

Stronger Evidence for Small Fiber Sensory Neuropathy in Restless Genital Syndrome: Two Case Reports in Males

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ABSTRACT

Introduction. Restless genital syndrome (ReGS) is characterized by unwanted, unpleasant genital sensations, restless legs, and/or overactive bladder, as well as neuropathy of the dorsal nerve of the clitoris. So far, ReGS has only been reported in females.

Aim. To report the occurrence of ReGS in two males.

Methods. Two males with unwanted genital sensations presented in our clinic. In-depth interview, routine and hormonal investigations, electro-encephalography, magnetic resonance imaging of brain and pelvis, manual examination of the pubic bone, and sensory testing of genital dermatomes were performed. In both males, conventional transcutaneous electrical nerve stimulation was applied bilaterally at the pudendal dermatome.

Main Outcome Measures. Oral report, questionnaire on frequency and intensity of restless genital feelings, restless legs, overactive bladder, and satisfaction with the transcutaneous electrical nerve stimulation (TENS) treatment.

Results. ReGS in a 74-year-old male manifested as unpleasant genital sensations of being on the edge of an orgasm with overactive bladder, in the absence of erection and ejaculation. Genital sensory testing elicited bilateral points of static mechanical hyperesthesia in the pudendal dermatome. Manual examination of the dorsal nerve of the penis (DNP) elicited the genital sensations. TENS application resulted in a 90% reduction of genital sensations and complaints of overactive bladder syndrome (OAB). ReGS in a 38-year-old male manifested as unwanted and unpleasant spontaneous ejaculations and complaints of OAB. Genital sensory testing elicited bilateral points of static mechanical hyperesthesia in the pudendal dermatome. Manual examination of the DNP elicited the genital sensations. TENS application had no effect on genital complaints and complaints of OAB.

Conclusions. ReGS is not a typical female disorder as it also affects males. This notion and the finding of typical sensory abnormalities of the genital end branches of the pudendal nerve in males and females—as previously reported—provides strong evidence for Small Fiber Sensory Neuropathy as a common cause of ReGS. **Waldinger MD, Venema PL, van Gils APG, de Lint GJ, and Schweitzer DH. Stronger evidence for small fiber sensory neuropathy in restless genital syndrome: Two case reports in males. J Sex Med **;***_**.**

Key Words: ReGS; Persistent Sexual Arousal Syndrome; PGAD; Small Fiber Neuropathy; Dorsal Nerve Of The Penis; Spontaneous Ejaculation

Introduction

Persistent Sexual Arousal Syndrome (PSAS) or Persistent Genital Arousal Disorder (PGAD) was, for the first time, reported in the medical

literature in 2001 by Leiblum and Nathan [1,2]. This syndrome has been put in a further clinical context when a combination of PSAS or PGAD with either Restless Legs Syndrome (RLS) and/or Overactive Bladder Syndrome (OAB)

and/or hypersensitivity of the urethra has been called Restless Genital Syndrome (ReGS), as described by Waldinger et al. [3–7]. In two systematic studies [3,5], it was found that ReGS is characterized by unwanted and unpleasant genital sensations, e.g., dysesthesias and/or paresthesias, which are often felt as feelings of an imminent orgasm in the absence of sexual desire or fantasies and/or are often perceived as a sort of “restlessness” in and around the genitals. Moreover, the persistent presence of dysesthesias often results in agitation and restlessness. Rather rarely, ReGS may also give rise to unpleasantly experienced spontaneous orgasms [3–7]. In addition, ReGS usually occurs in perimenopausal and postmenopausal women, but may also affect premenopausal women, for example, premenstrually or temporarily during pregnancy [3–7]. ReGS is highly associated with restless legs and complaints of overactive bladder, aggravates during sitting, and has the clinical characteristics of small fiber sensory neuropathy (SFSN) of the dorsal nerve of the clitoris (DNC) [5]. In the majority of women with ReGS, magnetic resonance imaging (MRI) scans of the pelvis show mild to moderate varices in the vagina, labia minora and/or majora, and uterus [3–7]. ReGS is neither associated with premorbid psychiatric disorders like major depression, anxiety disorders, or obsessive compulsive disorder, nor with previous sexual abuse [3–5]. However, nearly all of the women affected by ReGS report varying degrees of social withdrawal, desperate feelings, dysthymia, agitation, restlessness, depressed mood, and, sometimes, suicidal thoughts [3–7]. It has been postulated that SFSN of the DNC is the key feature of ReGS [5] and may give rise to associated restless legs and complaints of overactive bladder [5]. Preliminary research suggests that transcutaneous electrical nerve stimulation (TENS) in the genital region may lead to a diminishment of symptoms of SFSN [7]. Since its first description in literature, PSAS or PGAD has been considered a typical female sexual disorder [8]. However, and in contrast, although ReGS has so far only been reported in females, it has never been claimed to be a typical female sexual disorder. In the current report of two male patients, it will be argued that ReGS and, therefore, also the typical unwanted genital sensations of PGAD, may also occur in males.

