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Not Only Limbs in Atypical Restless Legs Syndrome

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Summary

Restless legs syndrome (RLS) typically affects the limbs, but the involvement of other body parts has also been reported. In this assay, we critically review all literature reports of atypical RLS cases with unusual localizations. Applying the updated diagnostic criteria of the International Restless Legs Syndrome Study Group (IRLSSG), which also consider symptoms localized outside of the lower limbs, a few of these atypical cases reported in the previous literature resulted in a definitive diagnosis of RLS. We also discuss the relationship between RLS and burning mouth syndrome (BMS) or restless genital syndrome (RGS). We conclude clinical sleep specialists should be aware of unusual RLS localizations because they respond to the usual treatment for RLS. All the IRLSSG diagnostic criteria should be applied in every suspected case, in order to establish a correct diagnosis of this disabling but treatable condition.

Key words: restless legs syndrome, restless bladder, restless genital syndrome, persistent genital arousal disorder, burning mouth syndrome

Abbreviations

BMS	burning mouth syndrome
IRLSSG	International Restless Legs Syndrome Study Group
PGAD	persistent genital arousal disorder
PLMS	periodic limb movements during sleep
PSAS	persistent sexual arousal syndrome
RGS	restless genital syndrome
RLS	restless legs syndrome/Willis-Ekbom disease
WED	Willis-Ekbom disease

Introduction

Since the first scientific description of the restless legs syndrome (RLS) by sir Thomas Willis in "De Anima Brutorum" (1672) [1], its most impressive motor phenomena have been reported to involve essentially the lower limbs. This has been a constant in the following centuries; as an example, in 1861, Theodor Wittmaack [2] reported a patient with probable RLS presenting with symptoms described as "*anxietas tibiarum*". Moreover, in the '40s, Karl Axel Ekbom introduced the term "restless legs syndrome" [3], which clearly focuses the attention of the clinician on the lower limbs. Additional focused attention on the legs was caused, finally, by the clinical recognition in 1953 by Symonds [4] of periodic leg movements during sleep (PLMS) that were first recorded polysomnographically and finely characterized by Lugaresi et al. in 1965 [5,6].

Nevertheless, RLS does commonly affects the limbs [7-9] but the involvement of other body parts sometimes hampers the diagnosis, especially when limb symptoms are lacking [7].

The International RLS Study Group (IRLSSG) recently revised the RLS diagnostic criteria adding to the four classical essential criteria (1.urge to move; 2.worse at rest; 3. relief by activity; 4. worse in the evening/night) a fifth criterion to exclude mimics (5. symptoms not solely accounted for by another medical/behavioral condition) [9,10]. The authors emphasized that all the IRLSSG criteria must be met for a reliable diagnosis in each RLS case, particularly those with atypical localizations [9].

In this review, we critically evaluate all literature reports of atypical RLS cases with unusual localizations.

Methods

We searched for publications on atypical topography of RLS symptoms from 1950 to May 2016 on PubMed, a service of the National Library of Medicine's National Center for Biotechnology Information: http:// www.ncbi.nlm.nih.gov. Search terms included RLS topography, RLS criteria, restless legs syndrome, abnormal sensations and restless, periodic movements and restless, genital restless, restless genital syndrome.

Of the 32 articles found, we excluded those in which RLS involved the upper limbs and/or concerned the same group of patients. Most of the remaining 20 papers were letters to the editor, brief communications and case reports. All the cases were independently analyzed by two of the authors (AT and FP) who verified the adherence to the updated IRLSSG diagnostic and supportive

criteria [9] classifying each case as positive or negative RLS. Disagreements were resolved by subsequent case review.

RLS with Atypical Localization

The final sample comprised 12 articles on 19 patients referring RLS symptoms in atypical localizations, and 8 articles on 41 subjects with RLS in sites other than the limbs.

