Successful Transcutaneous Electrical Nerve Stimulation in Two Women with Restless Genital Syndrome: The Role of Aδ- and C-Nerve Fibers

Marcel D. Waldinger, MD, PhD,*† Govert J. de Lint, PT,‡ Pieter L. Venema, MD, PhD,§ Ad P.G. van Gils, MD, PhD,¶ and Dave H. Schweitzer, MD, PhD**

*Department of Psychiatry and Neurosexology, HagaHospital Leyenburg, The Hague, the Netherlands; †Department of Psychopharmacology, Utrecht Institute for Pharmaceutical Sciences and Rudolf Magnus Institute for Neurosciences, Utrecht University, Utrecht, the Netherlands; ‡Department of Physiotherapy, HagaHospital Leyenburg, The Hague, the Netherlands; §Outpatient Department of Continence, HagaHospital Leyenburg, The Hague, the Netherlands; ¶Department of Radiology and Nuclear Medicine, HagaHospital Leyenburg, The Hague, the Netherlands; **Department of Internal Medicine and Endocrinology, Reinier de Graaf Groep of Hospitals Delft-Voorburg, the Netherlands

DOI: 10.1111/j.1743-6109.2009.01578.x

ABSTRACT

Introduction. Currently, efficacious treatment of restless genital syndrome (ReGS) is not available.

Aim. This study aimed to report the results of transcutaneous electrical nerve stimulation (TENS) for ReGS, being a combination of genital dysesthesias, imminent and/or spontaneous orgasms, and/or restless legs, and/or overactive bladder.

Methods. Two women with ReGS were referred to our clinic. In-depth interview, routine and hormonal investigations, electroencephalography, magnetic resonance imaging (MRI) of the brain and pelvis, manual examination of the ramus inferior of the pubic bone, and sensory testing of genital dermatomes were performed. Conventional TENS (frequency: 110 Hz; pulse width: 80 milliseconds) was applied bilaterally at the region of the pudendal dermatome in which immediate reduction of genital sensations occurred. Patients were instructed for self-application of TENS each day for 2 months.

Main Outcome Measures. Oral report, questionnaires on frequency of imminent and/or spontaneous orgasms, combined with questions on intensity of restless genital feelings, restless leg syndrome (RLS), overactive bladder syndrome (OAB), and satisfaction with TENS treatment.

Results. ReGS in a 56-year-old woman manifested as multiple spontaneous orgasms, RLS, and OAB. TENS applied to the sacral region resulted in immediate reduction of complaints and a 90% reduction of spontaneous orgasms, RLS, and OAB in 2 months. ReGS in a 61-year-old woman manifested as a continuous restless genital feeling, imminent orgasms, and OAB. TENS applied to the pubic bone resulted in a complete disappearance of restlessness in the genital area as well as OAB complaints in 2 months. Both women reported to be very satisfied and did not want to stop TENS treatment.

Conclusions. Conventional TENS treatment is a promising therapy for ReGS, but further controlled research is warranted. Preorgasmic and orgasmic genital sensations in ReGS are transmitted by Aδ and C fibers and are inhibited by Aβ fibers. A neurological hypothesis on the pathophysiology of ReGS encompassing its clinical symptomatology, TENS, and drug treatment is put forward. **Waldinger MD, Lint GJ, Venema PL, van Gils AP, and Schweitzer DH. Successful transcutaneous electrical nerve stimulation in two women with restless genital syndrome: The role of Aδ- and C-nerve fibers. J Sex Med **;**:**–**.**

Key Words. ReGS; TENS; PGAD; Persistent Sexual Arousal Syndrome; RLS; OAB; Pudendal Neuropathy; Small-Fiber Neuropathy; Dorsal Nerve of the Clitoris

