New Insights into Restless Genital Syndrome: Static Mechanical Hyperesthesia and Neuropathy of the Nervus Dorsalis Clitoridis

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ABSTRACT

Introduction. Systematic study of dysesthetic and paresthetic regions contributing to persistent genital arousal in women with restless genital syndrome (ReGS) is needed for its clinical management.

Aim. To investigate distinct localizations of ReGS.

Methods. Twenty-three women, fulfilling all five criteria of persistent genital arousal disorder were included into the study. In-depth interviews, routine and hormonal investigations, electroencephalographs, and magnetic resonance imaging (MRI) of brain and pelvis were performed in all women. The localizations of genital sensations were investigated by physical examination of the ramus inferior of the pubic bone (RIPB) and by sensory testing of the skin of the genital area with a cotton swab (genital tactile mapping test or GTM test).

Main Outcome Measures. Sensitivity of RIPB, GTM test.

Results. Of 23 women included in the study, 18(78%), 16(69%), and 12(52%) reported restless legs syndrome, overactive bladder syndrome, and urethra hypersensitivity. Intolerance of tight clothes and underwear (allodynia or hyperpathia) was reported by 19 (83%) women. All women were diagnosed with ReGS. Sitting aggravated ReGS in 20(87%) women. In all women, MRI showed pelvic varices of different degree in the vagina (91%), labia minora and/or majora (35%), and uterus (30%). Finger touch investigation of the dorsal nerve of the clitoris (DNC) along the RIPB provoked ReGS in all women. Sensory testing showed unilateral and bilateral static mechanical Hyperesthesia on various trigger points in the dermatome of the pudendal nerve, particularly in the part innervated by DNC, including pelvic bone. In three women, sensory testing induced an uninhibited orgasm during physical examination.

Conclusions. ReGS is highly associated with pelvic varices and with sensory neuropathy of the pudendal nerve and DNC, whose symptoms are suggestive for small fiber neuropathy (SFN). Physical examination for static mechanical Hyperesthesia is a diagnostic test for ReGS and is recommended for all individuals with complaints of persistent restless genital arousal in absence of sexual desire. **Waldinger MD, Venema PL, van Gils APG, and Schweitzer DH. New insights into restless genital syndrome: Static mechanical hyperesthesia and neuropathy of the nervus dorsalis clitoridis. J Sex Med 2009;6:2778–2787.**

Key Words. ReGS; RLS; OAB; Persistent Sexual Arousal Syndrome; PGAD; SFN; Pudendal Nerve; Dorsal Nerve of the Clitoris

Introduction

Restless genital syndrome (ReGS) is characterized by the five diagnostic criteria of persistent genital arousal disorder (PGAD) and the presence of restless legs syndrome (RLS) and/or overactive bladder (OAB) syndrome which occurrences are closely related to the genital symptoms [1,2]. The five diagnostic criteria of PGAD include: (i) involuntary genital and clitoral arousal that persists for an extended period of time (hours, days, months); (ii) the physical genital arousal does not go away following one or more orgasms; (iii) the genital arousal is unrelated to subjective feelings of sexual desire; (iv) the persistent feelings of genital arousal feel intrusive and unwanted; and (v) distress is associated with persistent genital arousal [3]. In 2001, persistent sexual arousal syndrome (PSAS) was for the first time reported in medical literature by Leiblum and Nathan [4]. In 2006, it has been renamed PGAD by Goldmeier and Leiblum [5]. The prevalence, etiology, and pathogenesis of the syndrome are unknown [1–5]. Current insight into PGAD has thus far been limited by a lack of systematic research, despite a number of case reports [4,6–16]. The first systematic medical study was recently conducted by Waldinger et al. [1,2] in 18 Dutch women fulfilling all five criteria of PGAD. It was found that the majority of women experienced PGAD during early menopause without preexisting psychiatric disorders and laboratory abnormalities. Most women had difficulties in describing the quality of the genital sensations, which were described in various terms and were diagnosed as dysesthesias and paresthesias. Electroencephalogram (EEG) analyses and brain magnetic resonance imaging (MRI) revealed no abnormalities, but MRI scans of the pelvis disclosed varices in 55% as confirmed by additional transvaginal ultrasonography [1,2]. The majority of women (67%) also reported preexistent or coexistent RLS, OAB, and hypersensitivity of the urethra. Notably, as a large burden of clinical evidence has pointed into the direction of a clinical cluster, this cluster of PGAD, RLS, OAB, and urethra hypersensitivity has been called restless genital syndrome [1,2]. In order to map the involved genital region in women with ReGS, we systematically examined this region, looking at tactile responses by means of a cotton swab. Each pressure point was evaluated by instructing women to report the evoked sensations. In the current study, we report on this test, which we have called genital tactile mapping test (GTM test).

