

Persistent Genital Arousal Disorder in 18 Dutch Women: Part II—A Syndrome Clustered with Restless Legs and Overactive Bladder

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DOI: 10.1111/j.1743-6109.2008.01114.x

ABSTRACT

Introduction. A systematic study in women with persistent genital arousal disorder (PGAD) is urgently needed to develop its clinical management.

Aim. To investigate the features, possible causes, and treatment of PGAD.

Methods. Eighteen women who fulfilled the five criteria for PGAD were included in the study. In-depth interviews were combined with laboratory and imaging studies as reported in Part I of the study. Clinical responses were observed with drugs exerting activity against a number of different neuro-regulatory mechanisms.

Main Outcome Measures. Detailed descriptions and clustering of some well established clinical syndromes.

Results. The majority of women experienced PGAD during early menopause without pre-existing psychiatric disorders and laboratory abnormalities. Most women had difficulties in describing the quality of the genital sensations. These were described in various terms and were diagnosed as dysesthesias and paresthesias. Their intensity was most severe during sitting. A few women reported PGAD during pregnancy and premenstrual. The majority of women also reported preexistent or coexistent restless legs syndrome (RLS) and overactive bladder syndrome (OBS). These strongly associated morbidities point into the direction of a clinical cluster, which harbors PGAD or PGAD plus these typical other disorders. Notably, as in RLS and OBS, it appeared that daily treatment with clonazepam 0.5–1.5 mg was effective in 56% of PGAD women. Also, oxazepam 10 mg and tramadol 50 mg elicited PGAD-reducing effect.

Conclusions. PGAD seems to belong to a highly associated disease cluster including morbidities, which share an imperative urge to suppress dysesthesias and paresthesias by firm manipulative actions. PGAD—or as proposed by our group, restless genital syndrome (RGS) in the context of its strong association with restless legs—is probably the expression of a nonsexually driven hyperexcitability of the genitals and subsequent attempts to overcome it by genital manipulations. **Waldinger MD, and Schweitzer DH. Persistent genital arousal disorder in 18 dutch women: Part II—A syndrome clustered with restless legs and overactive bladder. J Sex Med **;**:**_**.**

Key Words. PGAD; PSAS; RLS; OBS; restless genital syndrome

Introduction

Persistent sexual arousal syndrome (PSAS) [1] or persistent genital arousal disorder (PGAD) [2] was for the first time described in 2001 by Leiblum and Nathan [1] and has officially been defined in terms of five diagnostic criteria in 2003 [3]. The syndrome is characterized by unwanted

and distressing genital sensations that persist for long time periods without concurrent sexual desire or fantasies [3]. These genital sensations do not resolve with one or multiple orgasms [1,3]. Since 2001, several case reports [1,4–13], Internet surveys [14–17], review articles [18–20], and letters [21–24] have been published speculating about the etiology and pathogenesis of this syndrome. In

Part I of the current article [25], we have reported the results of electroencephalography (EEG), brain and pelvic magnetic resonance imaging (MRI), and transvaginal ultrasonography (TVUS) obtained from 18 Dutch women in whom PGAD was diagnosed according to the five diagnostic criteria. None of these imaging techniques revealed specific abnormalities, apart from an aneurysm in the frontal lobe in one woman and pelvic varices in more than half of the investigated group (55%) [25]. The current observation study comprised the same women and focused specifically at common clinical features and remarkable treatment experiences. The collected clinical data have finally led to speculation about pathogenesis and treatment strategies in women suffering from PGAD.

Materials and Methods

The current study reports on 18 women (with complaints of persistent unwanted feelings of genital arousal) who visited the Outpatient Department of Neurosexology of the HagaHospital Leyenburg, the Hague in the Netherlands between October 2004 and July 2008, and were diagnosed with PGAD according to the five established criteria and then provided written informed consent for publication of their data. The women were not actively recruited but were either referred by their general physician, gynecologist, sexologist, or contacted the first author after Internet information on the PGAD 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 experimental drugs were not taken. All patients were investigated by the first author following a standard procedure. After a neuropsychiatric and medical sexological interview of about 1 hour, women who were clinically diagnosed as having PGAD underwent routine and hormonal laboratory testing, an MRI examination of the brain and pelvis, an EEG, and a TVUS in case MRI was suggestive for pelvic abnormalities (See Part I). In addition to frequent visits at the outpatient clinic, all women were allowed to make telephone calls with the first author to discuss their experiences and worries. During these sessions and during the years of treatment, patients and their partners were extensively interviewed. The women were requested to report every detail of their experiences with PGAD. In addition, women, often in the presence of their partners,

were counselled or, on indication, required brief supportive psychotherapy by the first author, particularly in periods of increased distress related to PGAD. Cognitive behavioral therapy was not employed in the standard procedure and was not applied to the patients as most experienced confusion in periods of severe PGAD to correctly follow instructions associated with this kind of therapy. However, all reacted positively to a supportive and empathetic approach from the psychiatrist. In an attempt to further understand PGAD, additional blood samples were taken and, on indication, various drugs were prescribed to ameliorate symptoms. PGAD was defined according to the five diagnostic criteria developed by the international panel of experts in 2003 [3]: (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 [1]. Menopause was defined as the absence of menses for 12 months after the last menstruation. Routine blood chemistry and endocrine assessments were undertaken at the first visit and additional blood iron status was sampled during the study period (See Part I).

Statistics

Descriptive statistics were computed for the measures used in the analyses of the baseline characteristics, and are reported as mean \pm standard deviation. Two-tailed *t*-tests were performed on comparison of prevalence rates among studies.

Results

The characteristics of 18 women, diagnosed with PGAD, are shown in Table 1. At presentation, women were on average (mean \pm SD), 53.7 ± 9.7 years (median 55 years, range 30–70 years). Of all women with PGAD, 15 (83%) had a relationship with a male partner. Of them, 12 (80%) were married. The mean \pm SD duration of relationships was 24.7 ± 15.1 years. Of all women, 12 (67%) were menopausal, which occurred at the mean \pm SD age of 49.1 ± 3.9 years (median 50 years). Apart from the complaints of PGAD, all women were in good physical health. The genital symptoms started at the mean \pm SD age of 49.5 ± 11.8 years (median 50 years). Of the 12 menopausal women, the mean \pm SD age was $58.9 (5.7)$ years (median 58.5 years). In these women,

Table 1 Patient characteristics

Patient no.	Age of patient (year)	Marital status at intake	Age of partner (year)	Relationship (year)	Child	Education	Illnesses	The pill (age)	Psychiatric disorder before onset PGAD	SSRIs treatment	Sexual abuse	Orgasm	Coitus frequency
1	70	Married	76	50	2	LGSE	—	—	—	—	—	Clitoral	1 per 2 weeks
2	68	Partner	77	20	2	LVE	—	30–31	—	Sertraline (intake after start of PGAD)	—	Clitoral	—
3	61	Married	61	40	1	LGSE	UE	19–21	—	—	—	Clitoral	—
4	61	—	—	—	—	IVE	UE	—	—	—	—	Vaginal	—
5	59	Married	60	38	2	IVE	—	20–22	—	—	Yes	Vaginal	2 per week
6	60	Married	60	41	2	LGSE	—	20–51	—	—	—	Clitoral	2 per week
7	58	Married	63	35	3	IVE	UE	32–37	—	—	—	Clitoral	—
8	56	Married	56	34	2	IVE	E, PS, RA, MYS	—	—	—	Yes	Clitoral	1 in 4 weeks
9	57	Married	61	3	2	IVE	—	28–30	Depression (age: 53–54)	Citalopram (intake after start of PGAD)	Yes	Clitoral	3 per week
10	54	Married	54	18	—	HGSE	—	18–22	Anorexia nervosa (age: 22–33)	—	—	Clitoral	2 per week
11	54	Married	50	11	2	HGSE	SC	20–46	BOS (age: 49–50)	Paroxetine (intake before start of PGAD)	—	Clitoral	1 per week
12	51	Partner	48	1	—	LGSE	HP	12–16	—	—	—	Vaginal	1 per week
13	52	Divorced	—	—	2	HVE	MS, EG	18–30	Adjustment disorder (age: 48–49)	Citalopram (PGAD during dose reduction)	—	Clitoral	—
14	45	Married	49	27	2	LGSE	—	19–27	—	Nortriptyline (intake after start of PGAD)	—	Clitoral	2 per week
15	46	Partner	34	6	4	HGSE	—	—	Alcohol abuse	Mirtazapine (intake after start of PGAD)	—	Vaginal	—
16	45	Married	45	24	3	HVE	—	21–42	—	Sertraline (intake after start of PGAD)	—	AN	1 per 12 weeks
17	43	Married	50	24	2	IVE	BS	16–24	—	—	—	Clitoral	1 per 8 weeks
18	30	—	—	—	1	LVE	—	—	—	—	—	Clitoral	—

