SEXUAL MEDICINE REVIEWS REVIEW

Persistent Genital Arousal Disorder: Review of Pertinent Peripheral Nerves

Kevin M. Klifto, PharmD,[1] and A. Lee Dellon, MD, PhD[1,2]

ABSTRACT

Introduction: Persistent genital arousal disorder (PGAD) is a condition that is still poorly understood. Etiologies reported for PGAD are vascular, neurological, pharmacological, and psychological. Determining the neurophysiological etiology of PGAD began with developing an understanding of the underlying biomechanics of the pudendal nerve and the female sexual response.

Aim: To summarize the anatomy, physiology, etiologies, diagnostics, and treatments of the pertinent peripheral nerves involved in the pathology of PGAD.

Methods: We performed a PubMed, Cochrane, Embase, Web of Science, and Google Scholar search for English-language articles in peer-reviewed journals with no predefined time period for inclusion. Terms included "humans"[All Fields] AND "persistent"[All Fields] AND/OR ("genitalia"[All Fields] OR "genital"[All Fields]) AND/OR "arousal"[All Fields] AND/OR ("disease"[All Fields] OR "disorder"[All Fields]) AND/OR "nerve"[All Fields]. The main outcomes of the papers were reviewed.

Main Outcome Measure: The main outcome measures were the anatomy and physiology, etiologies, history and physical examination, diagnostic imaging, and current evidence for the treatment of PGAD related to the peripheral nervous system.

Results: Most of the literature for PGAD originates from case studies. The diagnosis of PGAD itself is still a debated topic of discussion. More recent data published indicate that this disease affects males, as well.

Conclusion: Nerve entrapment may be a source of continuous arousal. Associated PGAD symptoms would depend on the segment of the nerve involved. Unwelcomed or unwanted arousal has been observed as the most common detrimental symptom. Pelvic 3-tesla magnetic resonance imaging is recommended in all patients with suspected nerve entrapment. Lumbosacral 3-tesla magnetic resonance imaging is recommended if a Tarlov cyst or a herniated intervertebral disc is suspected. If the peripheral nerve is the source of the pathology, surgical intervention may be curative. A multidisciplinary team approach consisting of a medical provider, pelvic floor physical therapist, and sex therapist has demonstrated benefits. There are currently no Food and Drug Administration—approved evidenced-based treatments for PGAD. **Klifto KM, Dellon AL. Persistent Genital Arousal Disorder: Review of Pertinent Peripheral Nerves. Sex Med Rev 2020;8:265—273.**

Key Words: Arousal; Clitoris; Nerve; Nerve Compression Syndromes; Orgasm; Peripheral Nervous System; Pudendal Nerve; Sexual Behavior

INTRODUCTION

Persistent genital arousal disorder (PGAD) is a condition that is still poorly understood. Its prevalence in the population is still unknown, but it is believed to affect approximately 1% of women.[1] The rarity of the disorder may be due to women fearing consultation for PGAD and the social stigma of being hypersexual.[2] Cultural beliefs may also be a cause of underreported diagnoses.[3] Diagnosis of this rare disorder was first introduced by Leiblum and Nathan in 2001,[4,5] who determined that a diagnosis of PGAD requires patients to meet the following 5 criteria: (i) genitals are persistently aroused, (ii) arousal remains following orgasm or requires multiple orgasms to diminish, (iii) arousal is unrelated to desire, (iv) arousal is triggered by both sexual and non-sexual stimuli, and (v) symptoms are intrusive and unwelcomed.[4,6,7]

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Since then, authors have added and subtracted criteria based on clinical observation and evidence-based medicine with no absolute consensus.[8–10] Additional criteria include sensations of being on the verge of orgasm, compromised orgasm, certain situations aggravating symptoms, symptoms being present for at least 6 months, associated difficulties with psychosocial well-being, inconsistent evidence of genital arousal when symptoms are experienced, and comorbid conditions. Subtracted criteria include unclear trigger of symptoms and symptoms being unwanted, intrusive, and distressing.[5] Unwelcomed or unwanted arousal, however, was reported to be the most common detrimental symptom in 91.3% of women surveyed in the largest study identifying PGAD symptom characteristics.[11] Symptoms can be triggered by sexual stimulation, masturbation, stress, and anxiety.[12] PGAD is a debilitating disease that causes significant distress. It is associated with feelings of shame, isolation, suicidal ideation, and even suicide.[2,4,13–15]