Material and Methods

We prospectively evaluated 23 women with complaints of persistent unwanted feelings of genital arousal who visited our Outpatient Department of Neurosexology of HagaHospital Leyenburg in The Hague between October 2004 and May 2009, and who were diagnosed with ReGS. The women were not actively recruited but were either referred by their general physician, gynecologist, and sexologist or contacted the first author after Internet information on the PGAD and ReGS research and treatment facilities in our Outpatient Department. According to the regulations of the medical ethical committee, official permission for study participation was not required as the study was not placebo controlled and study drugs were not taken. All patients were investigated by the first author, who followed an evaluation procedure according to standard protocol. After a neuropsychiatric and medical sexological interview of about 1 hour, women who were clinically diagnosed as having ReGS underwent routine and hormonal laboratory testing, an EEG, and an MRI scan examination of the brain and pelvis.

The diagnosis PGAD was established when the symptoms of the patients fulfilled all five criteria of PGAD [3]. Menopause was defined as the absence of menses for 12 months after the last menstruation. Perimenopause was defined as a combination of irregular cyclic bleedings and postmenopausal gonadotrophin levels. RLS was diagnosed according to the criteria of the International Restless Legs Syndrome Study Group [17]; (i) Urge to move the legs, usually accompanied or caused by uncomfortable leg sensations; (ii) Temporary relief with movement, partial or total relief from discomfort by walking or stretching; (iii) Onset or worsening of symptoms at rest or inactivity, such as when lying or sitting; and (iv) Worsening or onset of symptoms in the evening or at night. OAB was defined as increased urgency for micturition, with or without urge incontinence, with frequency and nocturia.

Between September 2008 and May 2009, the current study protocol of the GTM test was strictly followed by the first two authors in the presence of a nurse. This test for tactile sensations of the genital region is designed to analyze static mechanical pressure with a cotton swab at the skin near the vicinity of the genitals, perineum, anal area, groins, and pubic bone.

The effect of tactile stimuli with a cotton swab was systematically recorded. The test starts with

Table 1 Patient characteristics

	Mean ± SD	Median	Range	N (%)
Total				
Age	54.3 ± 10.5 years	56 years	32–77 years	23
Onset genital sensations	51.1 ± 9.7 years	50 years	36–72 years	23
Onset restless legs + restless arms*	48.5 ± 11.7 years	48 years	25–72 years	19 (82%)
Age partner	54.3 ± 10.1 years	54 years	39–77 years	17 (74%)
Duration relationship	22.2 ± 13.5 years	24 years	1–41 years	17 (74%)
Number of children	2.1 ± 0.4	2.0		
Menopausal women				
Age	60.0 ± 6.7 years	59 years	51–77 years	15 (65%)
Onset menopause	49.1 ± 3.6 years	50 years	40–56 years	15 (65%)
Onset genital sensations	56.0 ± 7.2 years	54 years	48–72 years	15 (65%)
Onset restless legs + restless arms*	50.9 ± 1.3 years	54 years	25–77 years	13 (56%)
Time before seeking treatment	4.2 ± 3.9 years	3 years		
Nonmenopausal women				
Age	43.3 ± 6.7 years	44 years	32–54 years	8 (35%)
Age premenopausal women	38.5 ± 5.1 years	39.5 years	32–43 years	4 (17%)
Age perimenopausal women	48.0 ± 4.2 years	46.5 years	45–54 years	4 (17%)
Onset genital sensations	41.9 ± 6.5 years	42 years	36–50 years	8 (35%)
Onset restless legs	42.6 ± 5.1 years	45 years	35–48 years	6 (26%)
Time before seeking treatment	0.9 ± 1.0 years	0.6 years		

*Of all women, one woman developed restless arms without restless legs after the onset of the unwanted genital sensations.
SD = standard deviation.

examining the upper part of the pubic bone under the umbilicus and then gradually runs over the clitoris, vagina, perineum, and anal area. The examiner applies tactile stimulation spotwise with 2-mm distance intervals from right to left. Women examined were lying in supine position. The GTM test is performed in the presence of a nurse.

Available clinical data and imaging analyses of 12 (54%) women of the present study were previously published [1,2]. The ramus inferior of the pubic bone (RIPB) and GTM test were performed between September 2008 and May 2009 in both the 12 women of the first study [1,2] as in the new group of 11 women.

All published data in the current study were in agreement with the participants and all women provided written informed consent for publication of their data.

With increasing knowledge on and skills in interpreting MRI scans of the pelvis in women with ReGS, the MRI scans of all women were reevaluated for the presence of pelvic varices. This reevaluation resulted in finding a higher prevalence of pelvic varices in the 12 women, than has previously been reported [1,2].

Statistics

Descriptive statistics were computed for the measures used in the analyses of the baseline characteristics, and are reported as mean ± standard deviation (SD) and median.

Results

Patient characteristics of 23 women, diagnosed with ReGS, distinguished in menopausal and nonmenopausal women, and including the age of onset of RLS, are shown in Table 1.

Of all women, four (17%), five (22%), and eight (35%) had lower, intermediate, and higher vocational education; three (13%), two (9%), and one (4%) had lower, higher general secondary education, and university education, respectively.

Of all women, 15 (65%) were menopausal. Of these, definite menopause was confirmed by high FSH and LH values (Table 2).

Of all eight nonmenopausal women, four were premenopausal and reported intact menstrual cycles. Another four women were perimenopausal and reported irregular menstrual cycles (Table 2). Apart from the genital complaints, all women were in good physical health.