PGAD = persistent genital arousal disorder; SSRI = selective serotonin reuptake inhibitors; E = epilepsy; RA = rheuma; UE = uterus extirpation; EG = extrauterine gravidity; HP = hypoparathyroidism; BS = bladder surgery; SC = sectio caesaria; MS = meningioma surgery; MYS = myoma surgery; PS = prolaps surgery; LVE = lower vocational education; IVE = intermediate vocational education; HVE = higher vocational education; LGSE = lower general secondary education; HGSE = higher general secondary education; AN = anorgasmia; BOS = burned out syndrome.

PGAD started at 55.3 ± 6.6 years (median 53 years). PGAD started in the same year or within 4 years after the onset of menopause in 7 (58%) women. In another 5 (42%) women, PGAD started between 5 and 21 years after the onset of menopause. The mean \pm SD age of the six non-menopausal women was 43.3 ± 7.1 years (median 54 years). In the latter women, PGAD started at 37.8 ± 11.4 years (median 50 years). Of all women, 2 (11%), 6 (33%), and 2 (11%) had lower, intermediate, and higher vocational education; 5 (28%) and 3 (17%) had lower and higher general secondary education, respectively. The unwanted genital sensations were experienced at the clitoris, vagina, and labia in 14 (78%), 10 (55%), and 5 (28%) women, respectively; 8 (44%) women reported a combination of these localizations. One woman (5%) reported the sensations behind the pubic bone, and 2 women (11%) in the region of the groins. All women experienced symptoms continuously during the day in severe to very severe degrees, which varied over time. In 15 (83%) women, the sensations were expressed as an imminent orgasm, persistently remaining on the verge of an orgasm without completion, i.e., without the pleasurable feeling of an orgasm. Although the majority did not report any previous psychiatric disorders, a previous single depressive disorder, anorexia nervosa at a young age, a burned out syndrome (e.g., long-term exhaustion and diminished interest as a result of continuous overload of work), an adjustment disorder related to a meningioma, and periods of alcohol abuse during psychosocial stress were separately reported by 5 (28%) women. Moreover, 3 (17%) women reported sexual abuse at a young age. None of these women associated PGAD with their history of sexual abuse. A total of 7 (39%) women reported previous treatments against PGAD, none of which were considered successful. Previous psychotherapy, pelvic floor exercises, and drug treatment with cyproterone acetate were reported by 3 (17%) women in each category. Of all women, 16 (89%) had not used antidepressants before the onset of their PGAD problem; 5 (28%) women were treated with antidepressants by the general practitioner to suppress PGAD symptoms and/or associated depressive feelings. Out of the 2 (11%) women who were taking selective serotonin reuptake inhibitors (SSRIs) before the onset of PGAD, there was 1 subject who developed PGAD shortly after SSRI cessation. One woman reported the first "attack" of PGAD, lasting about 4 hours, after having smoked marijuana for the first time.

Another woman experienced the first sensations of PGAD during withdrawal of legal medical use of marijuana against hypoparathyroidism. Of all women, 13 (72%) and 4 (22%) subjects reported they were able to achieve an orgasm by clitoral and penile–vaginal stimulation, respectively. One woman reported to be anorgasmic. Of all women, 11 (61%) subjects had regular intercourse with their male partner.

All women experienced the symptoms continuously during the day in severe to very severe degrees, which varied in the course of weeks and months. The quality of the genital sensations was expressed in various terms (Table 2). Most women reported difficulties in finding the right words to express the quality of these sensations; nonetheless, in 15 (83%) women, the sensations were expressed as an imminent orgasm, persistently remaining on the verge of an orgasm without completion, i.e., without the pleasurable feeling of an orgasm. Acute exacerbation of existing genital sensations was reported by 14 (78%) women; in these women, the triggers for exacerbation were: tension (71%), being acutely frightened (36%), anger (21%), acute anxiety (14%), annoyance (14%), and acute stress (14%). Moreover, in two women, PGAD was triggered by the use of alcohol, particularly red wine.

Increased urgency for micturition was reported by 12 (67%) of the patients (Table 3). Decreased PGAD sensations after micturition, though only briefly, were reported by 12 (67%) subjects, some of which had no urgency. Conversely, 9 (50%) subjects reported undesired urethral excitabilities either after voiding or during PGAD. Of all women, 12 (67%) subjects reported that PGAD-related orgasms were more intense compared with any orgasm induced by sexual and non-PGAD-related sensations. Notably, the majority of women, i.e., 11 (61%) subjects, preferred having sex without the intensity of PGAD-related orgasm.

Elaborate and detailed interviewing indicated that the occurrence of PGAD genital sensations is related to body movements (Table 4). For example, sitting down aggravated the PGAD complaints in 13 (72%) women. Some body attitudes induced opposite effects in different individuals like lying stretched (no or less effect in 67%), walking (no or less effect in 72%), or standing (no or less effect in 83%), whereas lying, walking, and standing aggravated PGAD symptoms in 33%, 28% and 17%, respectively. In 61% of the women, PGAD symptoms were present both at day- and

Table 2 PGAD characteristics

Patient no.	Age (year)	Age of menopause	Age of PGAD onset	Duration of PGAD (year)	Localization PGAD	Quality of genital sensations	Triggers for acute onset PGAD	Previous PGAD treatments
1	70	53	67	3	Clitoris	IO, itching	Frightened, tension	—
2	68	48	68	0.5	Clitoris	IO, throbbing	Tension	—
3	61	50	57	4	Clitoris, Vagina	IO, itching	Alcohol (wine)	Cyproterone
4	61	50	50	11	Vagina, labia (left)	Tingling	Tension	Psychother, PME, PT
5	59	38	59	0.2	Vagina	IO	—	—
6	60	50	50	10	Clitoris, Vagina	IO, tingling, throbbing	—	PME
7	58	52	57	0.3	Clitoris	IO	Alcohol (wine)	—
8	56	50	54	1.5	Clitoris	IO	Stress	—
9	57	50	52	5	Clitoris, vagina, labia	IO, vibrations, tingling	Frightened, tension, anger	Psychother, cyproterone, haptonomy
10	54	52	52	2	Clitoris, vagina, groin	IO	Anger, anxiety, tension	—
11	54	—	50	1.5	Clitoris	IO	Frightened, anger, tension	—
12	51	50	48	3	Clitoris, vagina, labia, groin	Cramps	Tension, annoyance, fatigue,	Diazepam
13	52	46	50	2	Clitoris, vagina, labia	IO	—	—
14	45	—	44	0.6	Clitoris	IO, burning	Stress, anxiety, frightened	—
15	46	—	20	26	Clitoris, vagina, labia	Electric explosions	Tension	Psychother, cyproterone, acupuncture
16	45	—	42	3	Clitoris	IO	Tension, annoyance	PME
17	43	—	43	0.2	Os pubis	IO, spasm, burning	Tension, frightened	—
18	30	—	28	2	Vagina	IO, electric pulses	—	—

PGAD = persistent genital arousal disorder; IO = imminent orgasm; PME = pelvic floor muscle exercise; PT = psychotherapy.