Among the 19 cases, 7 fulfilling all 5 IRLSSG criteria [9,10] were classified as having definite RLS; 7 patients matching 4 out of the 5 criteria and 3 subjects matching 3 out of the 5 criteria were classified as probable and possible RLS, respectively. Two subjects met only the first criterion "urge to move" (Table 1). Remarkably, information on one or more criteria was lacking in 10 patients: the first criterion was not reported in 5 cases, the second in 2 and the fifth in 6 (Table 1). Among the supportive features, PLMS (supportive feature 1) were not reported in 13 patients; of 6 patients investigated with polysomnography 4 were positive for PLMS. Fifteen patients responded to dopamine or dopaminergic agonists treatment (supportive feature 2). Family history (supportive feature 3), examined in 11 patients, was positive in 5. Lack of profound daytime sleepiness (supportive feature 4) was never investigated.

RLS symptoms affected the face (6/19) [11-13], abdomen (6/19) [14-17], genitalia (4/19) [18-20], bladder (2/19) [21] and lower back (1/19) [22] (Table1). Symptom onset was at 51±12 years (mean±SD), while diagnoses were made on average at 57 years with a delay of 7±7 (mean±SD) years. In all cases, physical examination of the affected body area was normal; 2 subjects had trigger points eliciting unpleasant sensations in the genitalia [19]. Instrumental examinations of the symptomatic body areas were normal in all cases. Two patients presented venous stasis at pelvic ultrasound and MRI [18,19], 3 patients had iron deficiency [15,16] and 4 had comorbidities such as nephropathy [11], pancreatic cancer [16] and Parkinson's disease [20]. Four patients were reported as cases of burning mouth syndrome (BMS) [13] while 1 was described as Persistent Sexual Arousal Syndrome (PSAS), now known as restless genital syndrome (RGS) [18].

In the second group of 41 cases, RLS onset in atypical body parts coincided with the classical RLS in the limbs or spread from the limbs to unusual localizations after a variable time delay (0-9 years) (Table 2). In these cases, the RLS diagnosis could not be verified using the IRLSSG criteria, nor was the patient history described. The sites affected were urinary-genital tract (26/41) [7,23-25], trunk (8/41) [7,26-28], head and neck (5/41) [7,13,29] and the whole body (2/41) [27]. An augmentation effect was referred for 2 patients [29] and denied in 4 [27]. One patient was described

as BMS concomitant with RLS symptoms in the legs [13], while 19 had RGS (first described as persistent genital arousal disorder-PGAD) and/or overactive bladder and/or urethral hypersensitivity concomitant with limb RLS [23]. MRI scan frequently disclosed pelvic varices in the RGS group [23].

A short assay on "phantom" RLS

Although not exactly atypical but at least peculiar, it is of extreme interest to mention, in a narrative way rather than a systematic one, also the forms of "phantom" RLS where the limb has been amputee but the unpleasant sensations according to RLS diagnostic criteria develop [30-33], in some cases in conjunction with chronic renal failure [31,33]. These forms usually show a good response to traditional treatments for RLS [31-33] providing support for a central dopaminergic dysfunction of the somatosensory circuitry in the development of this disease [32]. In a large questionnaire study on phantom limb perception, the authors found a pattern of phantom pain that resembled RLS [34]. These findings lead to reconsider the hypothesis that RLS might be somehow a pain syndrome, at least in part [34].

An additional case of genital RLS

In the context of the studies on this topic, the Sleep Medicine group of the University of Bologna has recently followed-up a new case of RLS affecting the genitalia. Briefly, a 64-year-old woman presented with a six-month history of itching in the external genitals, labia minora and majora, groin, proximal side of both thighs and sometimes the perineum. She denied sexual thoughts, sensory impairment in the genital area or urinary urgency. The itching would start in the evening when she relaxed, increasing before falling asleep and disappearing with sleep onset. At careful history-taking, the patient reported that the unpleasant genital feelings forced her to stand up and move around to relieve the sensation. Consequently, she complained of sleep onset insomnia without excessive daytime somnolence. The itching recurred nightly and had progressively worsened in intensity and duration. Family history for RLS was negative. The patient husband denied she had PLMS at night. Neurological and gynecological examinations of the external genitalia were normal. Cystoscopy and urodynamic tests were unrevealing as were laboratory parameters including endocrine assessment, serum iron and ferritin levels. Brain and spine MRI

excluded any structural abnormality. The patient was treated with a low dose of pramipexole (0.09 mg before bedtime) with a complete disappearance of symptoms since the first administration. After a 6-month treatment follow-up, the patient confirmed the absence of any disturbance.