Introduction

In a number of publications, a newly recognized genital syndrome that was initially discovered through systematic evaluations of personal testimonies has been described. Based on careful categorization, persistent sexual arousal syndrome (PSAS) or persistent genital arousal disorder (PGAD) was, for the first time, reported in 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 restless legs syndrome (RLS) and/or overactive bladder syndrome (OAB) and/or urethra hypersensitivity has been called restless genital syndrome (ReGS), as described by Waldinger et al. [3–6]. The unwanted genital sensations of ReGS are typical dysesthesias and/or paresthesias and are often felt as an imminent orgasm or may, rather rarely, give rise to spontaneous orgasms in the absence of sexual desire or fantasies [3–6]. In two systematic studies [3,5], it was found that ReGS usually occurs in perimenopausal and postmenopausal women but may also affect premenopausal women, for example, premenstrually of temporally during pregnancy. In addition, ReGS is highly associated with RLS and OAB, aggravates during sitting, and has the clinical characteristics of small-fiber sensory neuropathy (SFSN) of the pudendal nerve, in particular, the dorsal nerve of the clitoris (DNC). In addition, MRI scans of the pelvis show mild to moderate varices in the vagina, labia minora and/or majora, and uterus in the majority of women with ReGS [3–5]. 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 these women report varying degrees of social withdrawal, desperate feelings, dysthymia, agitation, depressed mood and sometimes suicidal thoughts, and/or a wish for clitoridectomy as a result of the persistent presence of the unwanted genital sensations and the idea of a lack of successful treatment options [3–6]. It has been postulated that SFSN of the pudendal nerve, including the DNC, is the key feature of ReGS [5] and may give rise to associated RLS and OAB [5]. Consequently, we argued that the application of transcutaneous electrical nerve stimulation (TENS) in the genital region may lead to diminished symptoms of SFSN. In the two case reports presented here, it will be shown that the application of TENS may immediately, and in the short term, lead to a clinically relevant diminishment of the symptoms of ReGS, including RLS and OAB.

Materials and Methods

We prospectively evaluated two women with complaints of persistent unwanted feelings of genital restlessness, imminent orgasms, and spontaneous orgasms who visited our Outpatient Department of Neurosexology in HagaHospital and who were diagnosed with ReGS. Both women were not actively recruited but were referred by their general physician and sexologist, respectively. According to the regulations of the local 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. After a neuropsychiatric and medical sexological interview of about 1 hour, the women who were clinically diagnosed as having ReGS underwent routine and hormonal laboratory testing, an electroencephalography (EEG), and an MRI scan examination of the brain and pelvis.

The diagnosis of PGAD was established when the symptoms of the patients fulfilled all five criteria of PGAD [7]. RLS was diagnosed according to the criteria of the International Restless Legs Syndrome Study Group [8]. Menopause was defined as the absence of menses for 12 months after the last menstruation.

Physical examination of the patients included sensory testing of the genital region and manual examination of the ramus inferior of the pubic bone (RIPB) [5]. This was performed by a urologist (third 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 by 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 (second author) in the presence of the first author and a nurse. The physiotherapist prepared the skin by cleaning it with an alcohol wipe. 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 the application of TENS. At this point, a surface electrode (40×40 mm: DE-01 van Lent Systems, Oss, the Netherlands) with adhesive gel was placed. A second electrode was placed in the

same position on the left side. 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 microseconds, indicating high-frequency (HF) or conventional TENS. The intensity of stimulation was slowly increased by the physiotherapist until the patient could perceive the stimulation without being uncomfortable. At home, patients could vary the intensity (mA) but not the frequency and pulse width of the electrical current.

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

Two outcome measures were used to assess the patient perception of potential improvement. The first method was to note the frequency of imminent orgasms or spontaneous orgasms per day. The second measure was to express the magnitude of ReGS on a scale of 0–10, with 0 being "no ReGS at all" and 10 being "the worst ReGS you can imagine." Finally, a visual analog scale was used to assess the intensity of perceived ReGS, and showed a 10-cm line. The patient was asked to put a mark on the line according to the intensity of ReGS she experienced. The left end of the line represented "no ReGS at all," and the right end of the line represented the "worst ReGS you can imagine." The patient's mark on the line was measured (in cm).

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

Case Report A

Mrs. A. is a 56-year-old, married woman who has two children. Her general practitioner had referred her to our outpatient department. Her medical history revealed cardiac asthma since the age of 52. This was treated with a beta-blocker. At the age of 42 years, she underwent a hysterectomy for the removal of a myoma. She presumes to have become menopausal at the age of 52. She was not a tobacco user and does not drink alcohol. However, she formerly consumed significant amounts of coffee. At the age of 56 years, she started to experience spontaneous orgasms with profuse female ejaculation in the absence of sexual desire, thoughts, or fantasies. These spontaneous orgasms were accompanied by rhythmic movements of the hips and difficult to suppress vocalizations. In addition, she experienced genital sensations of imminent orgasm. These sensations and spontaneous orgasms were aggravated while sitting but diminished with walking. Mrs. A. further reported that her spontaneous orgasms were accompanied by restless sensations in both legs, particularly in the heels, with an urge to move both feet.

Restless genital feelings and spontaneous orgasms were experienced in the vagina, at the labia, and sometimes at the clitoris. These sensations were described as little shocks, little spasms, and tumescence of the vagina. Since the onset of spontaneous orgasms, the patient experienced an increased urgency to void, but only small amounts. She had previously only known mainly vaginal and, to a lesser extent, clitoral-induced orgasms, but with female ejaculation.