Table 3 Persistent genital arousal disorder (PGAD) and overactive bladder syndrome characteristics

Patient no.	Age (year)	Age of menopause	Age of PGAD onset	PGAD after voiding	Urethra sexual sensitive	Quality PGAD orgasm	Orgasm preference	Urge for micturition
1	70	53	67	No	Yes	—	—	Frequent
2	68	48	68	Worse	Yes	More intense, explosive	Non-PGAD	—
3	61	50	57	Less	Yes	More intense	Non-PGAD	Frequent
4	61	50	50	Less	No	—	—	Frequent
5	59	38	59	No	No	—	—	—
6	60	50	50	No	Yes	More intense	Non-PGAD	Frequent
7	58	52	57	Less	Yes	More intense	Non-PGAD	Frequent
8	56	44	54	Less	No	—	—	Frequent
9	57	50	52	Less	No	More intense	Non-PGAD	Frequent
10	54	52	52	Less	Yes	More intense	Non-PGAD	Frequent
11	54	—	50	Less	No	More intense, explosive	Non-PGAD	—
12	51	50	48	Less	No	More intense	PGAD	Frequent
13	52	46	50	Less	Yes	More intense	PGAD	—
14	45	—	44	Less	Yes	More intense	Non-PGAD	—
15	46	—	42	Worse	No	More intense	—	—
16	45	—	43	Less	Yes	Anorgasmia	—	Frequent
17	43	—	43	Less	Yes	—	Non-PGAD	Frequent
18	30	—	28	No	No	More intense	Non-PGAD	Frequent

Table 4 Persistent genital arousal disorder (PGAD) and movement characteristics

Patient No.	Sitting	Lying	Walking	Standing	Biking	PGAD day and night	PGAD in pregnancy	PGAD premenstrual	Onset PGAD after awakening
1	Less	—	Worse	Worse	—	—	—	—	After 5 minutes
2	—	—	—	—	—	—	—	—	After 1 hour
3	Worse	Less	Less	—	Worse	Yes	—	—	After 5 minutes
4	Worse	Less	—	Worse	Less	Yes	No pregnancy	Yes	After 10 minutes
5	Worse	—	—	—	—	—	—	—	After 15 minutes
6	Worse	Worse	Less	Worse	Less	Yes	—	—	After 2 minutes
7	Worse	Less	Worse	—	Worse	—	—	—	After 30 minutes
8	Worse	Worse	Less	—	Less	Yes	—	—	Immediately
9	Worse	Less	—	—	—	Yes	—	—	After 45 minutes
10	Worse	Worse	Less	Less	Less	Yes	No pregnancy	—	After 20 minutes
11	Worse	Less	Less	Less	Less	—	—	—	After 15 minutes
12	Worse	Less	Less	Less	—	Yes	No pregnancy	Yes	Immediately
13	Worse	—	Worse	—	Worse	Yes	—	—	After 4 hours
14	Worse	Less	Worse	—	Worse	—	—	—	After 15 minutes
15	—	Worse	Worse	—	Worse	Yes	Yes, age 20	Yes	After micturition
16	—	Worse	—	—	—	—	Yes, age 35	Yes	After 30 minutes
17	Worse	Worse	Less	—	—	Yes	—	—	—
18	—	—	—	—	—	Yes	—	—	After 20 minutes

Dashes indicate absence.

nighttime before falling asleep. Out of 15 women with children, 2 (13%) subjects reported that PGAD symptoms had also been present during pregnancy. Of all women, 4 (22%) subjects experienced PGAD symptoms in the second half of the menstrual cycle; 17 (94%) subjects reported waking up in the morning completely without PGAD sensations. Two women experienced activation of PGAD symptoms immediately after waking up, while in majority of the women (15, 83%), some 5–60 minutes after being awakened.

EEG, brain and pelvis MRI, and TVUS data have been published in Part I [25]. Neither EEG nor MRI scans of the brain disclosed specific alterations or abnormalities in line with the aforementioned PGAD-related sensations. In addition, there were also no abnormal routine laboratory findings or hormonal changes in this group of women [25]. However, MRI of the pelvis and additional TVUS disclosed that more than half of the patients (55%) had mild to moderate pelvic varices. Moreover, 39% of the current group of women with PGAD reported to have been known with varices of the legs.

Clustered Clinical Features to PGAD Symptoms

Remarkably, it appeared that 12 (67%) women had experienced restless legs—in one woman, combined with restless arms—in different degrees and frequencies (Table 5a); of these, 6 (50%) subjects reported having experienced restless legs for many years. Moreover, of all 18 women, 7 (39%) subjects reported the onset of restless legs shortly after the onset of PGAD. A few women experienced restless legs precisely when they suffered from PGAD symptoms. Based on the unexpected high prevalence of limb movement disorders, it was decided to determine the iron status in all 18 women. However, none of the women showed specific abnormalities of iron metabolism, as is noted in some patients with restless legs [26].

Table 5b shows the dosages and responses on daily treatment with clonazepam 0.5–1.5 mg. Sixteen (89%) women used clonazepam, while 2 subjects refrained from taking clonazepam because PGAD had completely disappeared (N = 1) or remained at mild intensity (N = 1). Clonazepam was not effective and had only 20% effect in 2 (12%) and 1 (6%) of the women. It ameliorated PGAD symptoms about 60–90% only during an initial period of 2–3 weeks in 4 (25%) women. In another 9 (56%) women, clonazepam persistently alleviated PGAD symptoms. In these women, an

Table 5 (A) Persistent genital arousal disorder (PGAD) and restless legs syndrome characteristics; (B) treatment of PGAD with clonazepam

(A) Restless legs			
Patient No.	Restless legs	Age of onset restless legs (years)	Restless legs in pregnancy
1	Yes	40	—
2	—	—	—
3	Yes	59 (after onset PGAD)	—
4	Yes	25	No pregnancy
5	—	—	—
6	—	—	—
7	Yes	10–58	Yes
8	Yes	30	—
9	Yes	54 (after onset PGAD)	—
10	Yes	53 (after onset PGAD)	No pregnancy
11	Yes	45–48	—
12	Yes	48 (after onset PGAD)	No pregnancy
13	Yes	50 (after onset PGAD)	—
14	—	—	—
15	—	—	—
16	Yes	45 (after onset PGAD)	—
17	—	—	Yes, at age 21
18	Yes	28 (after onset PGAD)	Yes, at age 24

(B) Clonazepam treatment		
Patient No.	Clonazepam dosage	% reduction of PGAD symptoms
1	0.5 mg 1dd	50
2	0.5 mg 2dd	70
3	0.5 mg 1dd	80
4	0.5 mg 2dd	No effect
5	—	*
6	0.5 mg 1dd	20
7	0.5 mg 1dd	No effect
8	0.5 mg 2dd	90
9	0.5 mg 2dd	90 ^{††}
10	0.5 mg 1dd	80%
11	0.5 mg 3dd	50
12	0.5 mg 1dd	60 ^{††}
13	0.5 mg 2dd	70 ^{††}
14	0.5 mg 2dd	70
15	0.5 mg 2dd	90
16	0.5 mg 2dd	90 ^{††}
17	0.5 mg 1dd	80
18	—	*

*Spontaneous recovery or very mild PGAD; ^{††}tachyphylaxis.

estimated 50, 70, 80, and 90% reduction of symptoms were reported in 2 (12%), 2 (12%), 3 (19%), and 2 (12%) women.

