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TITLE**A hypothesis for anatomical pathways of chronic pelvic pain “of unknown origin”.**

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Short title

Unsupported visceral plexuses may cause chronic pelvic pain.

ABSTRACT**Background**

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a disabling bladder condition. ESSIC, the IC/BPS society defines two types of IC/BPS: with Hunner’s lesion (HL) and without. Pathogenesis is stated as unknown, with no cure possible. Scheffler in 2021 reported cystoscopically validated cure of HL IC/BPS by repair of uterosacral ligaments (USL) and in 2022, Goeschen reported non-HL IC/BPS cure in 198 women following USL repair. Both Scheffler and Goeschen hypothesized IC/BPS may be a phenotype of the Integral Theory’s Posterior Fornix Syndrome “PFS” (chronic pelvic pain, OAB and emptying dysfunctions) and therefore potentially curable.

Summary

The hypothesis explores whether visceral plexuses (VP), due to weakened uterosacral ligaments support, serve as a primary source of pelvic pain impulses, leading to development of an inflammatory condition - for example,

Interstitial Cystitis/Bladder Pain Syndrome, a chronic inflammatory condition, which shares similarities with vulvodynia and Complex Regional Pain Syndrome (CRPS). According to our hypothesis, such conditions involve axon reflexes. Stimuli such as gravity applied to unsupported nerve branches within the visceral pelvic plexus, trigger centrally propagating impulses, which then progress antidromally to influence innervated tissues through cytokine release and nociceptor stimulation, perpetuating inflammatory processes at the end organs, and pain perception.

Key messages

The hypothesis raises the question, “are IC/BPS, vulvodynia, other pain sites, even non-bacterial “chronic prostatitis” in the male, different phenotypes of the chronic pelvic pain syndrome which includes PFS. If so, the hypothesis opens several new research directions, and would predict inflammatory findings in tender endorgan pain sites.

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Key words Chronic pelvic pain; posterior fornix syndrome; Integral Theory; vulvodynia; IC/BPS; uterosacral ligaments; visceral plexus.

INTRODUCTION

The current state of knowledge of pathogenesis of IC/BPS (Interstitial Cystitis/Bladder pain syndrome) is best described by Winston Churchill’s description of Russia.: *“a riddle wrapped in a mystery inside an enigma: but perhaps there is a key. That key is Russian national interests.”*

Whatever the IC/BPS works examined, the results are the same, “pathogenesis unknown, no cure possible” Our hypothesis hopefully will lead to a key for better understanding of IC/BPS.

The prevalence of IC/BPS varies between 21-197/100,000 in women with the proportion for men steady at 20% that of women [1]. However, the ratio can be as high as 10.1 [2]

The AUA (American Urological Association) guidelines conclude “IC/BPS is a heterogeneous clinical syndrome. Even though patients present with similar symptoms of bladder/pelvic pain and pressure/discomfort associated with urinary frequency and strong urge to urinate, there are subgroups or phenotypes within IC/BPS.”[3] “Treatment is categorized into behavioral/non-pharmacologic, oral medicines, bladder instillations, procedures, and major surgery”[3].

The hypothesis , VIDEO1, originates from the histologically validated case report by Scheffler et al. in 2021, documenting the cure of IC/BPS (Interstitial Cystitis/Bladder pain syndrome) [4]. Scheffler et al. applied the diagnostic and surgical criteria of the Posterior Fornix Syndrome (PFS) [5], a component of the Integral Theory of Female Urinary Incontinence. During pre-operative assessment, Scheffler utilized the speculum test to mechanically support the uterosacral ligaments (USLs) [6], resulting in alleviation of both pain and urge symptoms, indicating a potential for USL repair to provide a cure. Coincidentally, a Hunner’s lesion (HL) was discovered during routine cystoscopy, further underscoring the relationship between USL dysfunction and pelvic pain. Goeschen et al. subsequently corroborated Scheffler’s findings by re-examining PFS surgical data and found non-Hunner’s lesions among women with chronic pelvic pain [7].

A laparoscopically controlled study in 1996, reported cure of CPP in a significant proportion of cases following native vaginal USL plication [8]. Histological analysis revealed nerve fibers within the USL tissue, leading to the hypothesis that lax USLs fail to support visceral plexuses (VPs), resulting in aberrant pain impulses. This hypothesis was further tested in 2010, where local anesthetic injection into USLs provided immediate relief of pelvic pain in women with IC/BPS, supporting the role of VPs in pelvic pain perception [9].

