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A New Medical Treatment With Botulinum Toxin in Persistent Genital Arousal Disorder: Successful Treatment of Two Cases

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Persistent genital arousal disorder is described in a spontaneous, persistent, and uncontrollable genital arousal in women, with or without orgasm or genital engorgement, unrelated to any feelings of sexual desire. This study aimed to argue that application of Botulinum toxin in the periclitoral region in order to block the dorsal nerve of the clitoris might decrease symptoms of persistent genital arousal disorder. The authors presented 2 cases, in which application of Botulinum toxin resulted in improvement of the symptoms of persistent genital arousal disorder. Botulinum toxin type A treatment protocol is seen as a promising application for the persistent genital arousal disorder. However, further controlled studies in large samples are needed.

BACKGROUND

Persistent genital arousal disorder (PGAD) was described in a spontaneous, persistent, and uncontrollable genital arousal in women, with or without orgasm or genital engorgement, unrelated to any feelings of sexual desire (Leiblum & Nathan, 2001). PGAD, which was described by S. R. Leiblum and S. G. Nathan for the first time in 2001, is characterized by five diagnostic criteria: (a) persists for an extended period of time (hours, days, and/or months), (b) does not go away after one or more orgasms, (c) is unrelated to subjective feelings of sexual desire, (d) feels intrusive and unwanted, and (e) causes distress (Goldmeier & Leiblum, 2006; Leiblum & Nathan, 2001). In

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2009, the combination of PGAD with restless legs syndrome and/or overactive bladder syndrome and/or urethral hypersensitivity has been renamed as restless genital syndrome by Waldinger and colleagues (Waldinger, Venema, van Gils, & Schweitzer, 2009; Waldinger, Venema, van Gils, Schutter, & Schweitzer, 2009). At present, there is no clear idea about the etiology of PGAD, although restless genital syndrome has been attributed to a sensoric neuropathy of the dorsal nerve of the clitoris in women and the dorsal nerve of the penis in men (Waldinger, Venema, van Gils, Schutter, & Schweitzer, 2009; Waldinger, Venema, van Gils, de Lint, Schweitzer, 2011). Recently, Komisaruk and Lee (2012) suggested that Tarlov cysts might play a role as an etiologic factor in PGAD. In addition, there are insufficient data for the frequency and treatment of PGAD. In a study limited to 96 patients, only 1 women fulfilled all five diagnostic criteria for PGAD (Garvey, West, Latch, Leiblum, & Goldmeier, 2009). In the literature, regional nerve blocks with transcutaneous electrical nerve stimulation (Waldinger, de Lint, Venema, van Gils, & Schweitzer, 2010) and electroconvulsive therapy (Yero, McKinney, Petrides, Goldstein, & Kellner, 2006) have shown varying degrees of success in some cases. In this article, we argued that application of Botulinum toxin in the periclitoral region in order to block the dorsal nerve of the clitoris might decrease symptoms of PGAD. Two cases in which application of Botulinum toxin resulted in improvement of the symptoms of PGAD are presented here.