Early literature described PGAD as a disease in the female population; however, more recent published data indicate that this disease affects men, as well.[16–19] Men present differently than women. They may have sensations of arousal and ejaculation or orgasm without an erection.[5] The presence of Tarlov cysts may result in men presenting with erectile pain located in the penile shaft within seconds of arousal and an inability to ejaculate.[20] The pathology in the male population is still unknown.[5]

Etiologies reported for PGAD have been reported to be vascular, neurological, pharmacological, and psychological.[7,13,21,22] Determining the neurophysiological etiology of PGAD began with developing an understanding of the underlying biomechanics of the pudendal nerve and the female sexual response.[23] It is believed that the etiology of PGAD could be explained in terms of neurovascular dysfunction, genital peripheral neuropathy, and/or dysfunctional microvascular arteriovenous shunting.[23] A few authors have proposed that nerve entrapment may be a source of continuous arousal.[21,24,25] Understanding the anatomical locations of the nerve pathways can help explain the sources of pathology.[7]

With regard to peripheral nerve function in the hand, it was reported in 1980 that a minimal degree of chronic nerve compression was interpreted as a hypersensitive response to a vibratory stimulus when applied to the ulnar nerve in patients with cubital tunnel syndrome.[26] With more advanced degrees of ulnar nerve compression, there was decreased perception of the vibratory stimulus. In 2016, using a rat model of chronic nerve compression, it was also observed that the lesser degree of nerve compression resulted in a lowering of the sensory (pain withdrawal) response, indicating a lower threshold (hypersensitivity) for a minimal degree of nerve compression.[27] Therefore, it can be hypothesized that a core feature of PGAD may be the responses in the central and/or peripheral nervous system to a state of increased sensory perception and concomitant neuronal hyperexcitability or disinhibition.[28] The peripheral nerve compression theory can be supported by the altered nerve function that occurs after prolonged sitting or after wearing tight underwear, resulting in hyperesthesia.[7]

The peripheral nerve implicated in PGAD is the dorsal branch of the pudendal nerve, which can be traced from the clitoris/penis to the spinal cord (S2–S4).[29,30] Going from distal to proximal, the dorsal branch is the most distal branch of the pudendal nerve (Figures 1 and 2). It transmits the perception of stimulation from the clitoris/penis, which is then interpreted as the sensation of arousal. This nerve joins with the perineal branch and the inferior rectal branch to form the pudendal nerve in Alcock's canal or the pudendal canal.[31] Going from proximal to distal, the S2, S3, and S4 nerve roots join to form the pudendal nerve within the pelvis, from which the nerve exits with the posterior femoral cutaneous nerve and sciatic nerve through the sciatic notch and deep to the piriformis muscle. The pudendal nerve crosses over the ischial spine and beneath the sacrotuberous ligament. A minimal degree of nerve compression along the pathway of the pudendal nerve may provide a neurological hypothesis of PGAD etiology. Anatomical variations in pudendal nerve pathways have made classifying the degrees and locations of nerve entrapment challenging for this nerve.[24] These variations may predispose certain populations to PGAD and make a standardized diagnostic and treatment approach difficult.[24,32]

History and Physical Examination

From the perspective of a peripheral nerve surgeon, the history for PGAD should include questions about past or current sexual abuse; heightened and/or persistent arousal at the anorectal, urethral, and nipple areas; and orgasm. A medication review should include questioning the patient about the use of antidepressants, including indications for use, discontinuation, and timing in relation to the development of PGAD.[33–38] Inquiring about any trauma to the lumbar or genital area, surgical history, and pregnancy history for women may aid in understanding the natural history of PGAD.[15,28]

The physical examination should always be conducted prior to any diagnostic imaging modality. There is no objective method of detecting or diagnosing PGAD[15]; however, knowledge of nerve distributions can aid in determining the preliminary location of nerve entrapment or injury.[24] Patients should undergo a gynecologic exam focused on the presence of clitoral, vulvar, or labial hyperesthesia, engorgement, or visible varices by a gynecologist prior to being seen by the peripheral nerve surgeon.[28] A careful vaginal exam should assess for pelvic floor tone and the presence of pelvic masses. A cotton tip applicator exam must be performed on the clitoris to examine for hypertrophy or engorgement, hypersensitivity, dysesthesia, or numbness.[7]