MAIN TEXT

Focusing on pelvic pain etiology, our hypothesis addresses the anatomical and physiological pathways leading to the formation of Hunner’s lesion (HL) or urothelial ulceration, with similar pathophysiology for vulvodynia and other phenotypes of chronic pelvic pain, Figure1. Dismissing the urge component of IC/BPS [10], we emphasize the inflammatory nature of HL and Hunner’s ulcers, akin to Complex Regional Pain Syndrome (CRPS)[11-13]. Instead of limb trauma, we implicate gravity-induced stimulation of unsupported VPs in females with

characteristics of Posterior Fornix syndrome, leading to chronic pelvic pain. Incorporating the axon reflex concept [14,15], we elucidate the cascade of events involving cytokine release and nociceptor stimulation, perpetuating inflammatory changes and tissue injury in affected female individuals.

*predictably co-occurring symptoms of chronic pelvic pain, urge, frequency, nocturia, caused by uterosacral ligament (USL) laxity, and cured by USL repair

Hypothesis in brief

1. Gravity stimulates the pain receptors on the axons of nerves in richly innervated tissues.
2. Because of the axon reflex phenomenon the centripetal impulse on all affected axons also passes along all their axonal branches.
3. The terminals of these branches release a range of cytokines - some are strongly inflammatory others stimulate nociceptors.
4. The inflammatory cytokines induce a powerful inflammatory response on the adjacent vasculature, including "glomerulation" (dilated congested venules with extravasated erythrocytes).
5. The repeated stimulation of nociceptors (through gravity and through cytokines) results in the process being amplified and becoming chronic.

Evidence supporting direct stimulation of afferent axons includes observations which attributed pain relief to gravity, as it was alleviated by lying down [8]. Furthermore, in half of the women, the use of a ring pessary relieved pain, indicating a potential origin from the posterior vaginal fornix [8]. Palpation of the cervix reproduced pain at the site felt by the patient [8]. Additionally, the speculum test and the Bornstein Test (involving injection of local anesthetic into the lower end of USLs to anesthetize the VPs), provided immediate simultaneous relief of pelvic pain [8,16].

In the context of vulvodynia and chronic pelvic pain, immunohistochemical studies have revealed a tenfold increase in nerve fiber density in the stroma of women with vulvodynia compared to controls [17]. Nociceptor nerve fibers penetrate the basal membrane and continue vertically towards the epithelial surface, accompanied by increased numbers of immune cells such as T cells, macrophages, B cells, and mast cells in areas of heightened sensitivity [18,19]. Heparanase discharged from mast cells plays a pivotal role in degrading connective tissue and epithelial basement membranes, facilitating the penetration of proliferating nerve fibers into the epithelium [20].

Biopsies from patients with BPS/IC with Hunner's ulcer reveal ulceration with granulation tissue and a complete lack of the urothelium [21]. Thick nerve bundles are identified in deep granulation tissue, along with fine PGP9.5-positive nerve fibers and clusters of activated mast cells in the ulcer bed, suggesting sensory hyperinnervation [21]. Lymphocytic infiltration and urothelial defects are also observed, yielding high sensitivity and specificity for the prediction of BPS/IC with or without Hunner lesions [21].

Heparanase-mediated degradation of connective tissue and epithelial basement membranes facilitates the penetration of nerve fibers into the epithelium [20] in vulvodynia. It also explains the "bare areas" (ulcers) in the urothelium [21], which is much thinner than vulval tissue, and therefore more likely to break down into an ulcer than vulval tissue. Elevated heparanase levels in richly innervated tissues correlate with other pelvic inflammatory states [22]. Our hypothesis may extend to formation of glomerulations: heparanase could also degrade the connective tissue in the bladder veins causing them to bulge balloon-like if bladder wall distension by cystometry leads to venous blockage, venous bulging (glomerulations) and subsequent bursting of blood vessels.

Though not infrequently encountered in IC/BPS, the potential role of glomerulations as an objective diagnostic marker is controversial, and not supported by a systematic review [23]. Such group findings in systematic reviews, do not, however, necessarily invalidate the possibility of glomerulations as an early warning sign of IC/BPS in an individual patient. If so, our hypothesis provides an anatomical pathway. Our hypothesis also predicts evidence of inflammation upon biopsy of other end organ pain sites, such as the paraurethral area.

