-Díaz: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, contribution of vital reagents/tools/patients, acquisition of data, statistical analysis, and study supervision. Dr. Iranzo: drafting/revising the manuscript, study concept or design, and analysis or interpretation of data. Dr. Rye: drafting/revising the manuscript, analysis or interpretation of data, contribution of vital reagents/tools/patients, acquisition of data, and statistical analysis. Dr. Santamaria: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, and acquisition of data.

DISCLOSURE

Dr. Pérez-Díaz and Dr. Iranzo report no disclosures. Dr. Rye serves on a scientific advisory board for Merck Serono and the medical advisory board for Narcolepsy Network; has received funding for travel or speaker honoraria from UCB; serves as Deputy Editor for *SLEEP* and on the editorial boards of *Sleep Medicine*, *Experimental Neurology*, *Sleep Medicine Reviews*, and the *Sleep Research Society*; has filed a patent re: Methodology for pharmacological formulation for treatment of hypersomnia; and serves as a consultant for UCB. Dr. Santamaria performs polysomnographic studies in an academic public health system hospital in Barcelona (30% effort; Neurology Service, Hospital Clínic of Barcelona).

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