Diagnostic Imaging

Magnetic resonance imaging (MRI) can help identify causes of nerve compression and confirm any abnormalities in the nerve or

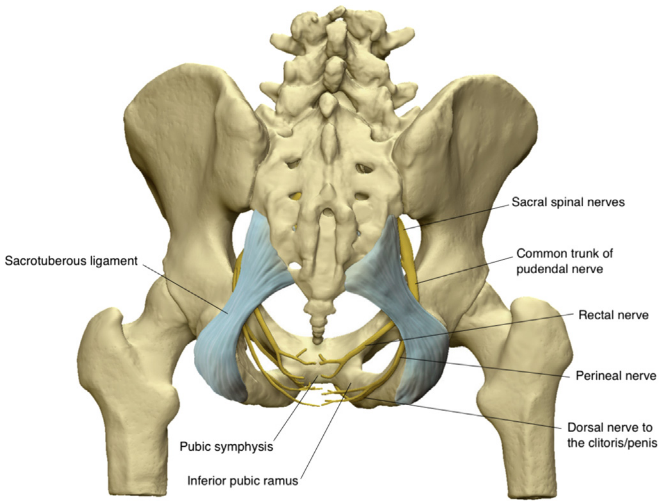

Figure 1. Three-dimensional posterior view of the pelvis.

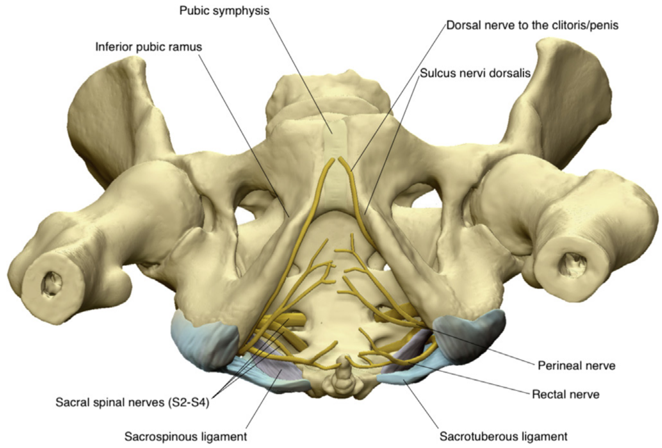

Figure 2. Three-dimensional inferior view of the pelvis.

adjacent structures. If cauda equina is suspected, a sacral and lumbar MRI should be performed.[39–41] Pelvic 3-tesla (3T) MRI is recommended in all patients with suspected nerve entrapment.[7,24]

General Treatment of PGAD

There are currently no Food and Drug Administration (FDA)-approved evidenced-based treatments for PGAD. All evidence comes from case reports and small case series.[14] Treatment should first focus on reversing any underlying causes of PGAD.[7] A multidisciplinary team approach model that consists of a medical provider, pelvic floor physical therapist, and sex therapist was shown to be associated with patient-perceived benefits, satisfaction, and value.[42] Study benefits included improved sexual function (58.1%), patients feeling validated (72.1%) and listened to (62.8%), patients feeling that they better understood their health concerns (65.1%) and that their partner better understood their health concerns (46.5%), and patients experiencing feelings of normalcy (46.5%).[42] If symptoms of PGAD resolve after a nerve block of the pudendal nerve, surgery should be considered as a possible treatment modality.[43] This would include neurolysis of the dorsal nerve to the clitoris/penis, bilaterally, in order to treat PGAD.[44]

DORSAL NERVE TO THE CLITORIS/PENIS

Anatomy and Physiology

The dorsal nerve is the last, or terminal, branch of the pudendal nerve. It arises from within the pelvis, just proximal to the sacrotuberous ligament. At this location, it is usually adjacent to the fascicles that will become the perineal branches and is usually separate from the fascicles that will form the rectal sensory branches. As is usually shown in anatomy textbooks, the dorsal branch may take the same pathway across the pelvis as the perineal branch, which is beneath the fascia of the obturator internus muscle, in which case it will exit the pelvis at the exit of Alcock's canal and follow the inferior pubic ramus to enter the inferior pubic ramus canal.[32] From there, it continues along a groove called the sulcus nervi dorsalis penis/clitoridis located anterior to the pubic bone.[32,44,45] This branch of the pudendal nerve supplies erectile tissue of the corpora cavernosa and the crus clitoris/penis and skin over the dorsal and lateral clitoris/penis.[30,46,47] However, in 90% of cadaver specimens, the dorsal branch takes a separate, more cephalad course across the obturator internus muscle, under its fascia, to exit directly, and obliquely, around the inferior pubic ramus and into the inferior pubic ramus canal. It exits from this location into the sulcus nervi dorsalis and then travels on to the dorsum of the penis.[32]