Mrs. A. reported that the use of a hot water bottle against her genitals reduces the frequency of spontaneous orgasms during the night. In contrast, touching the genitals with ice increases the frequency of spontaneous orgasms.

During medical interview, she experienced two spontaneous orgasms, together with female ejaculation, vocalizations, and rhythmic movements of the hips and legs, with an interval of about 20 minutes. She was desperate, completely exhausted, and begged for adequate treatment. Her medical history is unremarkable and does not reveal prior child abuse, mood or anxiety disorder, compulsive disorder, or traumatic sexual experiences. Routine laboratory assessments, including iron status and vitamin B12 as well as hormonal assessments with thyroid screen, were normal. The EEG was also normal. The MRI of the brain and pelvis had movement artifacts because of about five spontaneous orgasms that occurred during the MRI imaging. Despite these artifacts, no specific pathology was found. Sensory testing elicited multiple points of static mechanical hyperesthesia on the right, middle, and left side of the pubic bone, and bilaterally in the pudendal dermatome includ-

ing the perineal area. Manual examination of RIPB bilaterally elicited two spontaneous orgasms and various sensations of imminent orgasms. Remarkably, despite her very severe suffering, Mrs. A. remains able to clearly and critically contemplate on her illness. She agreed with immediate treatment with TENS.

During the short period of cleaning the genital area by our nurse and physiotherapist, the patient experienced five spontaneous orgasms with profuse female ejaculation. The electrodes of the TENS device were placed 2 cm medial to the tuber ischiadicum. This electrode placement was selected for the following reasons. First, this location is the place under which the pudendal nerve emerges from the pudendal canal and divides into three branches to the clitoris, perineum, and anal region. Second, it was believed that placing the electrodes on this position would be more convenient than placing the electrodes on the skin of the labia majora and clitoris, which belong to the pudendal dermatome.

During the first application of TENS of 20 minutes, she experienced a substantial reduction (80%) of spontaneous orgasms and feelings of ReGS. Indeed, no spontaneous orgasms occurred during this period. After the initial application of TENS and instructional session, the patient used the TENS unit as she wished to relieve ReGS. After 1 and 2 months, a strategy of 30 minutes of TENS combined with 1.5 hours of rest, six times a day, with an intensity of 3.0 mA provided a maximal reduction of complaints. She reports a 90% reduction of restless genital sensations and spontaneous orgasm, with a similar reduction of complaints of OAB and RLS. Moreover, having been nearly completely socially isolated before TENS treatment, Mrs. A. reports to experience hardly any difficulties anymore in her social life after 1–2 months of treatment.

Case Report B

Mrs. B. is a 61-year-old, single woman. She has been divorced and has two children. She was referred to our clinic by a sexologist. Her medical history revealed dystrophy of the wrist after a fall. Since the age of 52, she is menopausal. She is a tobacco user (five cigarettes per day) and does not drink alcohol. At the age of 61 years, she suddenly started to experience unwanted genital sensations with feelings of imminent orgasms in the absence of sexual desire, thoughts, or fantasies. The onset of these sensations occurred 2 days after blockade of the ganglion stellatum by 5 cc levobupivacaine, which she received as treatment for dystrophy of her left wrist. The sensations are experienced mainly not only on the left of the clitoris but also left above the pubic bone, in the vagina, and on the left labia. These feelings are present continuously during the day and are associated with engorgement of the clitoris and labia and increased vaginal lubrication. They are aggravated during masturbation and sitting but are diminished with walking. She also reported intolerance for wearing tight clothes. She reported an increased urgency to void but with only small amounts. The continuous presence of sensations and the idea that the sensations would stay forever make her desperate and suicidal. The application of Vaseline lidocaine 3% cream, which was prescribed by the sexologist, did not result in an improvement of her genital complaints. Out of despair, she regularly applied various sorts of bleach and deodorants on her genitals in order to feel a sharp pain that overshadowed the restless sensations and imminent orgasms. Although she admitted that this was only a temporary solution, she could not resist the urge to use this radical method to get rid of her most annoying genital feelings. Mrs. B. reports that the application of ice on the genitals aggravated the restless genital sensations. The medical interview did not reveal any prior history of child abuse, mood or anxiety disorder, compulsive disorder, or traumatic sexual experiences. Routine laboratory assessments, including iron status and vitamin B12 as well as hormonal assessments with thyroid screen, were normal. The EEG was also normal. The MRI brain imaging was in agreement with aging. The MRI imaging of the pelvis conducted without a Valsalva maneuver did not disclose varicose veins. Sensory testing elicited a few points of static mechanical hyperesthesia on the upper side left of the vagina. Manual examination of RIPB also elicits the genital feelings at the left upper quadrant, indicating pudendal neuropathy and particularly neuropathy of the left DNC. Before agreeing to the TENS treatment, she was treated by various drugs like 0.5 mg clonazepam, 10 mg oxazepam, 20 mg temazepam, and 75 mg pregabaline in various daily dosages without a clinically satisfying result. Local injections near the pubic bone, left to the vagina, with bupivacaine 0.5% and bupivacaine 0.5% combined with 40 mg methylprednisolon provided a complete disappearance of complaints of ReGS, but this effect was only temporary and lasted 3 and 7 days, respectively. The electrodes of the TENS apparatus are placed bilaterally on the

