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TOPIC PAPER

Etiology of chronic prostatitis/chronic pelvic pain syndrome: psychoimmunoneurendocrine dysfunction (PINE syndrome) or just a really bad infection?

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Abstract
Purpose To review the etiology and pathogenesis of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).
Methods A literature review for the years 1985–2012 was performed using the MEDLINE database of the United States National Library of Medicine.
Results The evidence for ongoing infection in men with CP/CPPS is lacking. However, men with CP/CPPS are twice as likely to have had a sexually transmitted disease (STD), and bacteria from men with CP/CPPS may be phenotypically different from those that cause cystitis or acute prostatitis. Evidence continues to support an alteration in both the afferent and efferent autonomic nervous systems. Functional brain imaging suggests changes in the gray matter as well as the importance of the anterior insula and anterior cingulated gyrus in pain processing. Neural function can be modulated by immune and endocrine factors. Alterations in cytokine function and autoimmunity appear to play a role in the immune dysfunction. Alterations in the hypothalamic–pituitary–adrenal axis can mediate the endocrine effects, similar to many other chronic pain conditions. Genetics may play a role in who may develop chronic pain after an initial insult. Finally, any biological changes must then be processed through the psychosocial environment, including the tendency to catastrophize, and degree of spousal support, to produce a given individual patient's pain experience.
Conclusions Infection with atypical bacteria or sequelae of an STD may lead to CP/CPPS in some men. Such a biological insult in the context of alterations in psychoimmunoneurendocrine factors produces the chronic pain experience.

Keywords Prostatitis · Chronic pelvic pain syndrome · Neuropathic pain

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Introduction

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a condition of chronic pelvic pain in men [1]. The diagnosis is made on the basis of symptoms of pain with or without voiding symptoms in the absence of other identifiable causes [2]. The etiology of symptoms in a given patient can be from many causes. Whether there are identifiable, repeatable patterns of causes of symptoms, or just individual patients with distinct individual phenotypes is unknown. However, in the last several decades, we have identified some of the factors that play a role in men with CP/CPPS.

Infection

The symptoms of CP/CPPS are similar to those of a true prostatic infection. Therefore, infection has been commonly assumed by patients and clinicians alike to be the cause of the symptoms, both historically and to this day. In the CPCRN study, using the 4-glass urine test for localization, men with CP/CPPS and asymptomatic controls showed almost identical numbers of bacteria isolated from urine, prostatic fluid, and post-prostate massage urine [3]. Eight percent of men had uropathogenic bacteria and roughly 70 % had some form of bacteria in each group.

This indicates that asymptomatic men appear to routinely have bacteria in the prostate, but may not by themselves produce disease or symptoms. Search for other infectious agents such as virus [4] or for other bacteria identifiable by polymerase chain reaction (PCR) [5] has not proven an infectious cause; there was however an association with improvement on antibiotics in men with bacteria detected by PCR compared to those with no detectable bacteria [6].

Since the discovery of *H. pylori* as the causative organism in stomach ulcers, a search for a previously unknown source has been carried out in many other unexplained conditions including CP/CPPS. A report indicated that blood samples examined for *H. pylori* antibodies were positive in 76 % of men with CP/CPPS compared to 62 % in controls ($p < 0.05$). Although this is significantly greater, a large number of the patients without symptoms were seropositive [7]. Nanobacteria have also been suggested as a possible infectious source in CPPS, as they commonly occur in prostatic stones, and anti-nanobacterial therapy has proven effective in small uncontrolled studies [8–11].

In a study of 30,000 male health professionals, men who reported a history of sexually transmitted disease were found to have 1.8-fold higher odds of prostatitis [12]. However, studies that have looked for the presence of sexually transmitted organisms such as Chlamydia trachomatis, Trichomonas vaginalis, Ureaplasma urealyticum, or Mycoplasma hominis have failed to show persistent infection [13]. Although the presence of an active infection was not evident in men participating in the NIH cohort study, patients with CP/CPPS were found to have a significantly greater history of urethritis compared to age-matched controls [14]. In susceptible men, urethritis could serve as a source of inflammation that could cause chronic pelvic pain well after the resolution of infection.