Injury of the Dorsal Nerve

Injury associated with the dorsal branch of the pudendal nerve manifests as sensory symptoms in the clitoris and penis.[21,48] This is the most distal nerve along the nerve pathway that is directly responsible for sensation in the clitoris/penis.[21] It has no motor components. Injury or compression to this nerve can produce localized symptoms of continual arousal, pain, and numbness associated with PGAD.[44] Given this understanding, PGAD can develop from any trauma or compression to the region of the inferior pubic ramus. This can be due to birth injury, falls, bicycle riding, surgical (sling procedures for stress urinary incontinence) or diagnostic procedures (colonoscopies), clitoral adhesions, and papillary hidradenomas or periclitoral masses.[21,44,49–52]

Treatment of the Dorsal Nerve

Ice or cold packs applied to the clitoris have historically provided temporary symptomatic relief by decreasing peripheral sensation and the feeling of arousal. The short duration of effect limits the utility of this treatment.[2,7] Botulinum toxin type A was administered for treatment in 2 women diagnosed with PGAD. Each received injections with botulinum toxin type A at the periclitoral region to block the dorsal nerve of the clitoris. It must be noted that Botox is FDA approved for muscle injection, and use for a sensory nerve is an off-label use.[53] Both women had resolution of symptoms following the injections. After 8 months, symptoms returned in one of the patients, and at 6 months the other patient still had no symptoms of PGAD. This treatment modality may be beneficial for patients who do not wish to undergo a surgical procedure who are willing to sustain multiple injections.[48]

Drainage and surgical excision of any mass or cyst impinging the dorsal nerve can resolve symptoms of PGAD. A 51-year-old postmenopausal woman presented with a papillary hidradenoma impinging the dorsal branch. Drainage of the mass resulted in symptom relief. When the impingement was surgically removed, the patient had resolution of all symptoms of PGAD.[21]

In a study by Klifto and Dellon,[44] neurolysis of the dorsal branch of the pudendal nerve resolved arousal symptoms in all 8 women with PGAD. There were no observed complications with the procedure. One patient with unilateral neurolysis had a return of symptoms. Treating patients with bilateral neurolysis can improve PGAD symptoms in patients with dorsal nerve involvement. With regard to a diagnostic indication and criterion for surgery, the 8 women with PGAD each showed tenderness or pain in response to palpation of the inferior pubic ramus canal, located where the inferior pubic ramus joins the pubic symphysis.[44]

PUDENDAL NERVE MAIN TRUNK

Anatomy and Physiology

The nerve originates from the branches of the sacral plexus.[54] It receives contributions mainly from the second to fourth sacral ventral primary rami (S2—S4). Parasympathetic outflow from S2—S4 is termed pelvic splanchnic nerves and goes to the ganglia impar. Axons and their origins from the spinal cord vary depending on a pre- or postfixed sacral plexus. In a prefixed sacral plexus, the main contributions originate from S2—S3. In a postfixed sacral plexus, the main contributions arise from S3—S4 (Figure 3).[32] The nerve is comprised of visceral afferent (sensory) and visceral motor fibers to the anal, perineal, and genital region. Voluntary contraction of muscle motor fibers may enhance arousal and pleasure during intercourse.[54] Motor branches of the pudendal nerve innervate the anal and urethral sphincters.[55] Stimulation of low-threshold pudendal sensory fibers leads to activation of motoneurons and contraction of the perineal muscles.[30,32,47]

Symptoms Related to Injury of the Main Trunk

Symptoms may manifest as pain, numbness, sexual, and sphincter dysfunction in the saddle area located between the legs. This area includes the genitalia, rectum, and terminal urinary tract.[24] Concomitant development of urinary or fecal symptoms