Materials and Methods

We prospectively evaluated two males with complaints of persistent unwanted feelings of genital

restlessness, imminent orgasm, and/or spontaneous ejaculations who visited our Outpatient Department of Neurosexology in The Hague. Both males were not actively recruited but were referred by their general physician and urologist, respectively. 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. Both patients were investigated by the first author, who followed an evaluation procedure according to standard protocol for the diagnosis and treatment of ReGS. After a neuropsychiatric and medical sexological interview of about 1 hour, both males who were clinically diagnosed as having ReGS underwent routine and hormonal laboratory testing, an EEG, an MRI scan examination of the brain and pelvis, and an ultrasound examination of the scrotum.

The diagnosis ReGS was established when the symptoms of the patients fulfilled a number of seven criteria of ReGS being (i) unwanted and unpleasant restless genital feelings in absence of sexual desire or sexual fantasies; and/or (ii) unwanted and unpleasant spontaneous orgasms in absence of sexual desire or sexual fantasies; and/or (iii) complaints of restless legs syndrome; and/or (iv) complaints of overactive bladder syndrome; and/or (v) aggravation of unwanted and unpleasant restless genital feelings by sitting; and (vi) static mechanical hyperesthesia of genital region on sensory testing; and (vii) triggering of unwanted and unpleasant genital sensations by manual examination of the ramus inferior of the pubic bone (RIPB) [7].

The diagnosis restless legs syndrome was established according to the criteria of the International Restless Legs Syndrome Study Group [9].

Physical examination included sensory testing of the genital region and manual examination of the RIPB [5]. This was performed by a urologist (second author) in the presence of the first author and a nurse. The test for tactile sensations of the genital region is designed to analyze static mechanical hyperesthesia using light pressure with a cotton swab at the skin near the vicinity of the genitals, perineum, anal area, groins, and pubic bone [5].

Conventional TENS was applied and explained by a physiotherapist (fourth author), in the presence of the first author and a nurse. The physiotherapist cleaned the skin with alcohol. With a surface electrode (test probe) the skin area at the pubic bone, genital area, and sacral region was investigated for the point at which ReGS symptoms most noticeably diminished after application

of TENS. At this point, a surface electrode (40 × 40 mm: DE-01 van Lent Systems B.V., Oss, the Netherlands) with adhesive gel was placed. A second electrode was placed at the pubic bone at the origin of the penis. Both electrodes were attached to a single channel of an i-Pulz TENS apparatus (Van Lent Systems B.V.) set at a frequency of 110 Hz and a pulse-width of 80 ms, indicating high-frequency TENS or conventional TENS. The intensity of the stimulation was gradually increased to optimize therapy efficacy, thereby avoiding overstimulation. At home, patients could vary the intensity (mA) but not the frequency and pulse width of the electrical current.

The first application of high frequency TENS was a 20-minute trial period in which a beneficial effect of TENS was investigated. In case the patient reported less ReGS sensations, he was instructed in self-administration of the TENS device. Both males were instructed to use TENS at home for 1 hour, seven times per day, spaced at regular intervals of 1 hour. During a 2–4-week period, readjustments of the stimulation variables (frequency and pulse width) were allowed. After this period, the effect of TENS was evaluated for an additional month, and the decision was made whether or not to continue with TENS. Follow-up visits took place at regular intervals.