Additional Drug Treatments

Women who did not experience any, or only temporary, effects of clonazepam subsequently agreed to take other potentially effective drugs such as estradiol, pramipexol, tramadol, and oxazepam.

Treatment with Estrogens

Two of the menopausal women accepted hormonal replacement therapy (HRT), but the majority remained reluctant despite unremarkable mammographies.

Estradiol in a dose of 2 mg per day for 1 month ameliorated PGAD sensations in one woman immediately after the first dose, but had no effect in the other subject. Both subjects were against continuous use of HRT because of potential side effects.

Treatment with Pramipexol

The notion that restless legs was present in the majority of women led to the idea to use dopamine agonists. Three women tried pramipexol, 0.125 mg t.i.d., however, without effects but with disturbing side effects that made them stop the medication.

Treatment with Tramadol

Three women who have tried clonazepam, either without amelioration of their PGAD symptoms or with side effects, were offered the on demand use of 50 mg tramadol, a μ -opioid agonist and weak selective serotonin and noradrenaline reuptake inhibitor. Notably, two women reported a significant PGAD reducing effect of 60–100%, which however only lasted some 4 hours in line with tramadol pharmacokinetics, but still sufficiently effective to temporarily restore quality of life.

Treatment with Oxazepam

Three women reported a PGAD reducing effect of oxazepam 10 mg. In one woman in which clonazepam had no or just a little effect, oxazepam was effective in diminishing PGAD sensations.

Discussion

The current study has shown a much higher prevalence of restless legs (67%), symptoms of overactive bladder (67%), varices of the pelvis (55%), and varices of the lower limbs (39%) in the group of women with PGAD compared with reported prevalence rates of these disorders in Dutch females [27,28] and females of other countries [29–32] (Table 6). Such large differences are most probably non-coincidence and suggest that these clinical features belong to a clustered disease entity, including PGAD. These observations could explain a common pathogenesis and unify some ideas and findings reported in previous studies.

Genital Dysesthesias and Restless Legs

Originally described as PSAS by Leiblum and Nathan in 2001 [1], it became obvious to call it PGAD [2] because of the genital sensations that occurred irrespective of sexual stimulation and in the absence of sexual desire or fantasies. The

Table 6 Prevalences of RLS, OBS, pelvic varices, and varices of the legs in the current study of women with PGAD in the general female population in the Netherlands and in other countries

Disorder	Prevalence in current PGAD study (%)	Prevalence in the Netherlands (%)	Prevalence in other countries (%)
Restless legs syndrome (RLS)	67	7.7 [27]	3–19 [29]
Overactive bladder syndrome (OBS)	67	15 [28]	17 [30]
Pelvic varices	55	—	9.9 [31]
Varices legs	39	—	32 [32]

PGAD = persistent general arousal disorder.

current findings are in agreement with the “non-sexual” nature of PGAD. For example, nearly all women felt remarkable difficulties in how to precisely describe their genital sensations. These sensations were not a priori expressed in sexual terms. On the contrary, various terms have been used, but overall, one agreed that the genital feelings were mimicking something as a feeling of being on the verge of an orgasm. The PGAD-affected women usually felt an imperative urge to get rid of the genital sensations by self-stimulation or intercourse, but often without success. This raises the question as to whether self-stimulation, intercourse, or orgasms are the required responses to the urge of the genital sensations. To our opinion, the “sexual response” of masturbation- or intercourse-induced orgasm to stop the “non-sexual” genital sensations is inadequate as the genital sensations are basically of a nonsexual nature. Therefore, and for a good understanding of PGAD, one should first of all correctly characterize and classify the genital sensations. These sensations appeared to be dysesthesias and paresthesias, particularly at the clitoris, vagina and labia, but also in the area around the genitals, like the pubic bone and groins. Moreover, these genital dysesthesias and paresthesias were expressed in very similar terms as sensations felt in the so called “restless legs syndrome” (RLS), e.g., uncomfortable feelings deep inside, tingling, ants walking, cramps, creeping sensations, burning feelings, painful spasms, and electric current-like or little explosive sensations. Also, such dysesthesias and paresthesias of the legs are uncomfortable, intrusive, and unwanted [33].

Interestingly, a substantial number of women reported the occurrence of RLS very soon after the start of PGAD—indeed several women were already known to experience RLS prior to the start of PGAD. Most women reported that the PGAD had a tendency to become worse while sitting, which is rather similar to the situation in RLS, e.g., worsening with sitting and improving with forced and firm limb movements. Consistent with the

imperative urge to move the legs for temporary relief of unpleasant sensations in RLS patients, we suggest the imperative urge to “move” and rub the clitoris—sometimes until complete exhaustion—in women with PGAD to be a measure to diminish the genital dysesthesias and paresthesias. However, this “measure” usually only lasts for a very short period and is leading to repeated masturbations and orgasms.

Genital Dysesthesias and Overactive Bladder

In the current study, the majority of women with PGAD reported symptoms of overactive bladder syndrome (OBS) such as urinary urgency and voiding frequency [34], often occurring at the moments of worsened PGAD. Interestingly, one woman reported that her OBS had disappeared and that her PGAD sensations were reduced for about 80%, while taking clonazepam. Furthermore, 67% of women reported PGAD disappearance for a short period after micturition. Interestingly, 50% of the women reported PGAD-like sensations by touching the urethra as if it was the clitoris. Based on the combined occurrence of PGAD and OBS in quite a number of women, it is questioned whether OBS is nothing else but a coincidence or a PGAD-associated dysfunction. This is currently under investigation by our group.

Restless Genital Syndrome

Based on the current study, and by integrating previous case reports on PGAD, we have found clinical evidence for the following hypothesis: PGAD is a clinical symptom complex of genital dysesthesias and paraesthesiae equivalent to leg sensations in RLS, and is called by our group “restless genital syndrome (RGS).” The evidence for our view is based on 16 clinical scientific arguments:

1. The 67% prevalence of RLS in the current group of women with PGAD is much higher than may be expected on the 3–19% prevalence of RLS in the general population [29].