CASE STUDY

We presented two women with complaints of spontaneous, persistent, and uncontrollable orgasms who were diagnosed as PGAD. The first case was a 23-year-old married woman who had one child. She was referred to our clinic for persistent unwanted genital sensations and feelings of imminent orgasm without sexual desire, thoughts, or fantasies. A detailed evaluation including routine and hormonal investigations, physical and ultrasonographic examinations, was performed. Oxford grading, which was used for assessment of pelvic muscle strength, resulted in a grade of 5/5. After a neuropsychiatric evaluation no abnormalities such as depression, epilepsy, obsessive/compulsive disorder, and past sexual assault were detected. As a result of all evaluations, no problems were found. The diagnosis of PGAD was established when the symptoms of the patients fulfilled all five criteria of PGAD (Leiblum & Nathan, 2001). The localizations of genital sensations were investigated by manual examination of the ramus inferior of the pubic bone, as described by Waldinger and colleagues (Waldinger, Venema, van Gils, & Schweitzer, 2009). These sensations were experienced in the vagina, at the labia, and especially around the clitoris. We thought that as a new treatment modality, periclitoral nerve block with Botulinum toxin could be performed. After being informed about the treatment protocol, the patient was operated under mask anesthesia. Clostridium Botulinum toxin type A 100 units (Botox, Allergan) containing vials were used for this purpose. Toxin was diluted with 2.5 mL of sterile saline and yielded 4 units toxin for each 0.1 mL. Two units of Botulinum toxin A were injected into four points surrounding the clitoris each being approximately 0.5 cm away from the center of the clitoris at 1, 5, 7, and 11 o'clock positions, with a total of 8 U (Figure 1; Liu et al., 2012). Shortly after the treatment, all the symptoms of the patient recovered. During the 8-month follow-up visit, patients' unwanted genital sensations symptoms reappeared. When we planned the second attempt of Botulinum toxin application, the patient's complaints became more bearable. Therefore, second application was cancelled. The second patient was a 38-year-old married woman with one child. She had

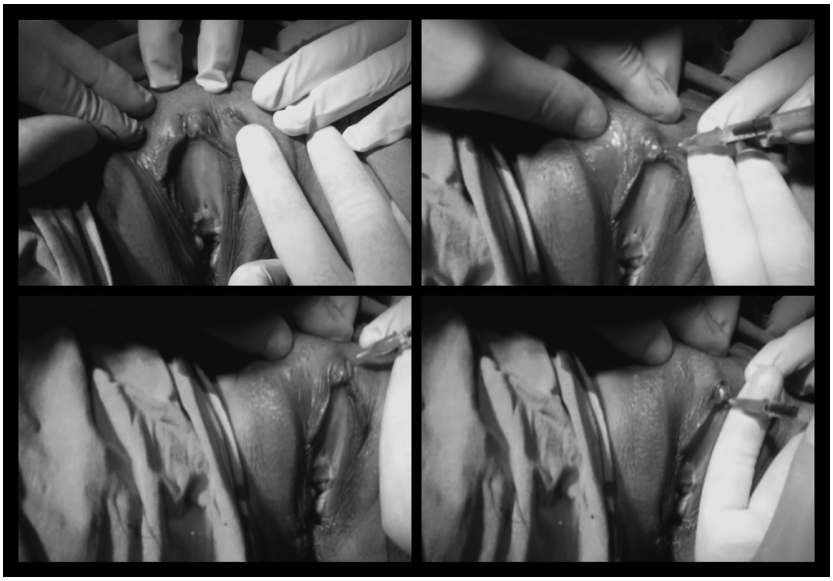

FIGURE 1 Botulinum toxin A was injected into 1, 5, 7, and 11 o'clock of the clitoris. (Color figure available online).

the same clinical features, unwanted genital sensations, and feelings of imminent orgasm. Same interview, routine investigations, and examinations were performed. Oxford grading of pelvic muscles resulted in a grade of 5/5. Neuropsychiatric evaluation was normal. Genital sensations were localized especially in labium and clitoral regions. Dorsal nerve of the clitoris block with Botulinum toxin was performed with the same method, and then genital arousal symptoms of this patient recovered. By the time this case was presented, it has been 6 months and the therapeutic effect of the toxin seem to continue.

DISCUSSION

At present, there is no sufficient information related to prevalence, etiology, pathophysiology, and management of PGAD. Research has shown that PGAD is often associated with depression and distress (Leiblum, Seehuus, Goldmeier, & Brown, 2007). Recent literature suggests that women with PGAD come from a wide variety of ages and backgrounds. Potential biological factors are shown in the etiology. For example, pelvic arterial-venous malformation with arterial branches to the clitoris and ovarian venous incompetence (Thorne & Stuckey, 2008), hormonal deficiencies (Amsterdam, Abu-Rustum, Carter, & Krychman, 2005), central nervous system trauma, epilepsy, pudendal nerve entrapment (Waldinger, Venema, van Gils, & Schweitzer, 2009), presence of Tarlov cysts (Komisaruk & Lee, 2012) and use or withdrawal of certain antidepressants can cause PGAD (Leiblum & Goldmeier, 2008). Genital sensation of spontaneous unwanted imminent orgasm in women is a physical disorder that might be caused by pudendal neuropathy. Restless genital syndrome "is highly associated with pelvic varices and with sensory neuropathy of the

