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PERSISTENT GENITAL AROUSAL DISORDER AND RESTLESS GENITAL SYNDROME: AN OVERVIEW OF THE CURRENT LITERATURE

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Abstract

Review

BACKGROUND: Persistent Genital Arousal Disorder (PGAD) and Restless Genital Syndrome (RGS) cause women to experience sexual arousal of the genitals without being psychologically aroused. This may be possible due to the fact that women have a lower degree of concordance, the agreement of physical and psychologically arousal, compared to man.
OBJECTIVE: This review will give an overview of the literature on PGAD and RGS to summarize the current knowledge of these syndromes and to explore starting points for future research.
RESULTS: PGAD physical symptoms exist of genital swelling, tingling, lubrication, throbbing and contractions. These symptoms may lead to women isolating themselves, developing a depression and eventually suicidal tendencies. Triggers for these symptoms can be visual, physical, or emotional. Masturbation, orgasms and exercise may give some form of relief, but will never completely resolve the symptoms. PGAD may be part of a bigger syndrome called Restless Genital Syndrome. Women with RGS would be afflicted by PGAD and Restless Legs Syndrome and/or Overactive Bladder. Currently, there is no consensus yet on the underlying pathology of PGAD/RGS. The most plausible hypotheses focus on neurological, vascular, or hormonal pathology or use/withdrawal of antidepressants. Currently, there are no evidence-based treatments, but clonazepam showed promising results. Other possible treatments like oestrogens and tramadol were only tested in smaller groups or case reports.
CONCLUSION: PGAD and RGS are relatively newly discovered syndromes with potentially socially invalidating symptoms which need more research to fully understand the pathophysiology of the syndromes and to find a successful, evidence-based treatment.

KEYWORDS: female, sexual, Restless Legs Syndrome, gynaecology, neurology

Introduction

Persistent Genital Arousal Disorder (PGAD) is a disorder solely found in women and causes almost constantly aroused genitals, while the brain is not aroused [1,2]. A comparable disorder in men is called priapism and is usually caused by Viagra [1]. PGAD may be part of a bigger syndrome called Restless Genital Syndrome (RGS) [2]. At the moment, it is still unclear how many women are affected by this disorder, mostly because afflicted women often feel ashamed of their symptoms, which prevents them from seeking the help of physicians [3,4]. This review aims to give an overview on the literature of PGAD and RGS to summarize the current knowledge of these syndromes and to explore starting points for future research.

Sexual arousal

To understand how and why PGAD exists, we first need to know some of the physiology of sexual arousal in women. Sexual arousal can be divided into physical and psychological excitement and may be described as "a combination of objective and subjective signs; the physical reactions as vulvar swelling, vaginal lubrication, heavy breathing and increased sensitivity of the genitalia, combined with the subjective experience of feeling pleasure and excitement" [5]. The correspondence of the physical and psychological excitement is called concordance [5]. Women have a lower degree of concordance compared to men, meaning that women may report sexual arousal when their genitalia aren't. The concordance also works the other way, women may report that they aren't sexually aroused while their genitalia are. Currently, it is still unclear how much of the physical and psychological arousal contribute to the full experience of arousal [6], however the lower concordance could explain how women can have genital sexual arousal without physiological arousal.

Persistent Genital Arousal Disorder

To diagnose a woman with PGAD, the symptoms she is experiencing needs to fulfil 6 criteria [4,7]:

1. The symptoms are those of sexual arousal (vulvar swelling and hypersensitivity) that last for hours or days and do not completely disappear on their own.
2. The physical symptoms of arousal do not resolve after one or multiple orgasms.
3. The physical symptoms are not related to a psychological sense of arousal.
4. The arousal can not only be triggered by sexual activity, but also by non-sexual stimuli or no stimuli at all.
5. The women experience these symptoms as intrusive, unbidden and unwanted.
6. The symptoms cause at least a moderate degree of distress.

Clinically, women with PGAD experience genital swelling (74.8%), tingling (78.6%), lubrication (75.7%), throbbing (72.2%) and contractions (70.9%). Triggers for these symptoms can be visual (60%), physical such as intercourse (50%), or emotional like stress or anxiety (30-45%) [3]. Driving in a car or riding a bus is one of the most reported non-

sexual triggers, caused by the vibrations. Although there are no known factors which completely resolve the symptoms, there are some that are frequently reported to give some form of relieve: masturbation (51%), orgasm (50%), distraction (39%), intercourse (36%), exercise (25%), and cold compresses (13%) [3,8]. Important to note is that these symptoms may cause afflicted women to isolate themselves, leading to depressions and some women eventually develop suicidal tendencies [4,7]. The exact prevalence of PGAD is still unclear. A survey in a sexual health clinic in the United Kingdom found that 1% of the questioned women met all the criteria of PGAD and 33% met at least 1 criterion [9].

Restless Genital Syndrome

Based on several studies and case reports, a group of Dutch researchers introduced the term Restless Genital Syndrome [2,10]. RGS consists of the criteria of PGAD accompanied by the symptoms of either Restless Legs Syndrome (RLS) and/or overactive bladder (OAB). This group of researchers came up with 16 arguments why PGAD and RLS could be part of a bigger syndrome of which the most important ones are summarized below [2].

The prevalence of RLS in women with PGAD is 67% compared to 3-19% in the general population [2,11]. In 39% of the women, reported symptoms of RLS started shortly after the onset of PGAD. Secondly, RLS and PGAD may both be caused by starting SSRI treatment, or withdrawal of the SSRI [12,13]. Furthermore, patients find it hard to describe the physical unpleasant sensation felt in PGAD and RLS, but in both cases movement and rubbing of the afflicted body part suppresses the unpleasant sensation. Although it is still unclear if RLS and PGAD are caused by varices, in both syndromes the prevalence of varices (leg or pelvic) is higher compared to the general population [14]. Lastly, successful treatment of both syndromes is hard to achieve, but clonazepam and tramadol have been reported to relieve the symptoms in both syndromes [15,16].