The genital symptoms started at the mean ± SD age of 51.1 ± 9.7 years (median 50 years). Of all women, three (13%) used selective serotonin reuptake inhibitors (SSRIs) before the occurrence of ReGS. Of them, two (9%) developed ReGS during or shortly after discontinuation of the drug. In addition, one (4%) woman started to complain of persistent genital sensations after smoking cannabis for the first time, and in one (4%) woman, these sensations started in the first week of discontinuation of cannabis that was used for medical purposes (hypoparathyroidism). In two other

Table 2 Hormonal profiles of 23 women with ReGS: FSH, LH, and Progestin concentrations in premenopausal women were timed in the first phase of the menstrual cycle as were the premenopausal normal values; nonmenopausal (Non-MP; premenopausal plus perimenopausal); menopausal (MP)

	Premenopausal (N = 4)			Perimenopausal (N = 4)			Menopausal (N = 15)			Normal Values	
	Mean ± SD	Median	Range	Mean ± SD	Median	Range	Mean ± SD	Median	Range	Non-MP	MP
Prolactine (mU/L)	156 ± 33	154	122–195	151 ± 48	139	109–216	175 ± 96	154	70–469	100–500	100–500
LH (U/L)	5 ± 3	5	3–8	34 ± 15	34	16–50	27 ± 9	28	22–41	4–15	>30
FSH (U/L)	7 ± 6	6	2–15	33 ± 19	29	14–60	60 ± 20	57	32–100	2–10	>30
Testosterone (nmol/L)	1 ± 0.3	1	0.8–2	1 ± 0.4	1	1–2	1 ± 0.6	1	0.1–2	0.7–3.3	0.7–3.3
Estradiol (pmol/L)	651 ± 642	569	31–1437	303 ± 323	251	20–689	52 ± 78	27	10–323	110–440	50–170
Progestin (nmol/L)	2 ± 0.5	2	1–2	1 ± 1	2	1–4	1 ± 0.5	1	1–2	0–5	0–5

SD = standard deviation.

women, ReGS started in the first week of norethisteron treatment and the day after ganglion stellatum blockade, respectively. The majority of women reported acute or subacute onset of symptoms without a recognizable presumed cause. Of all women, 2 (9%) reported sexual abuse at a young age. None of these women associated ReGS with their history of sexual abuse. A previous episode of depression was reported by one (4%) woman. A previous burnout syndrome and adjustment disorder were reasons for using SSRIs in the two women who reported the onset of ReGS shortly after discontinuation of these antidepressants.

The genital sensations were experienced at the clitoris, vagina, and labia in 21 (91%), 12 (52%), and eight (35%) women, respectively; seven (30%) and four (17%) women reported the sensations at the pubic bone and in the groin, respectively; 16 (69%) women reported a combination of these localizations. All women experienced the symptoms continuously during the day in severe to very severe degree, which varied in the course of weeks and months. The quality of the genital sensations was expressed in various terms. However, in 19 (83%) women, the sensations were experienced as an imminent orgasm without the genuine feeling of orgasm. Acute onset of permanent genital background sensations due to tension, anxiety, anger, or annoyance was reported by all women.

Sitting worsened the ReGS complaints in 20 (87%) of women. Lying stretched and walking either diminished ReGS or did not result in complaints in 16 (69%) and 19 (83%) of women. Other women had just opposite experiences, e.g., lying stretched and walking worsened the symptoms in seven (30%) and four (17%) of women.

Of all women, 19 (83%) women reported intolerance for various forms of clothes or tight underwear. It was reported that these clothes triggered the unwanted genital sensations or gave rise to inconvenient and difficult-to-describe irritancies in the genital region. Of all women, 16 (69%) reported difficult-to-describe waves or attacks of serious lack of energy and/or heavy fatigue.

Eighteen (78%) individuals reported RLS and one (4%) woman reported restless arms; eight (35%) had restless legs since many years. An additional 10 (43%) reported the onset of RLS shortly after the onset of genital sensations. Comparing the 12 women previously published with those 11 individuals currently reported for the first time, RLS appeared to be present in 10 (83%) and nine (82%) women, respectively.