A questionnaire designed by the first author was used to assess the patient perception of improvement by TENS application. It contained two questions on the severity and frequency of unwanted genital complaints per week, a question to express the severity of unwanted genital complaints on a scale of 0–10, with 0 being “no complaints at all” and 10 being “the worst complaints you can imagine,” and a question to express the intensity of unwanted genital sensations on a visual analog scale on a 10-cm line.

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

Case Report A

Mr. A. is a 74-year-old married man with three children. He was referred to our outpatient department by his general physician. His medical history revealed a laparoscopic radical prostatectomy due to local prostatic carcinoma at the age of 73 years. After surgery, continence remained normal with no problems of micturition, ejaculation disappeared but with intact sensations of orgasm, and previously existing erectile difficulties

became complete. Seven months after prostatectomy, Mr. A began to feel an increased “very unpleasant” sexual urge in his genitals as if he is on the edge of getting an orgasm in the absence of conscious thoughts or fantasies about sex. These genital sensations are experienced as a sort of “restlessness” in the genital area. These sensations were very disturbing and unwanted, making the patient feel upset, irritable, restless, and desperate. Although Mr. A and his wife accepted the loss of erectile function and abstained from sexual activity since prostatectomy, he attempted to masturbate simply to get rid of the genital sensations. However, after masturbation attempts, the unwanted genital sensations typically re-occurred within 15 minutes against his will. The genital sensations got worse when sitting and diminish during walking or lying down. Since the onset of the genital sensations, the patient recorded an increased urgency to void, but only in small amounts. Mr. A did not report restless legs. Since his prostatectomy, Mr. A has developed complete erectile dysfunction and anejaculation. Prior to his prostatectomy, intercourse frequency was once a week with an estimated intravaginal ejaculation latency time (IELT) of about 10 minutes. However, since the onset of the genital feelings, a sensation of orgasm occurs 20–60 seconds after start of masturbation. The weird sensations are described as a type of tingling and are located above the pubic bone, and along the penis or testes. The sensations are triggered by touch of the glans penis along his clothes (allodynia), sitting, and after defecation. His medical history does not reveal prior child abuse, mood or anxiety disorder, obsessive compulsive disorder, or traumatic sexual experiences. Mr. A was not complaining of sensations of heaviness or dragging-like or aching pain within the scrotum. Routine laboratory assessments in our hospital, including thyroid and hormonal screen, were normal, and EEG and MRI scan of the brain showed no abnormalities. Ultrasound examination and an MRI scan of the pelvis showed a varicocele at the inguinal canal bilaterally, but mainly at the left side, and around the spermatic cords. Sensory testing of the genital region elicited a considerable number of points of static mechanical hyperesthesia bilaterally of the pubic bone, and above the penis in the pudendal dermatome (Figure 1A). Manual examination of RIPB and, particularly along the dorsal nerve of the penis (DNP), elicited the sensations of an imminent ejaculation and sensation of restlessness at the previously mentioned trigger points. Mr. A