pubic bone, as she immediately experienced a reduction in genital sensation at this area. During the first application of TENS for 20 minutes, the reduction of restless genital sensations is roughly 90%. After the initial application of TENS and an instructional session, the patient used the TENS unit continuously throughout the day. After 1–2 months, she reported a reduction of restless genital feelings, imminent orgasms, and complaints of OAB of 100%. In addition, after the first and second months of TENS application, she reported experiencing no further limitations to social and daily activities. Before TENS application, she reported to have been socially isolated. On average, the patient uses an intensity of 1.4 to 3.2 mA for TENS self-treatment. While being very anxious with suicidal thoughts at the first visit to our outpatient department, 2 months after TENS treatment, she reported to be very satisfied with this treatment, had a more balanced mood, and was very motivated to continue TENS treatment.

Discussion

TENS

TENS is defined by the American Physical Therapy Association as the application of electrical stimulation to the skin for pain control and is a noninvasive and safe method to reduce pain [9]. The TENS device stimulates nerves in the skin area under the electrodes by the application of electrical currents without significant side effects [10].

The frequency, intensity, and pulse durations of stimulation of TENS may vary. Frequency of stimulation is broadly classified as HR (>50 Hz) and low-frequency (LF: <10 Hz) TENS [11].

In the current study, SFSN of the pudendal nerve and DNC was diagnosed in both women by sensory testing of the genital dermatomes and manual examination of the RIPB. This diagnosis is in line with our previous studies of ReGS [5]. In the current patients, TENS with a frequency of 110 Hz, and a pulse of 80 microseconds was applied. In both women, the intensity (voltage) was about 3.0 mA. The voltage was set by the patient at the most convenient level. First TENS application in both women resulted in an immediate and significant reduction of the unwanted genital sensations within 20 minutes. Additionally, after some readjustments of the TENS parameters by the patient, continuous daily use of TENS for 2 months resulted in a nearly complete disappearance of unwanted restless genital sensations, feelings of imminent orgasm, spontaneous orgasms, RLS, and OAB. This positive result of TENS treatment supports the view that ReGS is indeed associated with peripheral neuropathy of the pudendal nerve, for example, the DNC.

Peripheral Nerve Fibers

Peripheral nerves can be categorized according to the function and diameter of the involved nerve fibers [10]. The diameter of nerve fibers is distinguished into (i) large-diameter myelinated Aα- and Aβ-nerve fibers; (ii) small-diameter, myelinated Aδ-nerve fibers; and (iii) small-diameter, unmyelinated C-nerve fibers. The Aα fibers carry motor functions. The Aβ-nerve fibers carry touch functions. The Aδ-nerve fibers are distinguished in low- and high-threshold fibers. The high-threshold Aδ-nerve fibers are mainly involved in carrying "acute" pain sensations. The low-threshold Aδ-nerve fibers carry pressure sensations. The C-nerve fibers carry temperature, pain sensations, and autonomic functions. Notably, high-threshold Aδ-nerve fibers convey nociceptive information of acute pain, whereas C-nerve fibers transmit impulses of longer-lasting nociception.

Pain-Modulating Pathways

TENS treatment [12] emerged from the gate control theory of pain that was formulated in 1965 by Melzack and Wall [13], in which it was postulated that Aβ fibers inhibit Aδ and C fibers in the spinal dorsal horn (Figure 1A). Later, it was shown that, apart from Aβ fiber-induced inhibition of C fibers in the dorsal horn, C fibers are also inhibited by neurons that originate in the mesencephalon and brain stem [14]. Notably, from the periaqueductal gray (PAG), located in the mesencephalon, inhibitory pathways run to the nucleus raphe magnus (NRM) in the medulla oblongata. From the NRM, tonic inhibitory pathways descend to the dorsal horn of the spinal cord. These descending PAG-NRM pathways, containing serotonin and norepinephrine [15,16], inhibit C fibers in the spinal dorsal horn either directly or after the activation of inhibitory gamma amino butyric acid (GABA) [11,17–19] and opioid interneurons [20,21] as well as interneurons containing cannabis receptors [22].