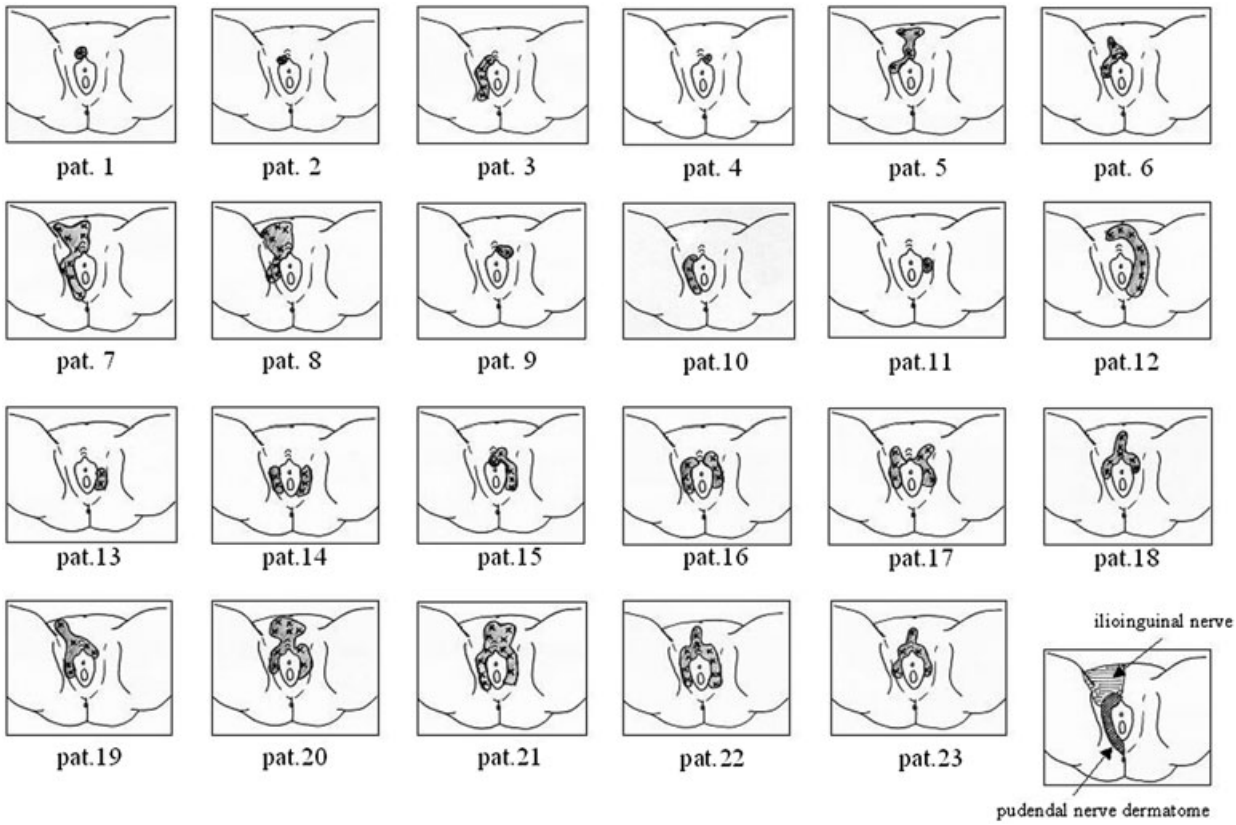

Figure 1 Localization of points of static mechanical hyperesthesia; the points are marked with an x. The external genitalia of the female are shown front-on in lithotomy position. The last picture shows the dermatomes of the pudendal nerve and ilioinguinal nerve.

Sixteen (69%) reported complaints of OAB, while seven (30%) had OAB since many years. An additional nine (39%) reported the start of OAB shortly after the onset of the genital sensations. Comparing the 12 women previously published with those individuals currently reported, OAB was present in seven (58%) and nine (82%) women, respectively. Decreased ReGS sensations after micturition, although only briefly, were reported by 16 (69%) of women. Conversely, 12 (52%) women reported undesired urethral hypersensitivity, e.g., unwanted feelings of restlessness and arousal in the urethra, either after voiding or during sensations of ReGS.

Routine laboratory tests, hormone profiles, EEG, and MRI brain imaging analyses were unremarkable in all women. The MRI scan of the pelvis showed no abnormalities of the clitoris and urethra. However, pelvis MRI scan disclosed high prevalence of pelvic varices in the wall of the vagina, the labia minora and/or majora, and uterus in 21 (91%), eight (35%), and seven (30%) women. Two (9%) and one (4%) women had varices of the cervix and ovaric vene, respectively. A combination of varices at these locations was found in 16 (69%) of women. Seven (30%) women had varices of the legs or reported their surgical treatment.

Figure 1 shows the findings of the GTM test. Static mechanical pressure provoked restless and pre-orgasmic genital sensations at different points. The number of trigger points varied among the women with a mean number of tactile hypersensitivity points of 5 (range 1–11). To excite the trigger points, only mild to moderate static mechanical pressure was required. The trigger points were located on the right side, the left side, and bilaterally from the vagina and clitoris in eight (35%), six (26%), and nine (39%) of women. In 11 (48%) women, trigger points were located above the pubic bone. In four (17%) women, the clitoris was the sole trigger point to provoke ReGS.

In three (13%) women, light static mechanical pressure elicited an uninhibited intense and repeated orgasm during the examination at various trigger points. In one (4%) woman, ReGS was

difficult to trigger in supine position. However, in a sitting position, combined with Valsalva, trigger points were inducible. In all women, pressure by finger control (second author) alongside the RIPB elicited one or more trigger points.