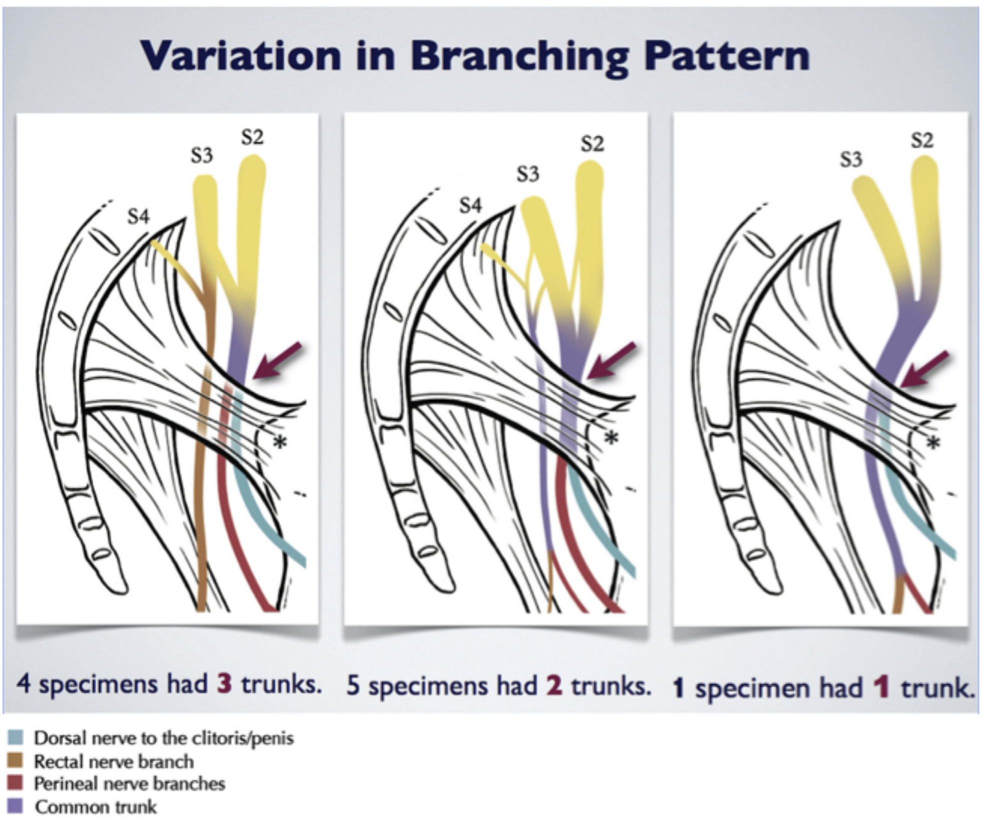

Figure 3. Left image (A) represents 40% of anatomy variations, center image (B) represents 50% of anatomy variations, and right image (C) represents 10% of the anatomy variations that were identified in the cadaver dissection; maroon arrow indicates the trunks posterior to the sacrospinous ligament; * indicates sacrospinous ligament attachment to ischial spine.[32]

can manifest as fecal incontinence, urinary urgency/frequency, and urge urinary incontinence.[56,57] Sexual dysfunction can include continuous sexual arousal, absence of sensation, male impotence, dyspareunia, or genital contractions.[24] The most common locations of symptoms in women are the clitoris, followed by the vagina, and labia.[7] PGAD can develop due to local trauma causing mechanical damage to the saddle area or from birth injury, small fiber polyneuropathy, strained muscles or muscle spasms from a hypertonic obturator internus or piriformis, masses, ganglion cysts, ureteral surgery, pudendal nerve transection resulting in a phantom phenomenon, and bicycle riding.[7,18,24,58–60]

Treatment of the Main Trunk

Bupivacaine, botulinum toxin type A, hyaluronidase, can be used alone or in combination for nerve entrapment. Different doses can be administered based on the site and target of application. Bupivacaine can be administered at decreasing volumes into the piriformis muscle, obturator internus, and the entrance to Alcock's canal.[24,61] If botulinum toxin type A is administered into the muscle, bupivacaine can be administered at 50% of the previous volume.[24] If hyaluronidase is administered along the nerve, bupivacaine can be administered at 50% of the previous volume, similarly to co-administration with botulinum toxin. Reports of responses to treatment with injections along the course of the pudendal nerve prove indicate that the procedure is highly effective. At a 1-year follow-up, longstanding relief with no recurrence was seen in 24 patients (12%).[24] Another study reported complete resolution of symptoms at the 3-month follow-up with botulinum toxin type A.[62] Injections require continual administration for symptomatic relief in most patients. They are valuable diagnostically to determine if the nerve is the source of involvement. If a patient requires longstanding relief other treatment modalities should be considered.[24,62]