Mechanism of Action of TENS

The effect of TENS to reduce pain is explained by two mechanisms of action [11] (Figure 1B). First, conventional TENS specifically activates Aβ fibers

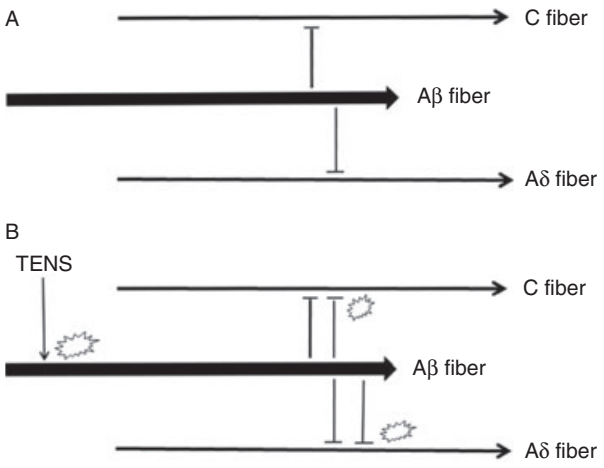

Figure 1 (A) Normal situation in the dorsal horn of the sacral spinal cord; Aβ fibers inhibit Aδ and C fibers of the pudendal nerve. (B) TENS treatment; selective activation of Aβ fibers results in an increased inhibition of Aδ and C fibers in the dorsal horn. TENS = transcutaneous electrical nerve stimulation.

in peripheral nerves that, once arrived in the spinal cord, inhibit the input of high-threshold Aδ and C fibers into the dorsal horn. Consequently, the information on pain transmitted by high-threshold Aδ and C fibers is inhibited to run to higher cortical centers. Secondly, TENS activates the PAG-NRM descending pathways. As a result, there is an increased supraspinal-induced inhibition of C fibers. In this respect, one should distinguish two different mechanisms of action exerted by LF and HF TENS [11]. LF TENS activates supraspinal μ-opioid receptors, which activate the release of serotonin (5-HT) in the spinal cord, which in turn activates 5-HT3 receptors on GABAergic neurons, resulting in an increased release of GABA, which finally decreases the activity of dorsal horn C fibers [18]. On the other hand, HF TENS activates supraspinal δ-opioid receptors, spinal δ-opioid receptors, and spinal cholinergic receptors, which release GABA and enkephalins in the spinal cord [11]. The increased release of GABA in turn diminishes C fibers in dorsal horn neurons [11]. Therefore, the application of TENS involves both local C fiber inhibition and supraspinal-induced C fiber inhibition [23]. Notably, in the spinal cord, nicotinic acetylcholine receptors (nAChRs) also modulate the transmission of nociceptive stimuli [24–26]. For example, some studies suggest that the α4β2 nicotine acetylcholine receptors on primary afferent C fibers are involved in the nociceptive responses [27,28]. SFSN preferentially affects small-diameter myelinated Aδ-nerve fibers and small-diameter unmyelinated C fibers, leaving the larger myelinated fibers relatively unaffected [10,29].

New Hypotheses

Based on the results of the current study, a number of new hypotheses can be formulated (Figure 2 and Table 1):

1. ReGS is caused by peripheral mononeuropathy of the pudendal nerve and particularly its distal branch the DNC. We presume that this mononeuropathy is most likely a result of mechanical compression or irritation of the DNC. However, nonmechanical causes cannot be excluded. In case of compression, there are no studies yet elucidating the exact types of mechanical pressure. Compression-induced damage of nerve tissue may have sensitized afferent pudendal fibers (peripheral sensitization). In addition, continuous irritation to the pudendal nerve may also lead to hypersensitivity of corresponding spinal dorsal horn neurons (central sensitization). As mechanical hyperesthesia and allodynia is associated with Aδ and C fibers, we postulate that, in ReGS, the mononeuropathy of the DNC and pudendal nerve is associated with dysfunction of its Aδ and C fibers.
2. As TENS inhibits Aδ and C fibers, we postulate that, in women with ReGS, sensations of orgasm and imminent orgasm are transmitted by Aδ and C fibers of the pudendal nerve, and particularly by its DNC. We postulate that the immediate onset of restless genital sensations in response to acute stress or tensions, as is frequently reported by women with ReGS, is mediated by Aδ fibers, analogous to the role of Aδ fibers in acute pain, whereas continuous sensations of imminent orgasms are transmitted by C fibers.
3. Touching the clitoris and labia (both parts of the pudendal dermatome) activates Aβ fibers of the DNC and pudendal nerve. Too much activation of these fibers may inhibit the transmission of (pre)orgasmic sensations by Aδ and C fibers to higher cortical centers. We suggest that this mechanism may form the neurobiological basis for the well-known situation that also anecdotally has been reported, that women who cannot become orgasmic by the "wrong" touch of their partners hand do become orgasmic by self-stimulation.
4. The C fiber–inhibiting effects of activated μ-opioid receptors and GABA-A receptors in