2. RLS was prevalent in 39% of the currently reported group, shortly after the onset of PGAD. Fifty percent sustained a period of RLS prior to PGAD, which suggest that PGAD and the reactivated RLS were linked.
3. Although only 11% of the current group of women reported the onset of PGAD during or after withdrawal of SSRIs, SSRI-induced PGAD has also been reported in a number of previous case reports [11,17,19,21,24]. Similarly, SSRI-treatment or SSRI withdrawal-induced RLS has previously frequently been reported [35–38]. These clinical experiences suggest a common pathway between serotonin metabolism and PGAD, as well as RLS.
4. The character of the genital sensations provokes an imperative urge to “move and rub the clitoris” through masturbation or coitus in order to overrule the disturbing genital sensations. This urge to “move and rub” the genital occurs likewise in RLS as a measure to suppress the unpleasant sensations of the legs [33].
5. The majority of women in our sample had difficulties describing exactly the genital sensations experienced, which is indicative of the presence of dysesthesias and paresthesias. The same holds true in patients with RLS when asked to describe their unpleasant sensations [33].
6. In the women studied, it was found that the PGAD became worse with sitting and alleviated with moving. Similarly, RLS was aggravated by sitting down and only diminished with the movement of the legs [33].
7. A high percentage (39%) of the current group of women had varices of the legs prior to PGAD. It has been reported previously that varices of the legs could provoke RLS [39].
8. More than half of the current group of women (55%) had moderate pelvic varices like a substantial number of patients with RLS have leg varices [39].
9. Both clonazepam and tramadol have been reported to diminish RLS [40,41]. Indeed, in the current study, both drugs were able to diminish PGAD complaints. However, similar to a clinical response in only part of RLS patients who receive these drugs, it has been currently shown that not all women with PGAD experienced an improvement on clonazepam. In addition, the risk of abuse and the danger of addiction to tramadol theoretically limit the clinical use of it in RLS and probably also in PGAD.
10. In the current group, two women reported acute aggravation of PGAD with the use of alcohol, particularly red wine. Alcohol is also notorious in provoking RLS [42].
11. The acute exacerbation of PGAD by sudden anger, fear, annoyance, and stress may be related to activation of the sympathetic nervous system. Similarly, there are indications that the sympathetic nervous system is involved in restless legs [43].
12. PGAD does not stop after one or more orgasms. Similarly, in patients with RLS, relief by leg movements does not persist and elicits the constant urge to continue moving, experienced as restless legs [44].
13. Gynecological examination of the vagina, clitoris, and labia is usually unremarkable. Similarly, in RLS, there are usually no objective abnormalities of the legs [44].
14. Women with PGAD report relief from physical stimulation (rubbing, hot or cold baths) and/or cognitive distraction strategies (hobbies, having a conversation). The same holds true for patients with RLS who frequently report firm movements and rubbing, extremely hot or cold baths, and/or distraction strategies such as hobbies [44].
15. In the current study, a considerable number of women reported varying intensities of PGAD symptoms in the course of weeks and during the day, with some women reporting sudden remissions and aggravations lasting for many weeks or months. This periodicity of sensory symptoms is rather similar to the periodicity of sensory symptoms in patients with RLS [33]. The severity of RLS can also vary greatly over time. Symptom occurrence may range from present several times a day to being almost totally absent. The sudden remission from restless legs, lasting for months or even years, is as difficult to explain as the relapses which appear without any apparent reason [33].
16. In the current study, PGAD started after the onset of menopause in the majority of women. However, some individuals had experienced PGAD previously during the first part of pregnancy or in the last week before having a period. Similarly, the prevalence of RLS is higher in women than in men and increases with ageing [33]. The occurrence of PGAD shortly after the onset of menopause could indicate that critical changes of estradiol and progesterone concentrations form a risk factor

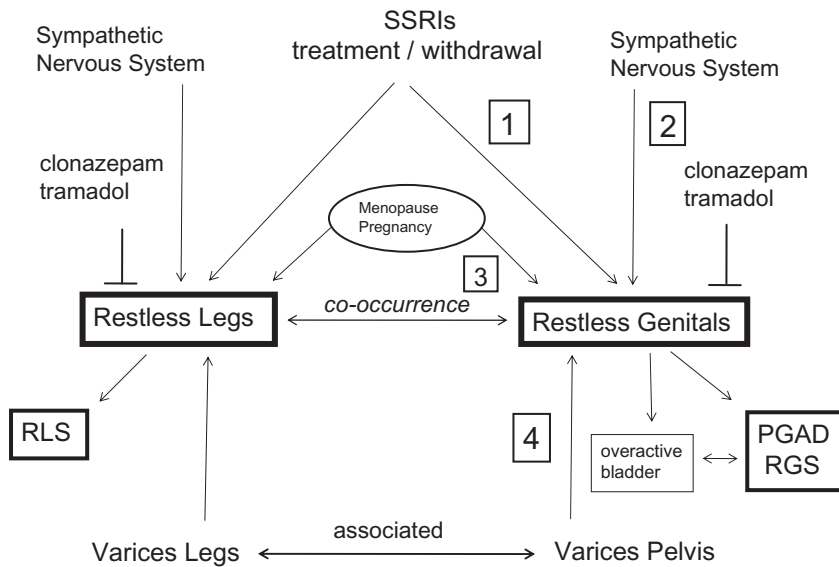


Figure 1 Association of restless genital syndrome (RGS) with restless legs syndrome (RLS) and overactive bladder syndrome. Analogous to RLS, it is suggested to use the name RGS for persistent genital arousal syndrome (PGAD). Similar to RLS, RGS may be induced by psychopharmacological (1), neurological (2), endocrinological (3), and vascular (4) pathways. Both RLS and RGS may be induced by varices, have an increased prevalence during menopause, may be induced by treatment or withdrawal from selective serotonin reuptake inhibitors (SSRIs), and are influenced by the sympathetic nervous system. Both RLS and RGS may respond to treatment with clonazepam and tramadol.

in the development of PGAD. The premenstrual occurrence of PGAD has previously also been reported in a case report of Riley [4].

After assessing all the clinical evidence, we speculate that PGAD and RLS belong together in a clinical cluster, further illustrated in Figure 1. In this respect, and based on the aforementioned scientific arguments, we find it more appropriate to use the term “RGS” rather than PGAD. Our view does not contradict previous case reports on PGAD. On the contrary, our view incorporates that not only SSRIs [17,19,21,24] but also serotonin and norepinephrine reuptake inhibitor (SNRI) [11] may induce PGAD, that activation of the sympathetic system is involved in PGAD [16], and that pelvic varices may induce PGAD [12], as has previously been reported by other authors. Based on the clinical similarities between the syndromes PGAD and RLS, it appears that RGS is nothing else but a physical disorder felt at the clitoral region whereas RLS comprises the same dysfunction but is confined to the limbs, commonly the legs and sometimes also the arms. Anatomical and structural tissue changes, or pathological lesions are rarely found in either syndrome. Both previous studies and the current study show evidence that PGAD may be caused by psychopharmacological, neurological, vascular, and endocrine disturbances. However, it should be noted that PGAD may manifest itself as a “functional” physical disorder, meaning that in the absence of anatomical lesions, only the function of the genitals is disturbed (for example, in SSRI-

induced, menopause- or pregnancy-induced PGAD). However, PGAD may also be the manifestation of anatomical lesions of neurological (for example, the brain, brainstem, spinal cord, and peripheral nerves) and vascular pathways (for example, pelvic varices), which contact female genital region. The current study has shown that some of the aforementioned changes may evoke PGAD and RLS but, remarkably, also OBS.

All these types of clinical entities may react to drugs that are commonly used in RLS. The involvement of several neurological, psychopharmacological, vascular, and endocrine disorders in PGAD has previously been noted by Goldstein and Johnson [7]. In addition, several cases of SSRI-induced or SSRI withdrawal-induced PGAD have also been previously reported by Leiblum and Goldmeier [17]. A case of SNRI-induced PGAD has been reported previously by Mahoney and Zarate [11]. Premenstrual-induced PGAD was reported by Riley [4], and OBS was seen in a case report by Thorne and Stuckey [12]. Our finding of clustering of PGAD and RLS may shed some light over a case reported by Wylie et al. [8] discussing a menopausal woman who experienced PGAD while falling asleep, and who felt an imperative urge to walk around her house to reduce the PGAD symptoms.