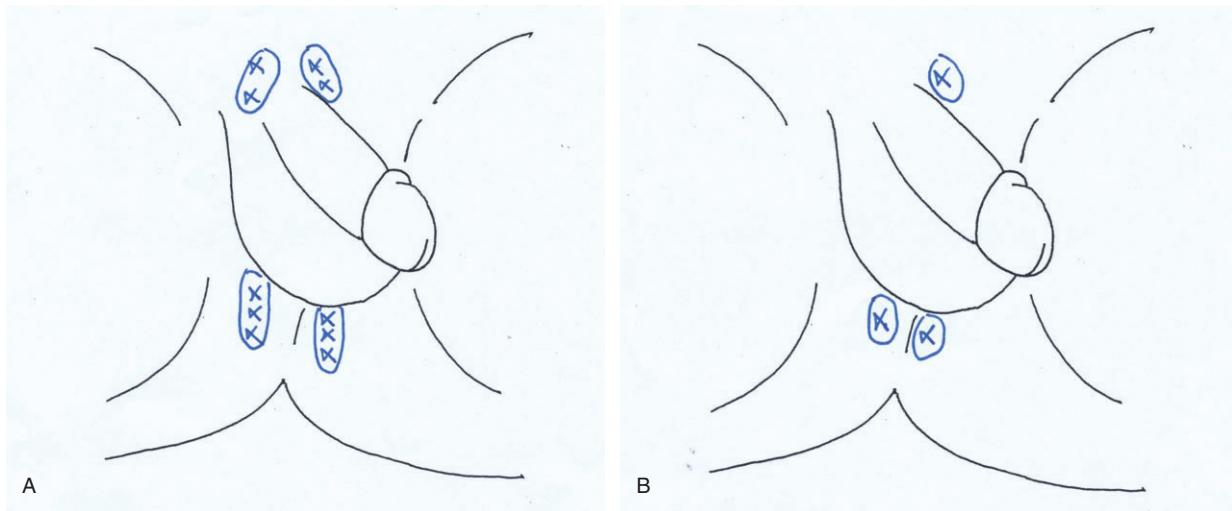


Figure 1 Points of static mechanical hyperesthesia in the pudendal dermatome and triggering points of unwanted genital sensations along the ramus inferior of the pubic bone in Patient A (Figure 1A) and Patient B (Figure 1B).

agreed with treatment with TENS, which he preferred over antiepileptics, antidepressants, or painkillers, including opiates that are often prescribed for neuropathies. Within 1 week, TENS treatment resulted in a clinically very relevant reduction of ReGS sensations of about 90% and disappearance of OAB complaints. Mr. A. reported that the daily and frequent use of TENS was not perceived as bothersome or interfering with his daily activities.

Case Report B

Mr. B. is a 38-year-old married man who has two children. He was referred to our outpatient department by a urologist. Apart from a sterilization at the age of 36, his medical history is unremarkable. Mr. B. reports spontaneous ejaculation that started at the age of 34 years. These spontaneous ejaculations occur when sitting behind his desk at work, during driving a car, or during sports in the absence of sexual arousal or an erection. Since the onset of these spontaneous ejaculations, he feels increased urgency to void but only small amounts. The spontaneous ejaculations occur once to three times a day and are accompanied by an unpleasant genital sensation of restlessness. They are triggered by sitting, defecation, micturition, and a cold environment. Notably, the spontaneous ejaculations are not accompanied by an erection and/or feelings of orgasm. After an ejaculation, feelings of an imminent ejaculation reoccur after 1–1.5 hours. Mr. B. does not report pain or numb feelings in the genital region nor does he

report sensations of restless legs. During sexual activity, he has no erectile difficulties and his sexual desire and ejaculation are without any problems. His medical history does not reveal prior child abuse, mood or anxiety disorder, obsessive compulsive disorder, or traumatic sexual experiences. Cystoscopy and investigations of the prostate and semen performed by the referring urologist were unremarkable. Routine laboratory assessments in our hospital, including thyroid and hormonal screen, were normal. An ECHO of the scrotum, an EEG, and MRI scan of the brain and of the pelvis showed no abnormalities. Sensory testing of the genital region elicited a few points of static mechanical hyperesthesia on the left and right side of the pubic bone and on the left side above the penis in the pudendal dermatome (Figure 1B). Manual examination of RIPB, and particularly along the course of the dorsal nerve of the penis, elicited sensations of an imminent ejaculation at the aforementioned genital points. Mr. B. agreed with treatment with TENS, as multiple drug treatments had no effect. However, TENS treatment did not result in any disappearance of his genital complaints.