Discussion

This is the second study of systematic blood analysis, MRI, and EEG examinations in a series of women with complaints of persistent restless and pre-orgasmic genital sensations in the absence of sexual desire, sexual thoughts, and fantasies. All 23 women included in this study met the five diagnostic criteria of PGAD. All women reported varying degrees of social withdrawal, desperate feelings, dysthymia, agitation, or depressed mood directly caused by persistent unwanted genital sensations. However, despite two women with a previous burnout syndrome and adjustment disorder, none of the women was known with previous psychiatric disorders, such as major depression, bipolar disorder, anxiety disorder, panic attacks, and/or obsessive compulsive disorder. The high prevalence of RLS (82%) and complaints of OAB (82%) in the 11 women of the current study, who have not participated in our previous study, is similar to their high prevalence in our previous study [1,2]. This, again, supports the concept that RLS, OAB, and PGAD belong to a clustered condition, which we have called restless genital syndrome. In addition, the current study showed that pelvic MRI disclosed a very high prevalence of pelvic varices of different seize in all women, suggesting that pelvic varices play an important role in the pathogenesis of ReGS. Such an association has also recently been reported in a case report [14]. However, in contrast to the latter case report, the pelvic varices in most of the women of the current study are mild to moderate in seize. In addition, although pelvic varices have been associated with chronic pelvic pain [18], none of the women in the current study complained of chronic pelvic pain. The current study demonstrated predilection of distribution of pelvic varices around the vagina and in the labia minora and/or majora, with relatively less presence in the uterus, cervix, and ovaric vene. The prevalence of pelvic varices found in the current series is remarkably high since 9.9% prevalence of pelvic varices has been previously reported in the general population [19]. In the current series, we found 100% prevalence of varices, based on MRI criteria, which suggests that ReGS and, particularly, vagina and labia varices are strongly associated. Interestingly, the prevalence of varices of the legs (30%) in the current series of women is not aberrant from the prevalence of 32% in the general female population [20]. The discrepancy of low and high prevalence of leg varices and pelvic varices in women with ReGS may suggest an independent pathogenesis of pelvic varices in these women.

In the current study, physical examination by means of finger touch along the RIPB and simple sensory testing with a cotton swab elicited the disturbing genital sensations, indicating static mechanical hypersensitivity around the genitals, at the labia minora and/or majora, at the clitoris, and above the pubic bone. Light pressure even evoked (repeated) orgasm in three women. This phenomenon was experienced with much distress and embarrassment and required reassurance and brief counseling. For this reason, presence of a skilled nurse during physical examination is critical. According to our knowledge, this is the first report on female orgasm that is triggered by pressure of the skin above the pubic bone and in the area next to the vagina.

The area of static mechanical hypersensitivity—bilaterally to the labia majora and above the pubic bone—is equivalent to the dermatomes of the pudendal and the ilioinguinal nerve. However, as it seems rather unlikely that the ilioinguinal nerve, a peripheral nerve originating of the lumbar plexus (L1), mediates orgasmic feelings, we suggest that the area of trigger points located above the public bone belongs to a variant expression of the dermatome of the pudendal nerve.

The pudendal nerve originates from the pudendal plexus (S2–S4) and divides into three terminal branches [21,22]. In the upper half of the pudendal (Alcock's) canal, it branches into the inferior rectal nerve. The inferior rectal nerve extends motor and sensory branches. Its motor branches innervate the levator ani muscle, and its cutaneous branches innervate the perianal skin and labia. At the end of the pudendal canal, the pudendal nerve branches into two branches, the perineal nerve and the dorsal nerve of the clitoris (DNC), which ends as a terminal branch to the clitoris. The perineal nerve divides into the labial branch and two branches toward the bulbocavernosus and the striated urethral sphincter. DNC is believed to be a purely sensory nerve, with no motor function. Bilaterally, the DNC pierces the perineal membrane at a distance of about 2.4–3.0 cm lateral to the external urethral meatus [21,22] and proceeds in the sulcus

nervi dorsalis clitoridis [22] together with the dorsal artery. It further traverses distally along the bulbospongiosus muscle and runs posterior to the crus before hooking over the crus to the anterolateral surface of the body of the clitoris [21]. The DNC then divides into two terminal branches that stop short of the tip of the glans clitoris at 11 o'clock and 1 o'clock positions.

Importantly, in our current study, we did not find static mechanical points of hyperesthesia in the anal and perineal area, although some women reported to have experienced radiation of ReGS symptoms into the anal area when ReGS was most severe. As we have found in the women studied here, the absence of static mechanical hyperesthesia in the perineal and anal regions suggests that isolated neuropathy of the DNC was involved. Another support for involvement of the DNC in ReGS comes from the physical examination by finger control. All patients reported the start of genital sensations on finger pressure at certain points alongside the RIPB into the direction of the symphysis, the area in which DNC runs through a sulcus. Together with the high prevalence of clothes intolerance or allodynia in the genital region, these clinical data are highly suggestive for neuropathy of DNC and/or pudendal nerve.

The extremely low threshold for static mechanical pressure in provoking pre-orgasmic and orgasmic sensations within the pudendal dermatome, innervated by the DNC, suggests the existence of central sensitization in the sacral spinal cord. Interestingly, this central sensitization is limited to pre-orgasmic and orgasmic feelings and is devoid of pain sensations. Currently, the exact function of the DNC is still unclear. Although one could postulate a role of the DNC in sexual function, it has not been proved. Based on the current analysis, it appears that the DNC evokes pre-orgasmic and orgasmic genital and pubic bone sensations in women with ReGS independent of sexual desire and fantasies.