Physical therapy directed at the pelvic floor can help reduce muscle hypertonicity and edema causing nerve compression.[2,63] This can help decrease muscle contraction responsible for compression and stimulation of the pudendal nerve. A 27-year old pregnant female benefited from pelvic floor manual therapy directed at the pudendal nerve.[25] This can help strengthen pelvic floor muscles. Daily pelvic floor exercises of 20 to 30 5-second pelvic contractions and swimming were prescribed along with a v-brace, a pregnancy garment belt that supports the vulva. Pelvic floor massage may be useful in women with increased tone of the pubococcygeus, iliococcygeus, and puborectalis muscles or abnormal bulbocavernosus reflex on pelvic exam.[2,7,25,62,63] The 27-year old female reported suffering less genital engorgement and vulvar pressure. Fourteen weeks after her treatment with physical therapy and a v-brace, she reported resolution of her PGAD symptoms.[25]

Application of a transcutaneous electrical nerve stimulation unit to the pudendal dermatomes was found to be effective in treating 2 patients (male and female) out of 4 with PGAD and restless leg syndrome.[8,17,64] This approach may provide a less invasive treatment option prior to surgery.

Pudendal nerve stimulation may magnify afferent pathway recruitment, permitting a greater response to therapy. It can remove the abnormal irritation of the pudendal nerve resulting from compression and globally modulate complex somatic and autonomic pathways with urological, sexual, and gastrointestinal dysfunction through stimulation at different levels with different parameters. It has the benefit of improving chronic pelvic pain, bowel, and bladder dysfunction.[55] Six women with PGAD underwent 2-stage implantation of a neuromodulator using an ischiorectal approach at the pudendal nerve under neurophysiologic guidance. With 50% resolution of symptoms, these patients had a second neuromodulator placed in the upper buttock region. Five patients had concurrent urinary and fecal symptoms, 5 patients had a resolution of symptoms after placement of both neuromodulators, 2 patients had device migration, and 1 device had to be reprogrammed. One patient requested that the device be removed.[56] Pudendal neuromodulation is not an FDA-approved treatment modality. It is an option for patients who have failed sacral neuromodulation for refractory overactive bladder and interstitial cystitis or chronic pelvic pain.[56]

PERCEPTION OF SEXUAL AROUSAL (SPINAL NERVES)

Anatomy and Physiology

The perception of sexual arousal is a complex phenomenon that involves many neurological pathways. A peripheral stimulus originating from the vagina and clitoris is transmitted by a combination of somatic and visceral afferent pathways. The pudendal nerve is responsible for transmitting the majority of somatic sensory information from the external genitalia and perigenital area to the spinal cord. The hypogastric, pelvic, and vagus nerves contain visceral sensory fibers that transmit information from pelvic organs to the spinal cord.[65] Intraspinal regulation by inhibitory gabaergic and excitatory glutamatergic interneurons is believed to contribute to the integration of peripheral information, along with the volume of information transmitted to supraspinal structures. When the signal reaches the spinal cord, autonomic motor outflow is mediated by preganglionic stimulatory parasympathetic and inhibitory sympathetic fibers. The sacral parasympathetic nucleus is at the sacral level and the dorsal gray commissure. The pelvic nerve (S2–S4) transmits parasympathetic stimulatory signals. The inhibitory sympathetic fibers can be found at the intermediolateral cell column at the thoracolumbar level (T12–L2).[54] The hypogastic nerve and paravertebral sympathetic chain transmits sympathetic inhibitory signals. The motor response to the sensory phenomenon of sexual arousal results in vasocongestion and neuromuscular events. This is observed as clitoral engorgement.[54,66] In males, ejaculation requires a sympathetic input.[67]