Discussion

The reported unwanted, unpleasant restless genital sensations of arousal, feelings of imminent ejaculations, and/or occurrence of spontaneous ejaculations, genital allodynia combined with the finding of hyperesthesia in the dermatome of the

DNP including triggering of the unpleasant genital sensations by manual pressure along the ramus inferior of the pubic bone, are indicative of SFSN of the DNP. As the unwanted genital sensations were aggravated by sitting, and were associated with complaints of overactive bladder, both males were diagnosed as suffering from ReGS. The absence of restless legs in both males does not contradict the diagnosis of ReGS. ReGS is, by definition, a clinical syndrome of dysesthesias in the surrounding of the genitals, which imperatively leads to restless genital sensations. ReGS, according to its definition, is frequently but not obligatory present.

Similar to the DNC, the DNP emerges from the pudendal nerve (PN) approximately 1 cm dorsal to its entrance into the pudendal canal [10]. After leaving the pudendal canal, the DNP runs in the sulcus nervi dorsalis penis (SNDP) at the inferior ramus and anteroinferior surface of body of pubis toward the dorsum penis, where it branches and innervates the penile shaft and glans penis. Similar to the DNC, the DNP is a solely sensory nerve [10].

It is of note that ReGS in the male should be distinguished from the clinical symptoms of entrapment of the DNP under the pubis, in the SNDP or in the pudendal canal, like glans and/or penile insensitivity, genital and/or perineal pain or numbness, and erectile difficulties as can be observed in cyclists [11–13]. These symptoms were not reported nor present in the currently reported patients. Although there are strong indications of SFSN of the DNP, the cause of its occurrence in both males remains unknown. Interestingly, both males experienced either a more rapid sensation of orgasm (case A) or even spontaneous ejaculations (case B). A relationship between the DNP and premature ejaculation has recently been considered in a Chinese study in which men with PE appeared to have more branches of the DNP [14]. However, as the Chinese study did not provide quantitative data of the IELT, it remains questionable whether PE in these men was diagnosed according to the ISSM definition of lifelong PE, in which the IELT is less than or about 1 minute or that these men had complaints of PE while having normal IELT values as has been called premature-like ejaculatory dysfunction by Waldinger et al. [15]. Further systematic medical research in a large cohort of males with ReGS is warranted to elucidate the key characteristics of its symptomatology, and potential risk factors, including hormonal features, of ReGS in the male.

Asymptomatic bilateral varicose veins were found in Mr. A. This finding is interesting, as varicose veins in the vagina and labia have been found previously in the majority of women presenting with ReGS [5]. Whether these genital varicose veins either in women with ReGS as in the presented male is causally related with the symptoms and complaints in ReGS still remains unknown.

In the current study, the use of TENS in one male clinically significantly reduced the symptoms of ReGS, suggesting that in males with ReGS (pre-)ejaculatory feelings of the genital area are mediated by A δ and C-fibers of the DNP and PN and that these fibers are inhibited by A β fibers in the spinal cord, similar as we have previously reported regarding the DNC and PN in females with ReGS [5]. The reason of the inefficacy of TENS in the second male remains unclear. It may be speculated that this is due to a variability of the location of the DNP along the pubic bone in relation to TENS application. Further controlled studies with TENS in larger samples of males with ReGS are warranted. Based on identical clinical data about restless genital sensory neuropathy in both genders, it appears that neuropathy of genital sensory end nerves of the PN is the pathogenesis of ReGS in men and women. Gender-related events (hormonal changes, pregnancy, and delivery trauma), as well as general factors (medical drugs, cessation of smoking, stressors), may trigger symptoms of SFSN of the genital pudendal end branches.

Conclusion

In the current study, two males reported unwanted and unpleasant restless genital complaints and were found to have neurological symptoms of SFSN of the DNP. Based on their complaints and results of neurological genital examination, it was concluded that both males suffered from ReGS. In one male, the use of TENS clinically significantly reduced the symptoms of ReGS. This is the first report of the occurrence of ReGS in males. It indicates that unwanted and unpleasant genital sensations and/or spontaneous ejaculations in the absence of sexual desire and fantasies, as originally described in terms of sexual arousal and orgasm in PSAS and/or PGAD, are not solely confined to females but also to males. Similar to appropriate medical practice in females to examine the DNC dermatome, we advocate to investigate the DNP dermatome in males complaining of unwanted and unpleasant restless genital feelings and/or spontaneous ejaculations.

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