The finding of static mechanical hyperesthesia in the dermatome area of the pudendal nerve and the DNC suggests sensory neuropathy of both nerves and their distal branches with unwanted restless sensations in the vicinity of the legs (RLS), the bladder (OAB), and urethra as previously reported [1,2]. Remarkably, an association between RLS and neuropathy has been suggested since its original description by Ekbom [23]. Moreover, a number of studies have confirmed this historically described phenomenon that restless legs can actually be caused by peripheral polyneuropathy [24–26]. Furthermore, there is also evidence of neuropathy among patients with RLS [27,28]. In addition, neuropathy of the pudendal nerve may give rise to complaints of overactive bladder and hypersensitivity of the urethra. It is of note as well that static mechanical hyperalgesia has previously been reported in patients with RLS [29].

In eight women of the current study, we investigated the effect of 1 cc bupivacaine hydrochloride monohydrate 0.5% injected under finger control around one or two trigger points. Five of these women reported a complete or nearly complete disappearance of ReGS, RLS, and OAB for the duration that varied between 12 and 96 hours, after which, ReGS returned in full intensity. Although the injection had no effect in three women, the disappearance of symptoms may be regarded as further indirect support for the view that neuropathy of the pudendal nerve and DNC is a key feature of ReGS. This concept encourages further studies with several anesthetic agents. Besides further research of this therapeutic approach, further electrophysiological investigations of the pudendal nerve and DNC in women with ReGS are required, and are currently conducted by our group.

The cause(s) of selective sensory neuropathy of the pudendal nerve and DNC remains to be elucidated. Interestingly, it may be speculated that pelvic varices are involved. Although not fully understood, some reports have shown that varices may trigger peripheral neuropathy [30] and one report mentioned pudendal nerve compression by pelvic varices in a woman with chronic perineal pain and numbness [31].

Our findings of involvement of the pudendal nerve and DNC together with our findings of sensory genital sensations (burning, tingling feelings), clothes intolerance (allodynia or hyperpathia), paresthesias, dysesthesias, and restless legs are arguments in favor of small fiber neuropathy (SFN) as underlying pathologic process in the pudendal and DNC neuropathy in women with ReGS. Also, the rather strange feelings of sudden lack of energy or extreme fatigue, incidentally reported by women with ReGS, may be associated with SFN. Although relatively few detailed descriptions of the clinical features of SFN have been published [32–36], this clinical entity has been generally recognized as a relevant syndrome with many features.

The sensory symptoms of SFN consist of paresthesias, dysesthesias, and pain, which is often of

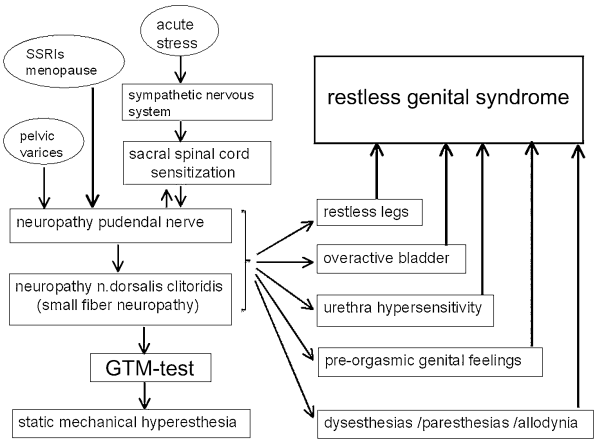

Figure 2 Hypothesis of neurological pathogenesis of restless genital syndrome. GTM = genital tactile mapping.

a burning, prickling, or shooting character. In addition, allodynia or hyperpathia (in women with ReGS expressed as intolerance to wear tight clothes) and cramps may occur. Sometimes patients with SFN present with late-onset RLS [37] and the sensory symptoms are usually distal. Symptoms of autonomic dysfunction may also occur. These may involve increased or decreased sweating, facial flushing, sexual dysfunction, diarrhea, or constipation. Remarkably, many patients with SFN complain of severe and disabling fatigue. In SFN, the small diameter myelinated A-delta nerve fibers and the small diameter unmyelinated C-fibers are mainly affected. These small fibers carry temperature and pain sensation and are involved in autonomic functioning. Assuming that SFN is fundamentally involved as an underlying cause of the symptoms of ReGS, future diagnostic research warrants electrodiagnostic investigations.

Based on our current and previous study in women fulfilling the five criteria of PGAD, we have further developed our view on ReGS (Figure 2).