Discussion

This interesting case report and the literature review demonstrate that any part of the body can be affected by RLS symptoms, particularly head and abdomen. Symptoms may even spread to the whole body [27]. In the absence of limb involvement, these cases have been assumed to be RLS phenotypic variants or equivalents [9,14,16,20].

Despite the increasing number of literature reports, our review showed that only 7 cases fulfilled all 5 IRLSSG criteria for a definitive RLS diagnosis. Nonetheless, RLS cannot be excluded in the other cases, mainly because of the lack of complete information on the IRLSSG criteria. In some cases, the new criteria were published after the case reports but in the future the IRLSSG criteria must be investigated and met in every suspected RLS patient. Three major criteria ("2. worse at rest; 4. worse in the evening/night; 5. symptoms not solely accounted for by a medical/behavioral condition) are easy to investigate, whereas the first and the third are more difficult to apply to body parts other than limbs. However, movements producing relief are not necessarily related to the affected part, so patients with abnormal sensations in atypical localizations frequently reported relief by standing up and walking around [29].

In addition, the supportive features of RLS were rarely studied, and the latest, "lack of daytime sleepiness", had never been investigated. Instead, PLMS and a positive family history are easily determined and useful to corroborate the RLS diagnosis along with a positive response to dopaminergic medication.

The spreading of RLS symptoms and augmentation

The spread of RLS symptoms to previously unaffected localizations in patients on dopaminergic therapy could be due to augmentation, an aggravation of RLS symptoms during treatment [10,14,35]. Augmentation is the main complication of long-term dopaminergic treatment of RLS and it is defined as an overall worsening of symptoms beyond pretreatment levels in patients who had experienced an initial positive therapeutic response [36]. Five major diagnostic features of augmentation were identified: 1) advanced usual time of RLS symptom onset each day; 2) increased number of body parts with RLS symptoms; 3) decreased latency to symptoms at rest,

4) increased severity of the symptoms when they occur; 5) decreased effect of dopaminergic medication on symptoms. A paradoxical response to changes in medication dose also designates augmentation [37,38]. The spread of symptoms can even involve, in the most severe cases, the entire body [39]. As the primary neural and molecular substrates underlying RLS are unknown, the pathophysiology of augmentation remains unclear, however there are several hypotheses that take into consideration the role of dopaminergic hyperstimulation, of iron deficiency, the genetic component, the effect of a reduction in responsiveness of tubero-infundibular dopamine receptors, and the role of chronobiotic mechanisms as previously reviewed [39]. Clinically, the symptoms of unusual RLS localizations do not differ from those involving limbs. Indeed, average symptom onset was in the fifth decade as in typical RLS and both males and females were equally affected. The long time-delay (up to 34 years) between the onset of the symptoms and RLS diagnosis probably reflects the diagnostic difficulties related to the atypical topography. However, specific causes of the spread to other body parts have not yet been identified.