CONCLUSIONS

The European Urology Guidelines which addressed chronic pelvic pain in both females and males, concluded that understanding the aetiopathogenesis of the condition remains inadequate, and current treatment strategies were frequently ineffective [24]. Our data as regards the endorgan inflammatory response is mainly from female experiments, and for USL etiology of CPP also. However, successful cure of post-prostatectomy incontinence by a TFS minisling using surgical protocol based on the female [25], and subsequent discovery of a male USL analogue [26] suggested that there may indeed be parallel anatomy between female and males. This caused us to extend the hypothesis to non-bacterial chronic prostatitis in the male, Table1.

How to test the hypothesis?

If our hypothesis for pathogenesis holds, the question then becomes what will act as a "circuit breaker" in this situation. There are two choices:

Pharmacologic

Theoretically, a Gabapentin-like drug which inhibits the voltage gated calcium channels in nerves – reducing both pain impulses and cytokine secretion may help. Though Gabapentin itself is said to be not effective for chronic pelvic pain [27], other pharmacotherapy which inhibits the voltage gated calcium channels in nerves may be effective.

Strengthen USL surgically or mechanically.

Testing the hypothesis surgically presents ethical challenges regarding the proposal of USL surgery as a diagnostic method for a condition with a multifactorial origin [24], despite the predictive value of local anesthetic and speculum tests [6,8,16]. Moreover, the reports of both Hunner's lesion (HL) and non-HL cases were based on surgery for Posterior Fornix Syndrome, rather than IC/BPS [4,7]. Thus, a less invasive approach is warranted. One such method under development is the "Control Plus" device, which employs two small inflatable balloons in the posterior fornix of the vagina to mechanically support lax USLs. Pre- and post-use cystoscopy, with or without biopsy, would be employed to assess inflammatory cells.

Chronic pelvic pain in the male The discovery of a male USL analogue via laparoscopy, confirmed by biopsy, near the VPs, offers insight into the possible applicability of our IC/BPS hypothesis to males with non-infective "chronic prostatitis," mirroring symptoms of women with Posterior Fornix Syndrome, Table1 [26]. Plication laparoscopy of the male USL analogue ligament is predicted to alleviate or improve symptoms of "chronic prostatitis." Such an initiative faces the ethical problem of experimental surgery without adequate proof of pathogenesis. Pre-operative mechanical support of USL, as in the female, is not possible in the male.

Concluding remarks The hypothesis explores whether weakened uterosacral ligament support of visceral plexuses (VP) serves to activate VPs as a primary source of pelvic pain impulses, leading to development of an inflammatory condition seen in both vulvodynia and IC/BPS. The hypothesis raises the question, "are IC/BPS, vulvodynia, and other pelvic pain sites (Figure1), different phenotypes of a chronic pelvic pain syndrome based on weak uterosacral ligaments? If so, the hypothesis opens several new research directions, and would predict inflammatory findings in tender endorgan pain sites, such as the paraurethral area of the vagina.

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CONFLICT OF INTEREST STATEMENT

Other than application for a patent for the Control Plus device, Peter Petros has no financial interest or royalties, or any form of support or financial involvement (e.g., employment, consultancies, honoraria, stock ownership and options, expert testimony, grants which took place in the previous three years). Peter Petros has received no sales or royalties. There are no sponsors to the study design, execution and analysis, and manuscript conception, planning, writing and decision to publish. There are no nonfinancial relationships (personal, political, or professional) that may potentially influence the writing of the manuscript.

John Papadimitriou and Jacob Bornstein have no conflicts of interest in the above or otherwise.

Author contributions- all authors PP,JP,JB contributed to conceptualization and writing. Figures and table by Peter Petros