Sensory neuropathy of the pudendal nerve and, specifically, the DNC is probably one of the key features or ReGS. This may lead to RLS, OAB, and/or urethra hypersensitivity. It is suggested that the neuropathy may be caused by pelvic varices and/or other so far unknown factors. It is speculated that premorbid existence of RLS, discontinuation of SSRIs, discontinuation of cannabis, and discontinuation of tobacco smoking, altered hormonal status, for example, due to menopause, the use of norethisteron and/or ganglion stellatum blockade might be risk factors for the outbreak of ReGS. All women who reported these self-presumed causes of ReGS also had pelvic varices and showed static mechanical hyperesthesia. Notably, most women reported acute or subacute onset of ReGS without any recognizable cause. The phenomenon of acute exacerbation of ReGS in relation to acute stress moments is probably mediated by acute activation of the sympathetic nervous system. In brief, we argue that ReGS is characterized by persistent unwanted restless genital sensations of pre-orgasmic and orgasmic nature, with the obligatory presence of neuropathy of the DNC and/or pudendal nerve, with at least one of the symptoms of RLS, OAB, and urethral hypersensitivity, in the absence of concurrent sexual desire, thoughts, or fantasies. It is furthermore assumed that pudendal sensory neuropathy in women with ReGS is an SFN, with involvement of small diameter A-delta and unmyelinated C nerve fibers. This may explain the sensations of paresthesias, dysesthesias, clothes intolerance (allodynia), association with RLS and the difficult-to-explain waves of extreme fatigue and loss of energy during the day. ReGS sensations are not confined to the genitals. They are also experienced above the pubic bone.

The evidence for a few parts of our view is not yet complete. Particularly, the idea that pelvic varices are causally related to the occurrence of pudendal and DNC neuropathy needs further research. Our group is currently investigating this. Another limitation of the current study is the lack of a control group. It is of particular importance to get more information on the prevalence of pelvic varices on MRI in aged-matched women with no complaints of unwanted genital sensations. This is currently also investigated by our group. However, our finding of a 100% presence of pelvic varices was not a coincidence and suggests a causal relationship between this anatomical feature and symptoms of pudendal and DNC neuropathy. These speculations need further confirmation by means of electrophysiological investigations. Currently, we are also investigating this issue.

Finally, the findings of our current study raise some questions on the description of the first criterion of the five criteria of PGAD. For a better description of ReGS, we suggest some additions to the first criterion. For ReGS, the current criterion of "involuntary genital and clitoral arousal that persists for an extended period of time (hours, days, months)" would be more appropriate as "involuntary unilateral or bilateral genital, clitoral, and/or pelvic bone arousal and restlessness that

persists for an extended period of time (days, months, years)".

Conclusion

The current study showed that women with ReGS, irrespective of the self-presumed cause (discontinuation of SSRI or menopause), have one or more points of static mechanical hyperesthesia above the pubic bone, at the clitoris, at the labia, and around the vagina. The points of hyperesthesia are located in the pudendal dermatome, and particularly in the area innervated by the DNC. It is suggested that ReGS is a physical disorder caused by sensory neuropathy, e.g., an SFN, of either the DNC and/or other branches of the pudendal nerve. It is speculated that this neuropathy gives rise to either RLS, OAB, hypersensitivity of the urethra, and clothes intolerance. Whether this sensory neuropathy is induced by pelvic varices or other factors needs further investigation. Notably, RLS in women with ReGS mainly manifests during the day and hardly at night. We recommend physical examination of the RIPB and sensory testing for static mechanical hyperesthesia as diagnostic tests for the diagnosis of ReGS in all women who complain of persistent unwanted genital arousal in the absence of sexual desire.

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Conflict of Interest: None.

Statement of Authorship

Category 1

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References

1 Waldinger MD, van Gils APG, Ottervanger HP, Vandenbroucke WVA, Tavy DLJ. Persistent genital arousal disorder in 18 Dutch women: Part 1. MRI, EEG and transvaginal ultrasonography investigations. J Sex Med 2009;6:474–81.
2 Waldinger MD, Schweitzer DH. Persistent genital arousal disorder in 18 Dutch women: Part II. A syndrome clustered with restless legs and overactive bladder. J Sex Med 2009;6:482–97.
3 Basson R, Leiblum S, Brotto L, Derogatis L, Fourcroy J, Fugl-Myer K, Graziottin A, Heiman JR, Laan E, Meston C, van Lankveld J, Weijmar Schultz W. Definitions of women's sexual dysfunctions reconsidered: Advocating expansion and revision. J Psychosom Obstet Gynaecol 2003;24:221–9.
4 Leiblum SR, Nathan SG. Persistent sexual arousal syndrome: A newly discovered pattern of female sexuality. J Sex Marital Ther 2001;27:365–80.
5 Goldmeier D, Leiblum SR. Persistent genital arousal in women—A new syndrome entity. Int J STD AIDS 2006;17:215–6.
6 Riley A. Premenstrual hypersexuality. J Sex Marital Ther 1994;9:87–93.
7 Hallam-Jones R, Wylie K. Case report. Traditional dance—A treatment for sexual arousal problems? Sex Relat Ther 2001;16:377–80.
8 Amsterdam A, Abu-Rustum N, Carter J, Krychman M. Persistent sexual arousal syndrome associated with increased soy intake. J Sex Med 2005;2:338–40.
9 Goldstein I, Johnson JA. Persistent sexual arousal syndrome and clitoral priapism. In: Goldstein I, Meston C, Davis S, Traish S, eds. Women's sexual dysfunction and dysfunction: Study, diagnosis and treatment. London: Taylor & Francis; 2005:674–85.
10 Wylie K, Levin R, Hallam-Jones R, Goddard A. Sleep exacerbation of persistent sexual arousal syndrome in a postmenopausal woman. J Sex Med 2006;3:296–302.
11 Yero SA, McKinney T, Petrides G, Goldstein I, Kellner CH. Successful use of electroconvulsive therapy in 2 cases of persistent sexual arousal syndrome and bipolar disorder. J ECT 2006;22:274–5.
12 Bell C, Richardson D, Goldmeier D, Crowley T, Kocsis A, Hill S. Persistent sexual arousal in a woman with associated cardiac defects and raised