Mental and Psychosocial State

Recently, Leiblum and Chivers [20] have postulated a psychological model on PGAD. These investigators presumed the existence of a vicious

circle starting with undesired genital sensations, which provoke anxiety with associated “uptuning” of the sympathetic nervous system. This increased physiological state of arousal augments the cognitive attention to genital sensations even further and could serve to maintain and even intensify unwanted genital responding [16]. Leiblum and Chivers presumed, and actually also found a higher incidence of anxiety disorder and obsessive compulsive disorder (OCD) prior to the onset of PGAD in an Internet survey of women who reported to suffer from PGAD, and who were distressed about it and could not cope with it [20]. Consequently, it is argued that interventions aimed at distracting attention from one’s genital state, restructuring interpretations of genital response, and reducing overall anxiety may prove useful in reducing PGAD complaints [20]. In the current study, most subjects were menopausal and the onset of PGAD started some time after menopause. Although a few women reported some appreciation for the suddenly started genital sensations during the initial 1–2 weeks, all women became aversive and even frightened within 3–4 weeks as soon as they realized that these new sensations remained permanent. In contrast to descriptions made by Leiblum and Chivers, most women studied here did not get anxious because of genital sensations, but because of the extreme intensity and continuous persistency, and particularly by the idea that these persistent sensations may stay for the rest of their life. It was particularly this idea that made some of these women completely desperate. Also in contrast to the studied women by Leiblum and Chivers, none of the currently investigated women were previously known or had been treated for anxiety disorder or OCD. Only one woman had sustained a depressive disorder. Notably, three women (17%) reported childhood sexual abuse in the current group, while its prevalence is 33% in Dutch women of 20–40 years [45], and while it has been reported as 32 and 22.7% in two studies conducted among female patients of two academic pelvic floor clinics in the Netherlands [46,47]. Finally, a prevalence of 17% as currently found is far more in line with the measured prevalence of 15.4% in Dutch gynecological patients with benign pathologies [48]. Besides this, none of the three sexually abused women in the current study felt associations of their PGAD symptoms with prior childhood abuse. Therefore, the current study does not provide evidence that sexual abuse is related to PGAD.

In contrast to the absence of previous mental disorders in the study group, after the onset of

PGAD, nearly all women experienced long periods of depressive feelings and sometimes even suicidal thoughts. All subjects studied were consecutively investigated by one psychiatrist (the first author) according to accepted clinical standards. Dedicated protocols, including questionnaires on depression, have not been used. Out of despair, 4 (22%) women also temporarily insisted on clitoridectomy, some of which were difficult to persuade to remain calm and to accept that such a radical approach would not do any good to them. The majority of women were forced to adjust their personal life to PGAD, which resulted in different degrees of social isolation, loss of contacts with friends and family, and sometimes unemployment. Social isolation was not only because of feelings of embarrassment but was also caused by practical factors, like masturbating, in an attempt to alleviate PGAD symptoms. Clearly, masturbation sessions to suppress symptoms were nearly only possible at home. Counseling and/or brief supportive psychotherapy were provided to nearly all women, except one individual who reported spontaneous disappearance of PGAD symptoms some weeks after her first visit to the outpatient clinic. Some women developed their own strategy to cope with the genital symptoms, for example by forced thought distraction, which has also been suggested by Leiblum and Chivers [20] and Hiller and Hekster [49]. This change of mindset was generally regarded as successful in fighting PGAD but never resulted in a complete disappearance or solid remission. The majority of male partners showed a deep feeling of understanding and decided to adjust their sexual life to the new situation. Moreover, a considerable number of women reported feelings of guilt for their negatively altered sexual behavior that affected the sexual life of their male partners. With time, nearly all couples were able to solve these difficulties by themselves. Only occasionally, some marital counseling by the first author was required to help some couples in finding solutions. Most women even reported to have a happy or very happy relationship with their partner.

Role of the Sympathetic Nervous System in a Clinical Cluster (OBS, RLS, PGAD)

Based on current findings, one could speculate about the central role of the sympathetic nervous system in linking PGAD symptoms to OBS. Women reported that any type of sudden onset of negative arousal (sudden fear, anxiety, annoyance, anger, or even PGAD thoughts) may not only

trigger genital sensations but also micturition urgency. It has been shown previously that genital arousal as well as micturition frequency is mediated by sympathetic activation [50–52] in which the annoying urgency to void in OBS bears remarkable resemblance with the annoying urgency to move the legs in RLS and the annoying urgency to move and rub the clitoris in PGAD.

Role of Sex Steroids in a Clinical Cluster (OBS, RLS, PGAD)

A rather high incidence of PGAD, which usually occurs either shortly after menopause, premenstrually, or during pregnancy, may suggest a putative role for sex steroids. Possibly, any rapid fall or critical swing of estrogen and/or progesterone levels may provoke any type of clustered combination of the abovementioned clinical entities.

Role of Receptors in a Clinical Cluster (OBS, RLS, PGAD)

The current finding of a suppressive effect of some benzodiazepines, i.e., clonazepam and oxazepam points into the direction of a pathogenic role of γ -aminobutyric acid-A (GABA-A) receptors. It is questioned whether central or peripheral receptor agonism or perhaps a combination of both receptors is involved. The existing literature considers γ -aminobutyric acid (GABA) receptors discovered in the vaginal wall of female rats [53] as well as involvement of central GABA-A receptors arguing that benzodiazepines can alleviate PGAD, RLS, and OBS in some women. OBS in some animal models is caused by the interruption of tonic GABAergic inhibitory pathways of the pontine micturition center (PMC), thereby activating N-methyl-D-aspartate (NMDA) receptors in PMC [54]. These NMDA receptors are involved in the facilitation of micturition [54]. In addition, GABAergic mechanisms are also involved in urethral function via effects on motor neurons to the urethral sphincter [55]. Involvement of these receptor sites may explain the effect of benzodiazepines on urethral sensitivity in women with PGAD. As PGAD often occurs directly at the onset of menopause with clear effects of clonazepam, a GABA-A receptor agonist, it seems that critical changes of estradiol levels could inhibit GABA-A receptor-induced inhibition of PGAD. It may well be that the excitability of the female genital region, e.g., the clitoris, vagina, and labia, becomes upregulated by tonic, inhibitory GABAergic signaling or reduced GABA-A receptor functioning. These speculations are confirmed

with data showing that estrogens maintain GABA-A receptor agonistic activity [56]. In case of relevant genital GABAergic modulation from supra- as well as spinal pathways, it is very thinkable that any type of lesions at both levels could lead to PGAD. Based on the efficacy of GABA-A receptor agonist clonazepam and the μ -opioid agonist tramadol to evoke downtuning of the sensitivity of the female genitals, it is hypothesized that the excitability of the female genital region is in part regulated by GABA-A receptors and μ -opioid receptors. In case of inhibitory GABAergic or μ -opioid receptor failure of any reason (e.g., critical fall of estrogens, spinal or supraspinal lesions, sudden arousal that drives the sympathetic nervous system), female genitals may become hypersensitive, resulting in a lower threshold for triggering sensations of imminent orgasm. Regarding the many similar biological and clinical similarities of PGAD and RLS, it is noteworthy to mention that studies on treatment effects in RLS disclose inhibited activity of the GABA and opiate neurotransmitter systems and/or enhancement of the adrenergic system and sympathicotonus [57]. Moreover, studies in RLS patients have confirmed that μ receptor (partial) agonists are effective in relieving RLS [58]. Clearly, possible effects of estrogen replacement therapy and many other drugs deserve careful evaluation in future studies. The current study reported PGAD induction by taking marijuana (immediately after cannabis in one woman and during cannabis withdrawal in another woman). To our knowledge there has not been any report over cannabis use and RLS and/or PGAD. We speculate that cannabis may alter neurotransmission (GABA, dopamine, noradrenaline, serotonin) by influencing the endocannabinoid system of the brain [59].