It is possible that more common bacteria can cause CP/CPPS, but the ones that do are likely different from those that may be present and cause no disease process. Uropathogenic bacteria including uropathogenic *E. coli* (UPEC) express virulence factors that produce the ability to infect [15]. Several reports have indicated that the bacteria isolated from men with CP/CPPS are phenotypically different than those from men without pain, including the ability to inhibit complement [16–20]. The bacteria from men with CP/CPPS have also been shown in a rat model to produce several different effects from *E. coli* that produce cystitis: (1) the strain CP1 from a man with CP/CPPS adhered to, invaded and proliferated within prostate epithelial cells in culture; (2) in a live animal model, CP1 induced and sustained chronic pelvic pain that persisted after bacterial clearance from the genitourinary tract; (3) the pelvic pain was produced in the NOD strain of mice but not C57BL/6J mice, indicating genetic despite similar invasion and proliferation in each species; this indicates a genetic susceptibility to pain but not the infection itself [21]. The NOD mice that developed pain are genetically prone to develop autoimmune diseases of specific organs [22]. The bacterium CP1 in this study was phenotypically different from cystitis strains in that it was group B1 and not B2, and lacked virulence factors found on bacteria associated with acute prostatitis. This study may be the equivalent of the Rosetta stone for CP/CPPS as it recreates many of the clinical phenotypes seen in our patients.

Inflammation

The term "prostatitis" implies inflammation of the prostate gland. However, it is clear that not all men with CPPS have inflammation related to the prostate. Only about one-third of men with clinical CPPS have been found to have prostatic inflammation on biopsy [23]. In those with inflammation, the degree of that inflammation does not correlate with symptoms [24, 25]. Men with category IIIB CPPS do not have inflammation in seminal plasma, expressed prostatic secretions, or post-massage urine. Men with category IV prostatitis [1] do not have pain. They were previously called "asymptomatic," but this may be only true from the standpoint of pain, as prostate inflammation seems to correlate with lower urinary tract symptoms (LUTS) [26].

Considerable effort has been made examining cytokines. Increased levels of IL-1 beta, IL-8, TNF-α, and ENA-78 have been found in EPS of patients with category IIIA prostatitis, but not in those with category IIIB prostatitis [27, 28]. Levels of the chemokines monocyte chemoattractant protein-1 and macrophage inflammatory protein-1-α were significantly elevated in patients with CP/CPPS compared to those without urological disease or BPH, regardless of WBC levels in EPS samples [29]. Furthermore, elevated MIP-1-α levels in CP/CPPS patients showed positive correlation not only with absolute NIH-CPSI scores, but also with pain components of the NIH-CPSI as well. The MCP-1 along with other pro-inflammatory cytokines TNF-α and IL-1β has recently been to be nonfunctional when incubated with expressed prostatic secretions from men with CPPS [30]. The mechanism involves heat labile extracellular proteases. Thus, it may not be the cytokines themselves in function or amount, but impairment of their normal function by an as-yet-unidentified protease in men with pelvic pain.

Autoimmune prostatitis in a rat model has been shown to produce pelvic pain, and pain localization to the prostate in this EAP model was suggested by attenuation of pain behaviors after intraprostatic lidocaine injection [31]. EAP mice also demonstrate increased total and activated mast

cells in the prostate [32]. Mast cell-deficient mice showed attenuated pelvic pain behavior, but no difference in inflammation from control mice. Treatment of EAP mice with a mast cell stabilizer and histamine receptor antagonist resulted in a synergistic decrease in pelvic pain. In the same study, EPS from men with CPPS was found to have increased mast cell tryptase compared to controls. Other evidence for autoimmune prostatitis in men with CPPS includes increased T-cell response to seminal plasma compared to controls [33]. Men with CPPS demonstrate an increased lymphoproliferative response to prostate antigens compared to controls and those with chronic prostatitis [34]. A region of the PAP molecule, 173–192, results in greater activation of CD4 cells and release of interferon-γ in men with CPPS than controls [35]. Men with CP/CPPS have also been reported to have autoantibodies against human seminal vesicle secretory protein 2 (SVS2), which in mice deficient in the autoimmune regulator gene (AIRE) develop B- and T-cell immune responses to this protein [36]. These data indicate the likelihood of autoimmunity in some men with CPPS.

Nervous system

Since pain is mediated by the nervous system, it is reasonable to consider abnormalities of the nervous system as a cause of symptoms in patients with CP/CPPS. Men with CP/CPPS were 5 times more likely to self-report a history of nervous system disease compared to asymptomatic age-matched controls in the Chronic Prostatitis Collaborative Research Network (CPCRN) Study [14]. In the NIH cohort, the symptom that most contributed to the difference in neurologic disease was numbness and tingling in the limbs. Also significant was a history of vertebral disc disease/surgery. One of the markers that correlate with pain in men with CP/CPPS is nerve growth factor [37]. NGF is a neuropeptide that plays a role in nociception and regulates the sensitivity of adult neurons to capsaicin which excites C-fibers, in addition to mediating long-term depolarization via NMDA receptors [38]. NGF is reported to also decrease in men with CPPS who respond to treatment, but not in those who do not respond [39]. However, a recent trial of an antibody to NGF resulted in only a modest reduction in pain [40]. There was no selection of patients with elevation of NGF levels as a criterion for inclusion in the study.