atrial natriuretic peptide. Int J STD AIDS 2007;18: 130–1.
13 Mahoney S, Zarate C. Persistent sexual arousal syndrome: A case report and review of the literature. J Sex Marital Ther 2007;33:65–71.
14 Thorne C, Stuckey B. Pelvic congestion syndrome presenting as persistent genital arousal: A case report. J Sex Med 2008;5:504–8.
15 Goldmeier D, Leiblum S. Interaction of organic and psychological factors in persistent genital arousal disorder in women: A report of six cases. Int J STD AIDS 2008;19:488–90.
16 Korda JB, Pfaus JG, Goldstein I. Persistent genital arousal disorder: A case report in a woman with lifelong PGAD where serendipitous administration of varenicline tartrate resulted in symptomatic improvement. J Sex Med 2009;6:1479–86.
17 Walters AS. International Restless Legs Syndrome Study Group. Toward a better definition of the restless legs syndrome. Mov Disord 1995;10:634–42.
18 Beard RW, Highman JH, Pearce S, Reginald PW. Diagnosis of pelvic varicosities in women with chronic pelvic pain. Lancet 1984;2:946–9.
19 Belenky A, Bartal G, Atar E, Cohen M, Bachar GN. Ovarian varices in healthy female kidney donors: Incidence, morbidity, and clinical outcome. AJR Am J Roentgenol 2002;179:625–7.
20 Evans CJ, Fowkes FGR, Ruckley CV, Lee AJ. Prevalence of varicose veins and chronic venous insufficiency in men and women in the general population: Edinburgh vein study. J Epidemiol Community Health 1999;53:149–53.
21 Vaze A, Goldman H, Jones JS, Rackley R, Vasavada S, Gustafson KJ. Determining the course of the dorsal nerve of the clitoris. Urology 2008;72:1040–3.
22 Sedy J, Nanka O, Walro JM, Jarolim L. Sulcus nervi dorsalis penis/clitoridis: Anatomic structure and clinical significance. Eur Urol 2006;50:1079–85.
23 Ekbom K. Restless legs. Acta Med Scand 1945; 158(suppl):122–3.
24 Rutkove SB, Matheson JK, Logigian EL. Restless legs syndrome in patients with polyneuropathy. Muscle Nerve 1996;19:670–2.
25 Gemignani F, Marbini A, Di Giovanni G, Salih S, Terzano MG. Charcot-Marie-Tooth disease type 2 with restless legs syndrome. Neurology 1999;52: 1064–6.
26 Salvi F, Montagna P, Pasmati R, Rubboli G, Cirignotta F, Veilleux M, Lugaresi E, Tassinari CA. Restless legs syndrome and nocturnal myoclonus: Initial clinical manifestations of familial amyloid polyneuropathy. J Neurol Neurosurg Psychiatry 1990;53:522–5.
27 Ondo W, Jankovic J. Restless legs syndrome: Clinicoetiologic correlates. Neurology 1996;47:1435–41.
28 Iannaccone S, Zucconi M, Marchettini P, Ferini-Stambi L, Nemi R, Quattrini A, Palazzi S, Lacerenza M, Formaglio F, Smirne S. Evidence of peripheral neuropathy in primary restless legs syndrome. Mov Disord 1995;10:2–9.
29 Stiasny-Kolster K, Magerl W, Oertel WH, Moller JC, Treede RD. Static mechanical hyperalgesia without dynamic tactile allodynia in patients with restless legs syndrome. Brain 2004;127:773–82.
30 Zikel OM, Davis DH, Auger RG, Cherry KJ. Venous varix causing median neuropathy. J Neurosurg 1997;87:130.
31 Maser T, Scheiber-Nogueira MC, Nogueira TS, Doll A, Jahn C, Beaujeux R. Pudendal nerve compression by pelvic varices. J Neurol Neurosurg Psychiatry 2006;77:88.
32 Gorson KC, Ropper AH. Idiopathic distal small fiber neuropathy. Acta Neurol Scand 1995;92:376–82.
33 Stewart JD, Low PA, Fealy RD. Distal small fiber neuropathy: Results of tests of sweating and autonomic cardiovascular reflexes. Muscle Nerve 1992; 15:661–5.
34 Jamal GA, Hansen S, Weir AI, Ballantyne JP. The neurophysiologic investigation of small fiber neuropathies. Muscle Nerve 1987;10:537–45.
35 Al-Shekhlee A, Chelimsky T, Preston D. Review: Small-fiber neuropathy. Neurologist 2002;8:237–53.
36 Lacormis D. Small-fiber neuropathy. Muscle Nerve 2002;26:173–88.
37 Polydefkis M, Allen RP, Hauer P, Earley CJ, Griffin JW, McArthur JC. Subclinical sensory neuropathy in late-onset restless legs syndrome. Neurology 2000;55:1115–21.