The current study has several limitations. The number of women being investigated is rather small, albeit still the largest clinical study that ever has been published on PGAD. The selected women met all five criteria needed to establish the PGAD diagnosis. Re-analysis of all 22 previously published clinical case reports between 2001 and 2008 [1,4–13] disclosed a similar age of (mean \pm SD) 50.0 \pm 14.0 years (median: 49.5/range: 29–81 years), which is not different from that of the current study, e.g., 53.7 \pm 9.7 years (mean \pm SD) (median 55.0/range: 30–70 years). Besides the current study and 22 case reports, another three Internet surveys were conducted among women with PGAD. The women investigated in two surveys were statistically significantly

younger, e.g., 38.9 ± 13.8 years (range 15–82 years) [14] and 38 ± 12.5 years [15] ($P < 0.05$). In the third survey, the mean age of 42 years [16] was also much lower, but as SD in this survey was not reported, a statistical comparison with our outcome data and that of the 22 case reports, was not possible. Obviously, the anonymous character of Internet surveys raises questions about some critical characteristics of participants, a potential confounder recognized indeed by the investigators. Indeed, one of the remarkable differences between these surveys and the currently investigated women was the high prevalence of depression, anxiety disorders, OCD, and sexual abuse in these surveys. The different prevalence of psychiatric illness may be explained by the number of women on SSRIs. These drugs are known to initialize PGAD from the first time of drug use and immediately after cessation. In case of Internet surveys conducted among many SSRI users, it is obvious that more psychopathologies will be found. This is supported by the current study showing a very low percentage of SSRI users prior to PGAD, no history of depression, anxiety disorders, or OCD prior to the onset of PGAD, but one woman who had depression indeed, and a low prevalence of childhood abuse.

It is critical to note that besides PGAD, there were specific overlapping clinical syndromes, which were (partly) clustered (e.g., RLS and OBS), and coincided with a high prevalence of pelvic and lower limb varices. We presume, therefore, a spectrum of clustered “restless features” that range from isolated syndromes, including PGAD, to more complex clinical manifestations with either one or both comorbidities (RLS and OBS). Obviously, this theory should be evaluated by future research. It should be emphasized that our study does not suggest that PGAD is always co-concurrent with RLS or OBS. On the contrary, PGAD also occurs as an isolated entity. In its isolated form, as well as combined with RLS and OBS, genital area sensations begin with genital dysesthesias and paresthesias. Such occurrence had been expressed, explicitly, by the women included in the study. The occurrence of a single syndrome in the absence of other associated symptomatology is well known in clinical medicine. For example, neurologists often report patients who suffer from diabetic polyneuropathies without symptoms of overt diabetes, such as polyuria and polydipsia, and with unseen subtle increases of blood glucose concentrations. Similarly, the sole manifestation of PGAD may be part of highly

subtle background symptoms of RLS and/or OBS. These are strong implications of the outcome results of the current study that certainly needs further exploration in larger series. In spite of efficacy of clonazepam and tramadol to ameliorate RLS and PGAD, it may well be that PGAD and RLS differ in sensitivity for various neurotransmitters. Besides, RLS patients do not respond uniformly against the action of one particular drug. Some patients have a positive experience by using pramipexol, a dopamine agonist, while others are more eager to use clonazepam, a GABA-A agonist. In the current study, the effects of pramipexol could not be adequately evaluated as a result of annoying side effects. Whether dopamine agonists should be used against PGAD, either in its isolated form or combined with the other symptomatology, can therefore not be answered yet.

Suggestions for Future Research

As restless legs, urgency, and frequent micturition are commonly not spontaneously reported by patients, and physicians do not usually inquire about varices of the legs during medical interview, the current study highlights the necessity to get informed about these symptoms in women with symptoms of PGAD. In-depth interviews, multidisciplinary physical examinations including laboratory investigations, and high technology imaging remains critical to position any woman who fulfills the five criteria of PGAD into a spectrum of comorbidities. Besides classifying patients, there remains an urgent need for new therapeutic developments. As various drugs, ranging from dopaminergic agonists, anticonvulsants, opioids, and benzodiazepines have been found to exert effects in isolated RLS, systematic research of these drugs not only in women with PGAD but also in any women who fit into the clustered spectrum of comorbidities earlier mentioned, is greatly encouraged. As the chronic use of any single drug may be effective in ameliorating PGAD to levels that are appropriate to (partly) restore quality of life, and realizing the potential danger to tachyphylaxis, different combined or altered drug regimes needs investigation.

Conclusion

In the current study, which is thus far the largest systematic clinical study in women with PGAD, the clinical data provide fundamental information about the variety of the clinical presentations and indicate the existence of a strongly associated

spectrum of morbidities: restless legs syndrome and overactive bladder syndrome. In this respect we favor the term restless genital syndrome as it underlines the various similarities with RLS. Obviously, as the terms PSAS and PGAD have become internationally recognized, it will probably be easier to stick to these terminologies. The idea to treat women with drugs that are effective against RLS and OBS comes from the observation that substantial overlap was observed with morbidities. Indeed, clonazepam seems to be effective in a number of women but there were also some effects from oxazepam, estrogen substitution, and tramadol. These treatment effects suggest a complex pathogenesis and points into the direction of GABA-A, sex steroid, and μ -opioid receptor involvement. In-depth interviews with women excluded pre-morbid existing psychiatric morbidities as well as childhood sexual abuse as key factors, and support the concept of hyper-sympathetic stimulation because of the persistent character of the genital sensations, which reinforces the imperative urge to overrule genital sensations through moving, rubbing, masturbation, and coitus. Secondary effects of a subsequent vicious circle may be anxiety, depression, and occasional suicidal thoughts. It is of note that current data argue against preexistent psychiatric morbidities and argue in favor of morbidities caused by the physically caused genital sensations. In Part I of the current study accompanying this article, we found a high percentage of mild to moderate pelvic varices and varices of the legs. Together with medical histories that were taken, disclosing a high percentage of preexisting restless legs, symptoms of overactive bladder and hypersensitive urethra, there may also be a role for long-lasting clinical or anatomical changes, including longer lasting critical swings of sex steroids. We suspect a number of strongly associated morbidities including PGAD, RLS, and OBS, which are possibly (in part) influenced by undetermined alterations leading to a switch of set point in neurophysiology. More studies are needed to objectify and detect these changes and to study treatment strategies. The role of early interventions seems to be imperative as the nature of these clusters of morbidities, being a vicious circle.

Acknowledgment

The authors would like to thank all women and their partners who have participated in this study for their generous support in times of their extreme personal difficulties.

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Conflict of Interest: None declared.