pudendal nerve and dorsal nerve of the clitoris, whose symptoms are suggestive for small fiber neuropathy," wrote Dr. Marcel D. Waldinger and colleagues (Waldinger et al., 2010). Some drugs such as trazodone might cause a medical condition such as PGAD as a side effect (Battaglia & Venturoli, 2009). In addition, the condition can sometimes begin only after the discontinuation of selective serotonin reuptake inhibitors (Goldmeier & Leiblum, 2006). In the literature, transcutaneous electrical nerve stimulation (Waldinger et al., 2010), electroconvulsive therapy (Yero et al., 2006), topical anesthetic agents (Wylie et al., 2006), psychological interventions and discontinuation of the triggering agent (Leiblum & Goldmeier, 2008) were used in the treatment of the PGAD. In one recent case, serendipitous relief of symptoms was noted from treatment with varenicline (Korda, Pfaus, & Goldstein, 2009). More recently, the symptoms of the condition have also been linked with pudendal nerve entrapment. Regional nerve blocks and less common surgical interventions have demonstrated varying degrees of success in some cases. It is known that the dorsal nerve of the clitoris is the primary somatosensory nerve mediating sensation from the clitoris, and its function and integrity are critical for sexual functioning. Reports in the literature suggest that many aspects still exist that are unknown about this organ (Ginger, Cold, & Yang, 2011). Ginger and colleagues (2011) reported that the dorsal nerve of the clitoris has not been as well characterized as its male homologue and the details about anatomy and innervation of the clitoris has not been clearly documented. The authors also suggested that more recently, gross anatomical studies have demonstrated the substantial nature of the erectile tissues of the clitoris and bulb, but detailed information of the innervation of the clitoris is still missing (Ginger et al., 2011). In the presented cases Botulinum toxin was injected in periclitoral region for the treatment of PGAD and PGAD symptoms recovered dramatically in these two patients. It is known that Botulinum toxin apparently blocks the release of acetylcholine at the neuromuscular junction. In addition, Botulinum toxin was suggested to be effective in treating postherpetic neuralgia, probably or possibly effective at treating postoperative/posttraumatic neuropathic pain, and probably effective at treating painful diabetic neuropathy (Francisco et al., 2012). The mechanisms of action of Botulinum toxin was suggested to decrease sensitized nociception in four ways: (a) inhibiting glutamate release in peripheral tissues, (b) decreasing calcitonin gene-related peptide release in peripheral tissue, (c) decreasing transient receptor potential cation channel subfamily V member 1 trafficking to peripheral neuron cell membrane, and (d) decreasing substance P release in peripheral tissue (Francisco, Tan, & Gren, 2012). For this reason, we used Botulinum toxin in the periclitoral region as a reversible and easily applicable method that has no surgical morbidity. For the first time in the literature, Botulinum toxin treatment was performed for this purpose and positive results were obtained. In both patients, treatment with Botulinum toxin resulted in a clinically very relevant reduction of PGAD sensations.

CONCLUSION

Botulinum toxin seems to have complex mechanisms of actions that are not clear yet, and the clitoris is such an organ that its anatomy and innervation have not been clarified in detail. Although the exact mechanisms of action is not clear, in the present cases periclitoral injection of Botulinum toxin significantly reduced the symptoms of PGAD. Botulinum toxin A treatment protocol seems as a promising application for the PGAD. However, further controlled studies with Botulinum toxin in large samples of women with PGAD are needed.

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