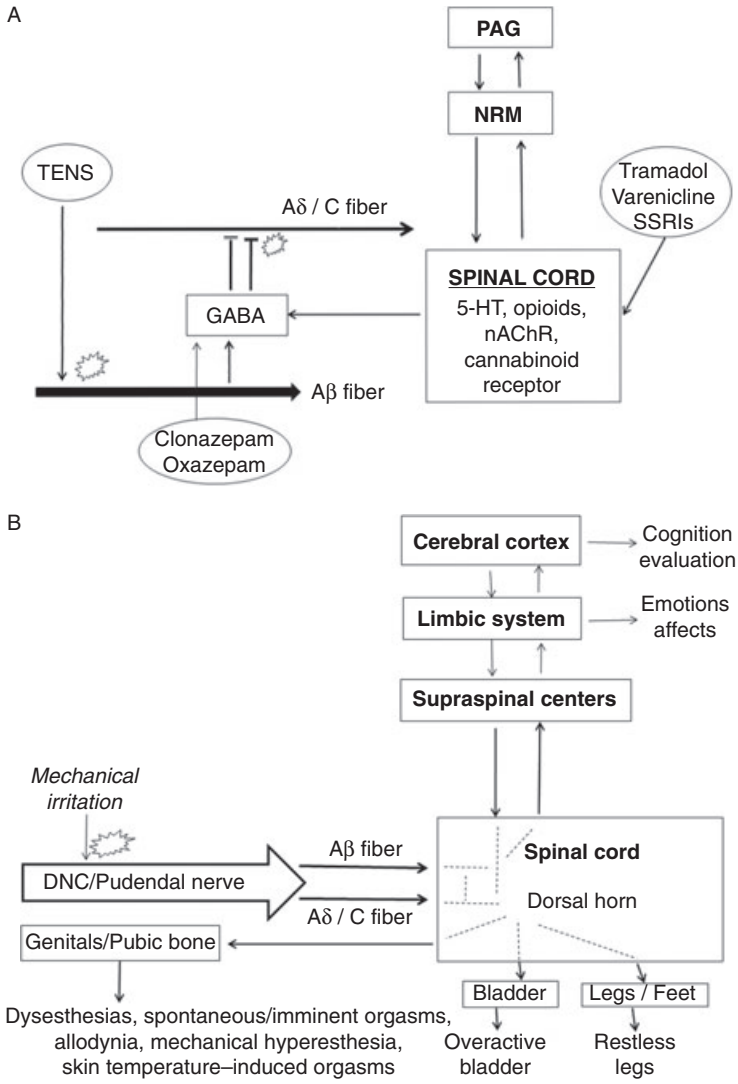

Figure 2 (A) Neurological hypothesis on the pathophysiology of ReGS (I). Spinal and supraspinal pathways activate various neurotransmitter receptors in spinal dorsal horn. These neurons activate spinal GABA-A receptors, which in turn inhibit Aδ and C fibers. It is postulated that clonazepam, tramadol, and varenicline reduce symptoms of ReGS by activating GABA-A receptors in the spinal cord. In addition, it is postulated that SSRI-withdrawal-induced ReGS results from disinhibition of C fibers in the spinal dorsal horn. (B) Neurological hypothesis on the pathyphysiology of ReGS (II). Peripheral neuropathy of the DNC and pudendal nerve elicits excitation of Aδ and C fibers, which, through "cross talk" with spinal neural circuitries, give rise to OAB and RLS. The peripheral impulses are also conveyed to supraspinal centers, the limbic system, and the cerebral cortex, influencing cognition, emotions, and affects. DNC = dorsal nerve of the clitoris; GABA = gamma amino butyric acid; nAChR = nicotinic acetylcholine receptor; NRM = nucleus raphe magnus; OAB = overactive bladder; PAG = periaquaeductal gray; ReGS = restless genital syndrome; RLS = restless leg syndrome; SSRI = selective serotonin reuptake inhibitor; TENS = transcutaneous electrical nerve stimulation.