Statement of Authorship

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References

- Leiblum SR, Nathan SG. Persistent sexual arousal syndrome: A newly discovered pattern of female sexuality. *J Sex Marital Ther* 2001;27:365–80.
- Goldmeier D, Leiblum SR. Persistent genital arousal in women—A new syndrome entity. *Int J STD AIDS* 2006;17:215–6.
- 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.
- Riley A. Premenstrual hypersexuality. *J Sex Marital Ther* 1994;9:87–93.
- Hallam-Jones R, Wylie K. Case report. Traditional dance—A treatment for sexual arousal problems? *Sex Rel Ther* 2001;16:377–80.
- 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.
- 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.
- 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.
- 9 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.
 - 10 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.
 - 11 Mahoney S, Zarate C. Persistent sexual arousal syndrome: A case report and review of the literature. *J Sex Marital Ther* 2007;33:65–71.
 - 12 Thorne C, Stuckey B. Pelvic congestion syndrome presenting as persistent genital arousal: A case report. *J Sex Med* 2008;5:504–8.
 - 13 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.
 - 14 Leiblum S, Brown C, Wan J, Rawlinson L. Persistent sexual arousal syndrome: A descriptive study. *J Sex Med* 2005;2:331–7.
 - 15 Leiblum S, Seehuus M, Brown C. Persistent genital arousal: Disordered or normative aspect of female sexual response? *J Sex Med* 2007;4:680–9.
 - 16 Leiblum S, Seehuus M, Goldmeier D, Brown C. Psychological, medical, and pharmacological correlates of persistent genital arousal disorder. *J Sex Med* 2007;4:1358–66.
 - 17 Leiblum SR, Goldmeier D. Persistent genital arousal disorder in women: Case reports of association with antidepressant usage and withdrawal. *J Sex Marital Ther* 2008;34:150–9.
 - 18 Leiblum S, Nathan S. Persistent sexual arousal syndrome in women: A not uncommon but little recognized complaint. *J Sex Relationship Ther* 2002;17:191–8.
 - 19 Goldmeier D, Leiblum SR. Persistent genital arousal in women—A new syndrome entity. *Int J STD AIDS* 2006;17:215–6.
 - 20 Leiblum SR, Chivers ML. Normal and persistent genital arousal in women: New perspectives. *J Sex Marital Ther* 2007;33:357–73.
 - 21 Freed L. Persistent sexual arousal syndrome (letter). *J Sex Med* 2005;2:743.
 - 22 Low NN, Low RB. Persistent sexual arousal syndrome—A descriptive study (letter). *J Sex Med* 2005;2:744.
 - 23 Leiblum S, Brown C, Wan J. Persistent sexual arousal syndrome—A response (letter). *J Sex Med* 2005;2:745.
 - 24 Goldmeier D, Bell C, Richardson D. Withdrawal of selective serotonin reuptake inhibitors (SSRIs) may cause increased atrial natriuretic peptide (ANP) and persistent sexual arousal in women? *J Sex Med* 2006;3:376.
 - 25 Waldinger MD, van Gils APG, Ottervanger HP, Vandembroucke WVA, Tavy DLJ. Persistent genital arousal disorder in 18 Dutch women: Part I. MRI, EEG and Transvaginal Ultrasonography Investigations. *J Sex Med* 2008 doi: 10.1111/j.1743-6109.2008.01113.x [Epub ahead of print].
 - 26 Connor JR. Pathophysiology or restless legs syndrome: Evidence for iron involvement. *Curr Neurol Neurosci Rep* 2008;8:162–6.
 - 27 Rijsman R, Knuistingh Neven A, Graffelman W, Kemp B, de Weerd A. Epidemiology of restless legs in the Netherlands. *Eur J Neurol* 2004;11:607–11.
 - 28 van der Vaart CH, de Leeuw JRJ, Roovers JPWR, Heintz APM. The effect of urinary incontinence and overactive bladder symptoms on quality of life in young women. *BJU Int* 2002;90:544–9.
 - 29 Garcia-Borreguero D, Egatz R, Winkelmann J, Berger K. Epidemiology of restless legs syndrome: The current status. *Sleep Med Rev* 2006;10:153–67.
 - 30 Milson I, Abrams P, Cardozo L, et al. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU Int* 2001;87:760–6.
 - 31 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.
 - 32 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.
 - 33 Montplaisir J, Nicolas A, Godbout R, Walters A. Restless legs syndrome and periodic limb movement disorder. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 2nd edition. Philadelphia, PA: W.B. Saunders; 2000:742–52.
 - 34 Abrams P, Cardozo L, Fall M, et al. The standardization of terminology in lower urinary tract function: Report from the standardization subcommittee of the international continence society. *Urology* 2003;61:37–49.
 - 35 Bakshi R. Fluoxetine and restless legs syndrome. *J Neurol Sci* 1996;142:151–2.
 - 36 Sanz-Fuentenebro FJ, Huidobro A, Tejadas-Rivas A. Restless legs syndrome and paroxetine. *Acta Psychiatr Scand* 1996;94:482–4.
 - 37 Page RL, Ruscin JM, Bainbridge JL, Brieke AA. Restless legs syndrome induced by escitalopram: Case report and review of the literature. *Pharmacotherapy* 2008;28:271–80.
 - 38 Hargrave R, Beckley DJ. Restless leg syndrome exacerbated by sertraline. *Psychosomatics* 1998;39:177–8.
 - 39 Popkin RJ. Restless legs. *J Am Geriatr Soc* 1963;11:570–3.
 - 40 Peled R, Lavie P. Double-blind evaluation of clonazepam on periodic leg movements in sleep. *J Neurol Neurosurg Psychiatry* 1987;50:1679–81.

- 41 Vetrugno R, La Morgia C, D'Angelo R, Loi D, Provini F, Plazzi G, Montagna P. Augmentation of restless legs syndrome with long-term tramadol treatment. *Mov Disord* 2007;22:424–7.
- 42 Aldrich MS, Shipley JE. Alcohol use and periodic limb movements of sleep. *Alcohol Clin Exp Res* 1993;17:192–6.
- 43 Wagner ML, Walters AS, Coleman RG, Hening WA, Grasing K, Chokroverty S. Randomized, double-blind, placebo-controlled study of clonidine in restless legs syndrome. *Sleep* 1996;19:52–8.
- 44 Allen RP, Earley CJ. Restless legs syndrome: A review of clinical and pathophysiologic features. *J Clin Neurophysiol* 2001;18:128–47.
- 45 Draijer N. Seksuele traumatisering in de jeugd; lange termijn gevolgen van seksueel misbruik van meisjes door verwanten. Amsterdam: Uitgeverij SUA; 1990.
- 46 Elzevier HW, Voorham-van der Zalm PJ, Pelger RCM. How reliable is a self-administered questionnaire in detecting sexual abuse: A retrospective study in patients with pelvic-floor complaints and a review of literature. *J Sex Med* 2007;4:956–63.
- 47 Beck JJH, Elzevier HW, Pelger RCM, Putter H, Voorham-van der Zalm PJ. Multiple pelvic floor complaints are related to sexual abuse history. *J Sex Med* 2008 doi: 10.1111/j.1743-6109.2008.01045.x [Epub ahead of print].
- 48 Van Lankveld JJ, ter Kuile MM, Kenter GG, van Hall EV, Weijnenborg PT. Sexual problems and experiences with sexual and physical violence in gynecological patients. *Ned Tijdschr Geneesk* 1996;140:1903–6.
- 49 Hiller J, Hekster B. Couple therapy and cognitive behavior techniques for persistent sexual arousal syndrome. *Sex Relation Ther* 2007;22:91–6.
- 50 Brotto LA, Gorzalka BB. Genital and subjective sexual arousal in postmenopausal women: Influence of laboratory-induced hyperventilation. *J Sex Marital Ther* 2002;28:39–53.
- 51 Sipski ML, Alexander CJ, Rosen R. Sexual arousal and orgasm in women: Effects of spinal cord injury. *Ann Neurol* 2001;49:35–44.
- 52 Miller J, Hoffman E. The causes and consequences of overactive bladder. *J Womens Health (Larchmt)* 2006;15:251–60.
- 53 Louzan P, Gallardo MG, Tramezzani JH. Gamma-aminobutyric acid in the genital tract of the rat during the oestrous cycle. *J Reprod Fertil* 1986;77:499–504.
- 54 Kontani H, Ueda Y. A method for producing overactive bladder in the rat and investigation of the effects of GABAergic receptor agonists and glutamatergic receptor antagonists on the cystometrogram. *J Urol* 2005;173:1805–11h.
- 55 Blok BFM, de Weerd H, Holstege G. The pontine micturition centre projects to sacral cord GABA immunoreactive neurons in the cat. *Neurosci Lett* 1997;233:109.
- 56 Maggi A, Perez J. Estrogen-induced up-regulation of γ -aminobutyric acid receptors in the CNS of rodents. *J Neurochem* 1986;47:1793–7.
- 57 Walters AS, Hening W. Clinical presentation and neuropharmacology of restless legs syndrome. *Clin Neuropharmacol* 1987;10:225–37.
- 58 Walters AS, Wagner ML, Hening WA, et al. Successful treatment of the idiopathic restless legs syndrome in a randomized double-blind trial of oxycodone versus placebo. *Sleep* 1993;16:327–32.
- 59 Lopez-Moreno JA, Gonzalez-Cuevas G, Moreno G, Navarro M. The pharmacology of the endocannabinoid system: Functional and structural interactions with other neurotransmitter systems and their repercussions in behavioral addiction. *Addict Biol* 2008;13:160–87.