The relationship between RLS, BMS and RGS

Furthermore, some cases described as BMS and RGS might be RLS cases; two patients described as BMS also fulfilled all the IRLSSG criteria [13]. RLS and BMS present many similarities such as age at onset, a female preponderance, a circadian pattern of symptoms and concomitant sleep disturbances [10,13]. Parafunctional BMS habits such as tongue thrusting or nibbling may correspond to the “urge to move” criterion of RLS. In addition, eating is a well-known relief factor in BMS patients [13]. BMS is an oral dysesthesia presenting as a burning sensation of the tongue and other oral and perioral mucosae; a painful symptomatology in extraoral bodily regions may also be a common feature of this disease. It is a diagnosis of exclusion, which is made only after nutritional deficiencies, fungal infections, mucosal disease, allergies, hormonal disorders and contact stomatitis have been ruled out and sometimes seems to be clinical condition in the context of RLS [40,41]. Starting from the point that both syndromes are idiopathic, it is likely that the above mentioned possibilities are both true, depending on the presence or the absence of IRLSSG criteria and the response to dopamine agonist, as an *ex-adjuvantibus* condition [41]. Therefore, a subset of patients with BMS may be a phenotypic variant of RLS and a trial of dopaminergic drugs should be given in patients with BMS who have a history suggestive of RLS or in patients who do not show a response to therapies for the other possible causes of this disturbance [13]. It is noteworthy that agents that block the dopaminergic system, such as olanzapine, aggravate RLS [42,43]; this happens, in particular, in patients with a family history of idiopathic RLS [44]. There is a report of two cases of BMS who were successfully treated with olanzapine [45] and the

authors argue that one possible explanation of the efficacy of this medication in treating BMS might due, in part, to its blockade of a subset of dopamine receptors. In fact, the patient clinical manifestations did not fulfill the IRLSSG criteria; this is an indirect demonstration that not all the subjects with BMS are atypical RLS sufferers and a scrupulous differential diagnosis is needed.

The term RGS has recently been proposed to indicate all cases of unexplained genital discomfort called vulvar dysesthesia, male genital skin pain, penoscrotodynia, PSAS [46] and PGAD [20,23,47]. Although PGAD characteristics differ from IRLSSG criteria, the genital discomfort reported by some patients could resemble RLS symptoms, especially when sensations begin or worsen at rest and improve with limb movements [23]. RLS has a higher incidence in females [48], which could indicate a role of estrogens in this condition; in fact, in basic science studies, estrogens have been reported to protect the nigrostrial dopamine neurons from toxic effects [49] and, in one study, 69% of female patients complained of an increase in RLS manifestations after menopause [50]. Therefore, it is conceivable that an interaction exists between ovarian hormones and RLS and that RGS might be a phenotype of RLS. Moreover, it has been proposed that RGS, in the context of RLS, might be the expression of a nonsexually driven hyperexcitability of the genitals, with subsequent attempts to overcome it by genital manipulations [51]. It is also intriguing that BMS occurs approximately seven times more frequently in women, mostly in perimenopausal age [52]. These data suggest that many atypical forms might have a hormonal pathogenic substrate.

Conclusion

Physicians should be aware of atypical RLS localizations. Syndromes such as BMS and RGS may conceal RLS so patients reporting unpleasant sensations in body parts other than the limbs should be investigated for possible RLS. The accurate application of the latest IRLSSG criteria is essential to establish a definite diagnosis. Moreover, a plentiful research agenda and insights for clinicians, in particular to arrange a multicenter database of atypical RLS cases, may arise from the considerations exposed in this brief assay in order to make a step from merely clinical case reports to randomized controlled trials.

Practice points

1. To use IRLSSG criteria in order to include RLS atypical cases.
2. To tune and validate a questionnaire for the evaluation of atypical forms.
3. To investigate for possible RLS those patients reporting unpleasant sensations in body parts other than the limbs.

Research agenda

1. To fill out a multicenter database of RLS atypical cases in order to reach more evidence about clinical manifestations and treatment options and responsivity.
2. To study those subjects with constant urge to genital manipulations for RLS.
3. To better define with future studies the course of RGS in different hormonal imbalance conditions.
4. The hypothesis that RLS may be, at least in part, a pain pattern warrants further investigation in chronic pain populations.

Disclosures: The authors declare no conflicts of interest.

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Table 1. Literature reports of patients presenting RLS/WED symptoms in atypical localizations.