Evidence has been growing over the last decade that men with CP/CPPS have alterations in the nervous system that may contribute to their symptoms. These efforts have been led by the group at the University of Washington. An early study of neurophysiologic testing examined differences in response to afferent fibers: A-β fibers which are large myelinated fibers mediating light touch and somatic pain, A-δ fibers which are smaller myelinated fibers that mediate cold stimuli and early sensations of pain, and C-fibers which are small unmyelinated fibers and mediate most autonomic signals including thermal stimuli and visceral pain. Compared to controls, no difference was seen in the myelinated fibers, but men with CP/CPPS reported higher pain intensity at lower temperatures indicative of altered C-fiber function [41].

Thermal sensitivity tests given to the perineum and anterior thigh in a much larger group of men with CP/CPPS and controls confirmed pilot data and again showed that men with CP/CPPS were more sensitive to heat in the perineum but not the anterior thigh compared to controls [42]. This indicates alterations in the afferent autonomic nervous system and suggests central sensitization of the nerves. Studies on the efferent side showed that when on 5-min resting supine and standing blood pressure measurements, men with CP/CPPS showed alterations in the heart rate variability compared to controls. When measures of parasympathetic activity decreased in the controls, there was little change in men with CPPS, and sympathetic activity increased in the controls and decreased in men with CP/CPPS [43]. This is a reflection of efferent autonomic activity. Overall heart rate variability has been reported as lower in men with CPPS than controls [44]. A more recent study examined sensory perception thresholds in the perineum, penis, palms, and soles. There were no sensory threshold differences between CPPS men and controls, indicating that there is no peripheral neuropathy [45].

There are subtle signs of neurologic abnormality in men with CPPS also. The segments of the tibial nerve that innervate the toes come from S2 to 3 roots, the same that innervate the pelvis. Men with CPPS are less often able to spread all toes as compared to men without CPPS. This is considered to possibly reflect neural deficits in the sacral roots [46]. One of the unanswered questions in CPPS is the association with cardiovascular disease. Men in the CPCRN study were six times more likely to self-report a history of cardiovascular disease, especially hypertension [14]. A recent report indicates that men with CPPS also have alterations in arterial stiffness and lower reactive hyperemia index, and measures of cardiovascular dysfunction [47]. Whether this is related to autonomic dysfunction and/or localized to the endothelium is unclear.

Neurological abnormalities are postulated to also cause spam in the pelvic floor [48]. Men with CPPS are noted on urodynamic studies to have detrusor sphincter dyssynergy in 73 % of cases. This is normally seen in patients with suprasacral spinal cord lesions [49]. In the study by Zermann et al. [48], CPPS patients were found to have pathological tenderness of the striated pelvic floor muscle and poor to absent function in ability to relax the pelvic floor efficiently with a single or repetitive effort. An EMG study

of the pelvic floor in men with CPPS showed that compared to controls, men with CPPS had (1) greater preliminary resting hypertonicity and instability and (2) lowered voluntary endurance contraction amplitude [50]. Men with CPPS also have more tender points in areas outside of the pelvis as compared to controls [51]. This adds to the evidence that CPPS may be a systemic pain syndrome.

Studies of brain anatomy and function have begun to describe changes in men with CPPS. Farmer et al. studied spontaneous pelvic pain, with men lying in the fMRI scanner for 10 min and rating their fluctuations in the absence of any external stimulus. Pain perception was localized to the anterior insula and correlated with the intensity of self-reported pain. Density of gray matter in the anterior insula and anterior cingulate cortex also correlated with pain intensity. There was no decrease in gray matter in this study, but there were differences in the relationship of gray and white matter in men with CPPS compared to controls [52]. It is not known whether changes in the CNS are as a result of the chronic pain or are abnormalities that lead to pain in the first place. The findings in men with CPPS differ from those in other pain conditions including low back pain [53]. The insula is involved in determining the intensity of pain magnitude [54]. A study from Switzerland reported that in a group of 40 men with CPPS, there was a significant reduction in relative gray matter volume in the anterior cingulate gyrus that correlated with overall NIH-CPSI score as well as the pain subscale [55]. The ACC is involved in emotional pain processing [56] and sympathetic activity [57]. Important to keep in mind is that brain anatomy is dynamic and not static. Cortical changes are noted in patients after treatment for back pain [58].