Table 1 Neurological hypothesis on the pathyphysiology of ReGS (III). Summary of primary afferent nerve fibers and their presumed roles in ReGS. Aδ and C fibers are polynodal; for example, they transmit impulses from mechano-, thermal-, and nociceptors to the spinal dorsal horn. The DNC is a pure sensory nerve that also transmits sensory information that is experienced as (pre) orgasmic sensations

Modality	Submodality	Fiber type	Role in perception	Role in restless genital syndrome (DNC small-fiber neuropathy)
Mechano-reception	Pacinian corpuscle	Aβ	Vibration	Driving-induced ReGS on a bumpy road
Thermo-reception	Warm, cold	Aδ, C	Warmth, cold	Temperature -induced ReGS
Nociception	Small myelinated, unmyelinated	Aδ, C	pain	Imminent orgasms Spontaneous orgasms Genital dysesthesias Restless legs (secondary) Overactive bladder (secondary) Allodynia Mechanical hyperesthesia Aggravation ReGS on acute Stress

the spinal dorsal horn provide a new point of view on some drugs that have been shown efficacious in the treatment of ReGS [3–5]. For example, we hypothesize that tramadol (a μ-opioid agonist), clonazepam, and oxazepam (both GABA-A agonists) relieve the symptoms of ReGS by their C fiber–inhibiting effects in the dorsal horn of the spinal cord (Figure 2A).

5. The C fiber–inhibiting effects of activated nAChR receptors in the spinal dorsal horn may explain the PGAD-reducing effect of varenicline, a partial nAChR receptor agonist (Figure 2A), as has previously been described in a case report [30].
6. As LF TENS first activates higher spinal regions before inhibiting spinal dorsal horn C fibers, we suggest that electroconvulsive therapy (ECT) may mimic the electric influences of LF TENS on some brain regions, like the PAG and NRM. This may perhaps explain the PGAD-diminishing effects of ECT, as has been reported in the literature [31].
7. Vasocongestion of the clitoris, labia, and vagina during ReGS is most likely associated with vasodilatation. This may be a result of the involvement of C fibers of the pudendal nerve. Apart from nociception, C fibers are also mediating autonomic functions, like vasodilation.
8. Selective serotonin reuptake inhibitor (SSRI)–induced genital anesthesia may be a result of the increased activation of spinal 5-HT receptors, which in turn increase inhibition on pudendal C fibers [32].
9. SSRI-withdrawal-induced ReGS or spontaneous orgasm [33,34] may be a result of reduced activation of spinal 5-HT receptors, which in turn disinhibit pudendal C fibers.
10. Cannabis-withdrawal-induced ReGS, as has recently been reported [3–5], may be a result of reduced activation of spinal cannabis receptors, which in turn disinhibit pudendal C fibers.
11. The often simultaneous occurrence of restless genital feelings (e.g., dysesthesias and genital sensations of imminent orgasms) and complaints of OAB and RLS may be related to pudendal Aδ and C fibers' "cross talk" in the spinal cord, with C fibers involved in eliciting RLS and OAB (Figure 2B). The exact pathways of this "neuronal cross talk" are to be elucidated. It is noted that pudendal nerve injury can induce increased activity of bladder C fiber afferent pathways leading to OAB [35] and that, in secondary RLS, the sensory deficits are in part caused by small-fiber neuropathy [36].
12. The increased frequency of imminent and spontaneous orgasms and restless genital sensations after applying ice at the genital region and the reduced frequency after using a hot water bottle is most probably associated with the involvement of Aδ and C fibers. Although it has been shown that cold stimuli activate both Aδ and C fibers [37,38], their physiology in temperature-induced spontaneous and imminent orgasms in ReGS remains to be elucidated.

In both patients, TENS treatment resulted in a clinically very relevant reduction of ReGS sensations. However, many questions on TENS treatment for ReGS remain to be elucidated. For example, what is the success rate of HF TENS in a larger sample of women with ReGS? What is the effect of HF TENS in the long term? Although the results of the current study appear to be promising for women with ReGS, the study has also some methodological limitations, such as its open design, the lack of a control group, and the small number of patients. Therefore, controlled research of TENS treatment in large series of women with ReGS and with a longer application duration is needed.