RLS/WED symptom localizations	Authors	Sex	Age at RLS/WED onset (yrs)	Age at RLS/WED diagnosis (yrs)	IRLSSG criteria								
					Criterion 1: Urge to move	Criterion 2: Worst at rest	Criterion 3: Relief by movements	Criterion 4: Worse in the evening or night	Criterion 5: Symptoms not solely accounted for by a medical/ behavioral condition	Supportive Feature 1: PLMs	Supportive Feature 2: Dopaminergic response	Supportive Feature 3: Family history	Supportive Feature 4: Lack of profound daytime sleepiness
Face	Fukunishi et al., 1998	M	51	52	n.r.	Y	Y	Y	Y	n.r.	Y	n.r.	n.r.
	Stuginski-Barbosa et al., 2008	F	65	68	n.r.	n.r.	Y	Y	Y	n.r.	Y	n.r.	n.r.
	Prakash et al., 2012	M	37	46	Y	Y	Y	Y	Y	n.r.	Y	Y	n.r.
		F	44	48	n.r.	n.r.	Y	Y	Y	n.r.	Y	N	
		F	49	52	Y	Y	Y	Y	Y	n.r.	Y	Y	
		M	37	42	n.r.	Y	Y	Y	Y	n.r.	Y	Y	
Back	Suzuki K et al., 2013	M	82	82	Y	Y	Y	Y	Y	n.r.	Y	n.r.	n.r.
Abdomen	Perez-Diaz et al., 2011	M	48	62	Y	Y	Y	Y	n.r.	Y	Y	N	n.r.
		M	56	62	Y	Y	Y	Y	n.r.	Y	Y	N	
		F	47	62	Y	Y	Y	Y	n.r.	Y	Y	N	
	Esaki et al., 2014	M	43	43	n.r.	Y	Y	Y	n.r.	Y	Y	n.r.	n.r.
	Suzuki M et al., 2014	F	54	54	Y	Y	Y	Y	Y	n.r.	n.r.	N	n.r.
	Baiardi et al., 2015	M	47	81	Y	Y	Y	Y	Y	N	Y	Y	n.r.
Bladder	Antelmi et al., 2013	M	38	43	Y	Y	Y	Y	n.r.	n.r.	Y	N	n.r.
		F	43	47	Y	Y	Y	Y	n.r.	n.r.	Y	Y	n.r.
Genitalya	Wylie et al., 2006	F	61	66	Y	Y	Y	Y	Y	n.r.	n.r.	n.r.	n.r.
	Waldinger et al., 2011	M	73	74	Y	N	N	N	N	n.r.	n.r.	n.r.	n.r.
		M	34	38	Y	N	N	N	N	n.r.	n.r.	n.r.	n.r.
	Aquino et al., 2014	F	62	65	Y	Y	Y	Y	Y	N	Y	n.r.	n.r.

Legend: F= female; M= male; Y= yes; N= no; n.r.= not reported.

Table 2. Spread of RLS symptoms from limbs to atypical localizations.

Localizations	Authors	N. of patients and sex	Age at onset (yrs)	Time delay RLS symptoms in the legs and/or arms and spreading to atypical localizations
Head				
	Buchfuhrer, 2008	1 M 1 F	57 25	9 years 2 months
Face	Prakash et al., 2012	1F (case 5)	35	0
Head and neck	Koo et al., 2013	2 pts out of 80	n.r.	n.r.
Trunk				
	Buchfuhrer, 2008	1M	57	9 years
	Koo et al., 2013	3 pts out of 80	n.r.	n.r.
Chest/back	Umehara et al., 2010	1M	55	3 days
Chest/ epigastric area	Karroum et al., 2012	1 pt out of 44	n.r.	within 5 years
Abdomen	Karroum et al., 2012	1 pt out of 44	n.r.	within 5 years
Abdomen/lower abdomen	Lombardi et al., 2003	1M	68	0
Genitalia and lower urinary tract	Waldinger et al., 2009	19 F out of 23	n.r.	prior, concomitant, after
Genitalia				
	Ackali et al., 2009	1F	34	n.r.
	Koo et al., 2013	1 pt out of 80	n.r.	n.r.
	Pink et al., 2014	5 F out of 15	n.r.	n.r.
Whole body	Karroum et al., 2012	2 pts out of 44	n.r.	within 5 years

Legend: F= female; M= male; n.r.= not reported; pt= patient, where sex was not reported by the authors