One of the unifying hypotheses of chronic pain syndromes is that of central sensitization. Original theories of nervous system function believed that the CNS was directly determined by the duration, intensity, and location of a stimulus. However, as described by Woolf in [59], it is now widely recognized that there can also be sensitization of the nerves such that even after a stimulus is terminated, there is continued nerve activity in the absence of stimulation or which requires a very low level of nociceptive stimulation to continue. One of the hallmarks of central sensitization is also an expansion of the field of pain to areas of non-injured tissue [60]. We commonly see this phenomenon in men with CPPS, in which pain in one area, for instance the testis or from epididymitis, eventually leads to pain in the area between the umbilicus and midthigh. Experimental evidence for central remodeling is provided by the finding that chemical irritation of rat prostate and bladder causes c-fos expression at spinal cord levels L6 and S1 along with plasma extravasation at the identical L6 and S1 dermatomes, underscoring the overlap of afferent nerve fiber distribution [61].

Psychosocial factors

The same biological nociceptive process will result in a different pain experience in different individuals on the basis of the psychosocial context of that process. Assessing quality of life with the 12-item short-form (SF-12) instrument, [62], the mental component summary score for CPPS patients is lower than that observed in the most severe subgroups of congestive heart failure (CHF) and diabetes [63]. In the CPCRN study, men with CP/CPPS self-reported a history of anxiety or depression twice as often as age-matched controls with no pain [14]. The factors that contributed most to the reduced quality of life were pain intensity and quality of life subscale of the NIH-CPSI [64]. Further detailed investigation of psychological variables in this cohort showed that helplessness/catastrophizing predicted overall pain along with urinary symptoms and depression [65]. The helplessness subscale of catastrophizing also predicts the mental subscale scores on the SF-12 in these patients [66]. Catastrophizing can mediate ethnic differences in pain response, pointing out the importance of the social context on the pain experience [67]. It is postulated that catastrophizing may activate central attention centers and inhibit the suppression of significant pain leading to chronic pain [68].

Another important modifier of the pain experience in men with CP/CPPS is spousal support. Lower perceptions of spousal support also contribute to lower mental component scores on the SF-12 in the CPCRN study [66]. Pain and disability are greater at higher levels of solicitous responses by spouses; the less the spouse tries to distract the patient from the pain, such as by trying to get them involved in other activities, the greater the pain and disability connection [66]. Spousal response also changes the physiology of the patients. In category III prostatitis patients, the degree of spousal concern and support as well as effort to distract the patient from his symptoms correlates with lower seminal plasma IL-6 and IL-10 concentrations [37]. The term "stress prostatitis" was used in the late 1980s to describe CP/CPPS given the common association between psychological stress and symptoms. Later studies have confirmed this association. Ullrich and colleagues used measures of perceived stress in a study of men with CPPS and found that greater perceived stress during the 6 months after the health care visit was associated with greater pain intensity ($p = .03$) and disability ($p = .003$) at 12 months, even after controlling for age, symptom duration, and pain and disability during the first 6 months [69].

Early adverse experiences may contribute to later symptoms of chronic pain. In the Boston Area Community Health Survey (BACH), men who reported having experienced sexual, physical, or emotional abuse were more likely (OR 1.7–3.3) to report symptoms of CP/CPPS in the

survey [70]. It is known that stress has physiological consequences, as in addition to many other stimuli such as cytokines, bacterial toxins, and hypoxia, mast cells release their contents in response to stress [71]. Chronic stress also changes DNA by epigenetic modifications, in which biochemical changes alter the DNA and affect function [72]. Some of these changes are reversible and some are not [72].

Endocrine abnormalities

Also effecting both immune and nervous system functions are endocrine factors. Men with CP/CPPS are more likely to have other chronic pain conditions such as irritable bowel syndrome, fibromyalgia, and chronic fatigue syndrome [73]. One of the common findings in chronic pain conditions is alterations in the hypothalamic–pituitary–adrenal axis [74, 75]. Similar findings have been reported in CP/CPPS. On awakening, serum cortisol levels rise; there is a significantly greater cortisol rise in men with CPPS compared to controls [76]. Men with CPPS also have a lower baseline ACTH level and blunted ACTH rise in response to stress than men without symptoms [76]. One report has indicated reduced activity of CYP21A2 (P450c21), the enzyme that converts progesterone to corticosterone and 17-hydroxyprogesterone to 11-deoxycortisol [77].