Although the authors did not specifically involve OAB in their arguments for the existence of RGS, they did find a prevalence of 67% in women with PGAD (39% started shortly after onset of the PGAD symptoms), compared to 15% in the general population.

Pathophysiology

There is no consensus yet on the underlying pathology of PGAD/RGS. The most plausible hypotheses focus on neurological, vascular, or hormonal pathology or use/withdrawal of antidepressants (mostly SSRIs and SNRIs).

Neurological: PGAD may be caused by small-fibre neuropathy of the n. dorsalis clitoridis, which would cause hyperesthesia and hyperalgesia of the genital area. Firstly, women with PGAD reported an increase in the genital symptoms when wearing tight underwear and/or after prolonged periods of sitting [17]. Secondly, researchers tested women with PGAD for several trigger points using a cotton swab. All women showed genital arousal, even up to orgasmic sensations, when slightly touched by the cotton swab in a certain area. The area which lead to arousal differed per woman. Other neurological causes may be mechanical compression of the n. pudendus possibly caused by varices or a tarlov cyste, a cerebrospinal-fluid-filled sac most frequently located in the sacral region of the spinal cord [17-19].

Vascular: Another possible cause is the existence of pelvic varices [2,10,19]. A study found a prevalence of pelvic varices of 55%, in contrast to a prevalence of 9,9% in healthy women [10]. In another study the same researcher found even higher prevalences of varices; in the wall of the vagina (91%), the labia minora/majora (35%) and uterus (30%) [2]. The varices could mechanically compress the n. pudendus which could lead to the symptoms as described in PGAD and RLS. However, these studies were small with 18 and 23 women, and the researchers mentioned that most of the varices were small to moderate in size, making it unlikely to really cause mechanical compression. Furthermore, because of the design of the study only correlation but no causation can be demonstrated.

Antidepressants: Several studies found adverse effects of antidepressants on sexual function [20-23]. Administration of paroxetine (SSRI) and venlafaxine (SSRI), and duloxetine (SNRIs) inhibited the increase in blood flow after pelvic stimulation in rabbits. Although these drugs all increase the amount of serotonin, administration of serotonin or escitalopram (a highly selective inhibitor of serotonin reuptake) did not result to inhibition of the blood flow. Therefore, the inhibition of blood flow after stimulation is not due to the increase of serotonin, but due to other effects of the drugs. The same study showed that administration of L-arginine (a precursor of nitric oxide (NO) which causes vasodilation) reversed the inhibition caused by paroxetine. Phentolamine, an alpha-adrenergic antagonist which also causes vasodilatation, prevented the inhibitory effects of venlafaxine. Both L-arginine and phentolamine partly blocked the inhibition of duloxetine. These data suggest that it's not the increase in serotonin, but rather the inhibition of the production of NO (countered by L-arginine) or the increase of norepinephrine (countered by phentolamine) that causes the vasoconstriction. However, it's still unclear if and how the inhibition of blood flow leads to the development of RGS.

Hormonal: Another possible cause of RGS is dysregulation of the hormones, usually caused by the menopause [23]. Animal studies showed that estrogen treatment increase the amount of norepinephrine in adrenergic nerves, demonstrating that hormones can also affect the physiology of our nervous system [24,25]. Interestingly, in contrary to increasing the amount of noradrenaline, estrogen reduces the density of innervation. Another study showed an increase in the density of the nerves in the vaginal area in rats that underwent an ovariectomy [26]. Furthermore, this density reduced when the rats where treated with estrogen. The increase in density was attributed to true axonal proliferation and not just altered tissue volume. Ting et al. also reported that the new nerves could mediate vasoconstriction and nociception, suggesting that these changes may explain the sensitivity and hyperalgesia of the vagina in postmenopausal women (and possibly women with RGS). However, another study found no such increase in density in rats after an ovariectomy [23].

These studies suggest that our hormones also regulate our innervation and neurotransmitters, but more research is needed to clearly define the roles of the different hormones.

Treatment options

Since PGAD and RGS are relatively recently discovered syndromes, no randomized controlled trials are conducted yet. Most known possible treatments are the result of case reports or small trials. Waldinger et al. treated 16 women with clonazepam in different dosages [2]. In two women no effect was found, while one woman reported a reduction of symptoms of 20%. The other 13 women reported a reduction of the symptoms of at least 50%. The women in this trial who did not experience any, or only a temporary effect, agreed to try other treatments. This included estrogens (one woman had beneficial effects, but both women were against continuing because of potential side effects of hormonal replacement therapy), pramipexol (a dopamine agonist, without beneficial effects in all three women but with disturbing side effects), tramadol (which did have a significant effect in all three women, but has the downside of lasting only four hours and thus needs to be taken often which in turn leads to addiction) and oxazepam (with successful effect in one of the three women).

Other case reports showed positive effects of electro-convulsion therapy [27], pudendal neuromodulation [28] and hypnotherapy [29].

Conclusion

PGAD and RGS are relatively recently discovered syndromes and much research still needs to be done to fully understand the pathophysiology. Also, it is still unclear how many women suffer from PGAD or RGS. Since these symptoms are accompanied by a lot of shame, it might be of value that physicians (mostly gynaecologists and neurologists) actively inquire about PGAD symptoms in women with restless legs and/or overactive bladder. Furthermore, although clonazepam shows some promising results, well-constructed studies are needed to find an evidence-based treatment for these potentially socially invalidating syndromes.

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