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A Hypothesis for Anatomical Pathways of Chronic Pelvic Pain of "Unknown Origin"

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Hypothesis in Brief

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

Keywords
Chronic pelvic pain · Posterior fornix syndrome · Integral theory · Vulvodynia · Interstitial cystitis/bladder pain syndrome · Uterosacral ligaments · Visceral plexus

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 (USLs) 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 (VPs), due to weakened USLs support, serve as a primary source of pelvic pain impulses, leading to development of an inflammatory condition – for example, IC/BPS, 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

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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 nonbacterial "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 end organ pain sites. © 2024 S. Karger AG, Basel

Introduction

The current state of knowledge of pathogenesis of interstitial cystitis/bladder pain syndrome (IC/BPS) 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 American Urological Association (AUA) 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, online supplementary VIDEO1 (for all online suppl. material, see https://doi.org/10.1159/000539647), originates from the histologically validated case report by Scheffler et al. [4] in 2021, documenting the cure of IC/BPS. 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 preoperative 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. [7] subsequently corroborated Scheffler's findings by re-examining PFS surgical data and found non-HLs among women with chronic pelvic pain.

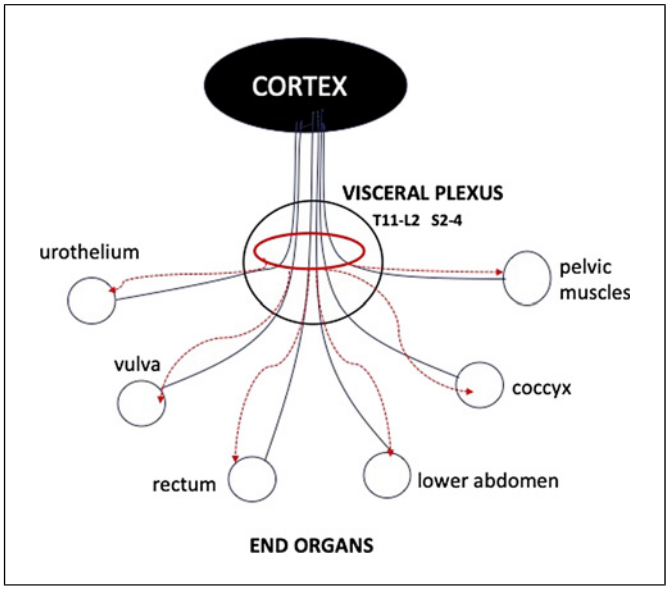

Fig. 1. General hypothesis role of the Axon reflex in female chronic pelvic pain. The black lines to the cortex represent afferent visceral nerves which enter the visceral plexuses (VPs) and proceed onwards to a ganglion. The VPs are supported by the lower end of the uterosacral ligaments (USLs), about 2 cm before the USLs insert into 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) is 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 centers with the speculum tests and local anesthetic injection into the USLs. Activation of the axon reflex sends antidromic impulses back to the end organ receptors which stimulate an inflammatory reaction which can cause pain.

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].

Focusing on pelvic pain etiology, our hypothesis addresses the anatomical and physiological pathways leading to the formation of HL or urothelial ulceration, with similar pathophysiology for vulvodynia and other phenotypes of chronic pelvic pain (Fig. 1). Dismissing the urge

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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.

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 toward 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 HLs [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.

Table 1. Comparison of nonbacterial "chronic prostatitis" and posterior fornix syndrome symptoms

Chronic prostatitis	Posterior fornix syndrome
• Pain constant or variable	• Pain constant or variable
• Frequency	• Frequency
• Urgency	• Urgency
• Nocturia	• Nocturia
• Perineal pain	• Perineal pain
• Pain in testicles/scrotum	• Pain in vagina/vulva
• Pain ejaculating	• Dyspareunia
	• Low abdominal pain

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 end organ inflammatory response are 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 analog [26] suggested that there may indeed be parallel anatomy between female and males. This caused us to extend the hypothesis to nonbacterial chronic prostatitis in the male (Table 1).