Genetic predisposition to CP/CPPS

The idea of genetic differences that may predispose CP/CPPS patients to develop the condition has been explored in several targets. Differences in the DNA sequence, or polymorphisms, have been identified in the promoter regions of several cytokines. Polymorphisms in the genes or promoters for IL-10 AA and TNF-α are associated with low IL-10 [78] or TNF-α production [79]. In one study, significantly more men with CPPS expressed the IL-10 AA genotype compared to controls (11 of 36, 31 % vs. 33 out of 272, 12 %; $p = .007$) [80]. All eight IIIa patients had the low TNF-α production genotype. There was no difference in the TNF-α genotype in the 22 IIIb patients versus 272 controls but all 8 of the IIIa patients had the low TNF-α genotype. The cytokine polymorphisms also correlated with the clinical response to treatment with the antioxidant quercetin. Differences have been reported in the frequency of three alleles near the phosphoglycerate kinase (PGK) gene, between CPPS patients and controls [81]. The alleles differed in the number of short tandem repeats (STRs). The PGK1 gene in the region assessed has been found to be associated with familial prostate cancer, hypospadias, and androgen insensitivity. Another gene in the same region of the X chromosome, Xq11–Xq13, is the androgen receptor [82]. This finding raises the possibility of androgen insensitivity or dysfunction in the pathogenesis of CPPS. Dinucleotide sequences have also been found to be common in genes for neural development [83]. Investigation of SNPs in the gene for manganese superoxide dismutase has reported significant differences between men with CP/CPPS and controls but not between category IIIa and IIIb CP/CPPS [84]. The enzyme levels of manganese superoxide dismutase and glutathione peroxidase were higher in control subjects than prostatitis patients, indicating lower antioxidant status in men with CP/CPPS.

Conclusion

It was much easier to discuss mechanisms in prostatitis when all symptoms were thought to come from an infection. We now know that CP/CPPS is nothing if not a chronic pain syndrome. The complexity of chronic pain

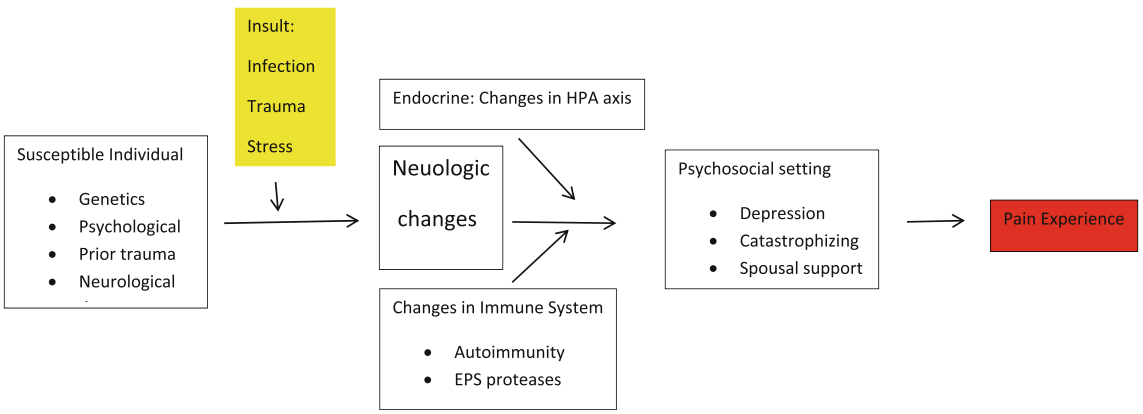

Fig. 1 Proposed mechanisms in development of pain in CP/CPPS

conditions is becoming apparent. There are a myriad of possible phenotypes that may be seen [85]. Figure 1 outlines the author's current perspective on the development of CP/CPPS. It is unlikely that a given insult such as infection, trauma, or even extreme stress will cause symptoms in all individuals. Men who develop CP/CPPS probably have some risk factor or factors that predispose them to developing chronic pain. The common denominator is then neurologic alteration. The neurological insult is modified by immune and endocrine factors; deficits in these areas can contribute to the chronic state. Finally, the biological insult must be put into the psychosocial context to produce each patient's pain experience. Much like we are also responsible for dermatologic lesions in the genitourinary organs, we are responsible for treating a chronic pain condition that occurs in our area of interest. We must become on some level a pain doctor.

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