Apart from the above-mentioned pathways, nociception is distinguished by the following components: (i) sensoric-discriminative system: the somatosensoric cortex (in the postcentral gyrus) receives nociceptive information from lateral spinal pathways in order to precisely locate the location of pain in the body [39]; (ii) affective-emotional system: the limbic system receives nociceptive information from medial spinal pathways and mediates the negative emotional evaluation of nociception; and (iii) cognitive-evaluation system: thoughts about the cause and meaning of nociception are processed by various frontal and parietal cortical areas.

Both the affective-emotional and cognitive-evaluation of nociception are often pivotal for the way a patient deals with pain. The very relevant reduction of unwanted genital sensations and spontaneous orgasms by TENS treatment in the current women indicates that these sensations belong to the category of nociception. Indeed, both patients varied in their affective-emotional and cognitive-evaluation response to the symptoms of ReGS. Mrs. A. was exhausted but cog-

nitively, she critically observed the various manifestations of ReGS. In contrast, Mrs. B. was desperate, highly anxious by the least manifestation of genital sensations, and regularly suicidal by the thought that these sensations would not disappear anymore. Therefore, TENS treatment of ReGS should always also include counseling, psychoeducation, investigation of coping styles, and reassurance in case of catastrophic cognitive reactions of the patient.

Because a number of causes of ReGS have been published in a series of case reports, any general concept of the pathogenesis of ReGS must ideally cover all its manifestations and explain positive and negative treatment results. Basing on all evidence thus far, including the TENS results as reported in the current study, we have come to a neurological hypothesis summarized in Figure 2 and Table 1. In summary, presumed mechanical irritation of the DNC and the pudendal nerve becomes clinically manifest as peripheral SFSN. Excitation of Aδ and C fibers of the peripheral nerve is heading to the dorsal horn of the sacral spinal cord, and, through "cross talk" with other spinal and/or supraspinal neural circuitries, symptoms of RLS and OAB are induced. In addition, peripherally or centrally sensitized nerve fibers convey impulses to supraspinal centers, the limbic system, and various areas of the cerebral cortex, giving rise to cognitive difficulties (e.g., concentration disturbances, catastrophic thoughts, suicidal thoughts) and emotional dysfunction (e.g., depressed mood and increased anxiety). Inhibition of pudendal C fibers may occur not only by the application of TENS but also by drugs that activate different receptors (GABA-A, μ-opioids, nAChR, cannabinoid receptors) in the dorsal horn of the spinal cord. Oppositely, medical withdrawal of SSRIs and cannabis have been reported to provoke ReGS symptoms [3–5]. We presume that this is caused by disinhibition of C fibers. Notably, cognitive and emotional distraction (e.g., hobbies and thought distraction) may improve coping with this often very serious physical disorder.

Conclusions

In the current study of two women, the use of TENS clinically significantly reduced the symptoms of ReGS, for example, restless genital sensations, sensations of imminent orgasms, spontaneous orgasms, RLS, and OAB and substantially increased the social activity of the previously incapacitated patients. TENS was delivered by using two electrodes positioned bilaterally over either the sacral region and on the pubic bone. The current findings suggest that TENS may represent a valuable and promising treatment for the relief of symptoms of peripheral SFSN of the pudendal nerve in women with ReGS. However, further controlled studies with TENS in larger samples of women with ReGS are warranted. This is currently performed by our group.

The results of the current study provided indications that, in women with ReGS (pre)orgasmic feelings of the genital area are mediated by Aδ and C fibers of the DNC, and pudendal nerve and that these fibers are inhibited by Aβ fibers in the spinal cord.

The outcomes of the current study have put insights in the pathogenesis of ReGS being a cluster of genital complaints with OAB and/or RLS, mediated by Aδ and C fibers of the DNC and the pudendal nerve. In a normal situation, these fibers are sufficiently inhibited by Aβ fibers in the spinal cord, but in case of ReGS, this inhibition has become inappropriate. In other words, the successful applications of TENS in women with ReGS have clearly contributed to our previously formulated neurological hypothesis that ReGS is caused by small-fiber sensory pudendal neuropathy [5,6] that is associated with a high tonus of Aδ and C fibers, which are insufficiently inhibited by the various neurotransmitter systems in the spinal dorsal horn.

Acknowledgment

The authors are indebted to Mrs. Janny de Jonge, urologic nurse in continence, for her excellent assistance and her warm support to the two women who participated in this study.

Corresponding Author: Marcel D. Waldinger, MD, PhD, Department of Psychiatry and Neurosexology, HagaHospital Leyenburg, Leyweg 275, The Hague 2545 CH, The Netherlands. Tel: +31 70 210 2086; Fax: +31 70 210 4902; E-mail: md@waldinger.demon.nl

Conflict of Interest: None.

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