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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 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 analog via laparoscopy, confirmed by biopsy, near the VPs, offers insight into the possible applicability of our IC/BPS hypothesis to males with noninfective "chronic prostatitis," mirroring symptoms of women with Posterior Fornix Syndrome (Table 1) [26]. Plication laparoscopy of the male USL analog 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. Preoperative mechanical support of USL, as in the female, is not possible in the male.

Concluding Remarks

The hypothesis explores whether weakened USL support of VPs 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 (Fig. 1), different phenotypes of a chronic pelvic pain syndrome based on weak USLs? If so, the hypothesis opens several new research directions and would predict inflammatory findings in tender end organ pain sites, such as the paraurethral area of the vagina.

Statement of Ethics

Patient consent statement, permission to reproduce material from other sources, and clinical trial registration are not applicable.

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 3 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.

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Author Contributions

P.P., J.P., and J.B. contributed to conceptualization and writing. Figures and table were contributed by P.P.

References

1 Clemens JQ, Meenan RT, Rosetti MC, Gao SY, Calhoun EA. Prevalence and incidence of interstitial cystitis in a managed care population. J Urol. 2005;173(1):98–102; discussion 102. https://doi.org/10.1097/01.ju.0000146114.53828.82

2 Hand JR. Interstitial cystitis: report of 223 cases (204 women and 19 men). J Urol. 1949;61(2):291–310. https://doi.org/10.1016/S0022-5347(17)69067-0

3 Clemens J, Erickson DR, Varela NP, Lai HH. Diagnosis and treatment of interstitial cystitis/bladder pain syndrome. J Urol. 2022;208(1):34–42. https://doi.org/10.1097/JU.0000000000002756

4 Scheffler KU, Hakenberg OW, Petros PE. Cure of interstitial cystitis and non-ulcerating Hunner's Ulcer by cardinal/uterosacral ligament repair. Urol Int. 2021;105(9–10):920–3. https://doi.org/10.1159/000515647