Etiology of Sacral Nerve Involvement in PGAD

Compression at the location of the sacral nerve roots of S2, S3, and S4 can produce radiculopathy symptoms such as sacral, perineal, buttock, lower back, and leg pain or numbness. The bladder, bowel, and function of sexual organs can be involved, as well, manifesting as bladder dysfunction, incontinence, retrograde ejaculation, and impotence in men.[7,68,69] PGAD can develop from meningeal cysts found in the sacral spinal canal.[68,70] The most common meningeal cysts are extradural cysts that arise from the dura of the spinal sac or nerve roots and project into the spinal canal.[68] Tarlov or perineurial cysts are the most common extradural cysts impinging surrounding neurological structures.[68–70] They are estimated in 1.5% of the general population.[70] More important than the type of cyst involved is the location of impingement.[68] Cysts located near the spinal cord entry of the pudendal, hypogastric, and pelvic genital sensory nerves can reproduce PGAD symptoms.[22,68,70] Tarlov cysts in males may manifest as rapid onset of pain exclusively along the penile shaft with erections and the inability to ejaculate.[20,71] Recently, cauda equina–based lumbar and sacral pathologies have been found to result in radiculitis of sacral spinal nerve roots, causing PGAD.[72]

Treatment of Spinal Nerve Involvement

Nerve blocks with epidural anesthesia might temporarily suppress arousal symptoms if Tarlov cysts are the cause.[43,70] Needle aspiration, fibrin glue injection, cyst fenestration, cyst resection, and subarachnoid drainage are potential treatment modalities for Tarlov cysts.[7] A sacral nerve stimulation device may be permanently implanted into the patient to primarily target the somatic response.[55] It can be placed either by a transcutaneous technique under fluoroscopy or by direct surgical approach if there has been prior surgery in the region.[73,74] Targeting the conus medullaris will directly affect all nerves downstream. If the patient's underlying pathology is located in the spinal canal or at the conus medullaris, this approach can be beneficial; however, targeting the conus medullaris has not been attempted exclusively in women with PGAD.[72]

In a prospective series of 27 patients with pudendal neuralgia that failed to improve after pudendal nerve decompression surgery, the patients responded well to spinal cord stimulation at the level of the conus medullaris. Twenty-two of the patients had bilateral symptoms, explaining the importance of a bilateral decompression. This may explain the lack of response to unilateral decompression and the trial of sacral neuromodulation.[44,74] Superficial infections and device migration can occur with placement of the device.[74]

A case study reported treating a patient diagnosed with PGAD by bilateral release of the pudendal nerve and insertion of a 4-lead neuromodulator. Two leads were placed at the sacral hiatus to target pelvic and perineal pain, and 2 leads were placed adjacent to the pudendal nerves to target urinary and arousal symptoms. The leads in each location were programmed specifically to target symptoms. Six months following treatment, the patient had resolution of her sensation of arousal, no pelvic pain, and mild urinary urgency and frequency.[55] A similar case study of sacral neuromodulation reported a greater than 50% improvement in PGAD symptoms in a female patient.[57]

Surgery may be performed for nerve impingement. In a case-series study of 15 women suffering from PGAD, meningeal cysts in the sacral spinal canal caused sacral nerve root compression. Eight of these cysts were Tarlov cysts. Patients suffered from bladder, bowel, and perineal symptoms. Following surgery, 91% of the women had resolution of PGAD symptoms.[68] PGAD has been reported to resolve in other studies following surgical removal of meningeal cysts if they are the source of symptoms.[33,69,70]

CONCLUSION

Most of the literature for PGAD comes from case studies.[18,21,25,56,75,76] The diagnosis of PGAD itself is still a debated topic of discussion.[15] A multidisciplinary team approach consisting of a medical provider, pelvic floor physical therapist, and sex therapist has been shown to be beneficial.[42] There are currently no FDA-approved evidenced-based treatments for PGAD. Pelvic 3T MRI is recommended in all patients with suspected nerve entrapment(7, 24). Lumbosacral 3T MRI is recommended if a Tarlov cyst or a herniated intervertebral disc (involving cauda equina) is suspected.[72] Associated PGAD symptoms will depend on the segment of the nerve involved. If the peripheral nerve is the source of the pathology, surgical intervention may be curative.[14,62] Future studies should focus on a multidisciplinary group collaboration of experienced providers and recruitment of patients into larger prospective clinical trials. The development of a patient-reported outcome instrument could better assess treatment outcomes and quality of life.

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