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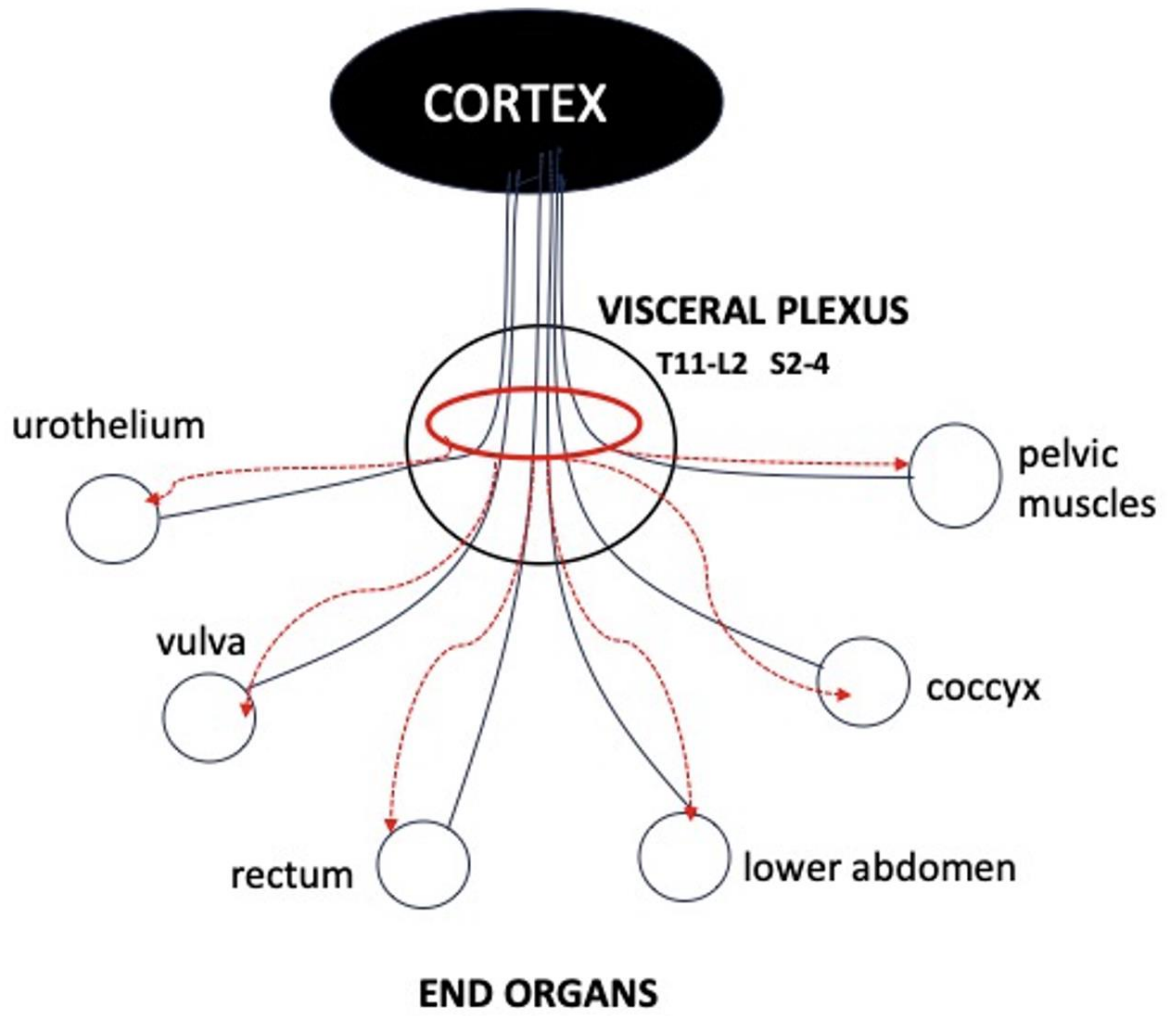
Figure 1 A general hypothesis role of the Axon reflex in female chronic pelvic pain

The black lines to the cortex represent afferent visceral nerves which enter the visceral plexuses (VPs) and proceed onwards to a ganglion. The visceral plexuses are supported by the lower end of the uterosacral ligaments (USLs), about 2cm before the USLs insert not the cervix.

The red ellipse shows the bunching of the afferent axons in the VPs. In the standing position, each of the component axons in the unsupported VPs (unbroken lines) are stimulated by the force of gravity and they send afferent signals to the cortex.

This “bunching” in the ellipse explains the simultaneous relief of several pain centres with the speculum tests and local aesthetic injection into the USLs. Activation of the axon reflex sends antidromic impulses back to the endorgan receptors which stimulate an inflammatory reaction which can cause pain.

Accepted Manuscript



Accepted

Table 1 Comparison of non-bacterial “Chronic Prostatitis” and Posterior Fornix Syndrome symptoms.

Chronic Prostatitis

- Pain constant or variable
- Frequency
- Urgency
- Nocturia
- Perineal pain
- Pain in testicles/scrotum
- Pain ejaculating

Posterior Fornix Syndrome

- Pain constant or variable
- Frequency
- Urgency
- Nocturia
- Perineal pain
- Pain in vagina/vulva
- Dyspareunia
- Low abdominal pain