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5 Petros PE, Ulmsten U. The posterior fornix syndrome: a multiple symptom complex of pelvic pain and abnormal urinary symptoms deriving from laxity in the posterior fornix. Scand J Urol Nephrol. 1993;27(Suppl 153): 89–93.
6 Wu Q, Luo L. Petros PEP Case report: mechanical support of the posterior fornix relieved urgency and suburethral tenderness. Pelviperineology. 2013;32:55–6.
7 Goeschen K, Gold D, Liedl B, Yassouridis A, Petros PE. Non-Hunner's interstitial cystitis is different from hunner's interstitial cystitis and may Be curable by uterosacral ligament repair. Urol Int. 2022;106(7):649–57. https://doi.org/10.1159/000524321
8 Petros PP. Severe chronic pelvic pain in women may be caused by ligamentous laxity in the posterior fornix of the vagina. Aust N Z J Obstet Gynaecol. 1996;36(3):351–4. https://doi.org/10.1111/j.1479-828x.1996.tb02727.x
9 Petros PEP. Interstitial cystitis (painful bladder syndrome) may, in some cases, be a referred pain from the uterosacral ligaments. Pelviperineology. 2010;29:56–9.
10 Liedl B, Inoue H, Sekiguchi Y, Haverfield M, Richardson P, Yassourides A, et al. Is overactive bladder in the female surgically curable by ligament repair? Cent Eur J Urol. 2017;70(1):53–9. https://doi.org/10.5173/ceju.2017.938
11 Dubuis E, Thompson V, Leite MI, Blaes F, Maihofner C, Greensmith D, et al. Longstanding complex regional pain syndrome is associated with activating autoantibodies against alpha-1a adrenoceptors. Pain. 2014;155(11):2408–17. https://doi.org/10.1016/j.pain.2014.09.022
12 Shim H, Rose J, Halle S, Shekane P. Complex regional pain syndrome: a narrative review for the practising clinician. Br J Anaesth. 2019;123(2):424–33. https://doi.org/10.1016/j.bja.2019.03.030
13 Huygen FJ, De Bruijn AG, De Bruin MT, Groeneweg JG, Klein J, Zijlstra F. Evidence for local inflammation in complex regional pain syndrome type 1. Mediators Inflamm. 2002;11:47–51. https://doi.org/10.1080/09629350210307
14 Wardell K, Naver HK, Nilsson GE, Wahlin BG. The cutaneous vascular axon reflex in humans chartered laser Doppler perfusion imaging. J Physiol. 1993;460:185–9.
15 Yaprak M. The axon reflex. Neuroanatomy. 2008;7:17–9.
16 Bornstein J, Zarfati D, Petros PEP. Causation of vulvar vestibulitis. ANZJOG. 2005;45: 538–41.
17 Bornstein J, Goldschmid N, Sabo E. Hyperinnervation and mast cell activation may be used as histopathologic diagnostic criteria for vulvar vestibulitis. Gynecol Obstet Invest. 2004;58(3):171–8. https://doi.org/10.1159/000079663
18 Bohm-Starke N, Hilliges M, Falconer C, Rylander E. Neurochemical characterization of the vestibular nerves in women with vulvar vestibulitis syndrome. Gynecol Obstet Invest. 1999;48(4):270–5. https://doi.org/10.1159/000010198
19 Bashkin P, Razin E, Eldor A, Vlodavsky I. Degranulating mast cells secrete an endoglycosidase that degrades heparan sulfate in subendothelial extracellular matrix. Blood. 1990;75(11):2204–12. https://doi.org/10.1182/blood.V75.112204.2204
20 Bornstein J, Cohen Y, Zarfati D, Sela S, Ophir E. Involvement of heparanase in the pathogenesis of localized vulvodynia. Int J Gynecol Pathol. 2008;27(1):136–41. https://doi.org/10.1097/pgp.0b013e318140021b
21 Regauer S, Gamper M, Fehr MK, Viereck V. Sensory hyperinnervation distinguishes bladder pain syndrome/interstitial cystitis from overactive bladder syndrome. J Urol. 2017;197(1):159–66. https://doi.org/10.1016/j.juro.2016.06.089
22 Xu H, Shi X, Li X, Zou J, Zhou C, Liu W, et al. Neurotransmitter and neuropeptide regulation of mast cell function: a systematic review. J Neuroinfl. 2020;17(1):356–71. https://doi.org/10.1186/s12974-020-02029-3
23 Wennevik GE, Meijlink JM, Hanno P, Nordling J. The role of glomerulations in bladder pain syndrome: a review. J Urol. 2016;195(1):19–25. https://doi.org/10.1016/j.juro.2015.06.112
24 Engeler DS, Baranowski AP, Dinis-Oliveira P, Elneil S, Hughes J, Messelink EJ, et al, European Association of Urology. The 2013 EAU guidelines on chronic pelvic pain: is management of chronic pelvic pain a habit, a philosophy, or a science? 10 years of development. Eur Urol. 2013;64(3):431–9. https://doi.org/10.1016/j.eururo.2013.04.035
25 Muctar S, Ende D, Petros P. Retropubic TFS Minisling for postprostatectomy male incontinence: first report. Urol Int. 2022;106(3): 249–55. https://doi.org/10.1159/000520629
26 Farag A, Nasr SE, Elbarmelgi MY, Farag AA, Petros P. Prostato-sacral Ligament, description of a new anatomy in males, its clinical significance and anatomic similarity to female anatomy. Pelviperineology. 2019;38:115–7.
27 Horne AW, Vincent K, Hewitt CA, Middleton LJ, Koscielniak M, Szubert WAL, et al. Gabapentin for chronic pelvic pain in women (GaPP2): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2020; 396:909–17 Issue 10255 P909-917 September 26 2020. https://doi.org/10.1016/S0140-6736(20)31693-7

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