Similarities Between Interstitial Cystitis and Male Chronic Pelvic Pain Syndrome

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Current Urology Reports 2002, **3:**313–318
Current Science Inc. ISSN 1527-2737

Few clinical conditions encountered by the urologist cause more patient and clinician frustration than interstitial cystitis and male chronic pelvic pain syndrome, also know as nonbacterial prostatitis. This frustration is fueled by the chronicity of often disabling urogenital (and often associated systemic) symptoms coupled with delayed care, misdiagnosis, and suboptimal clinical responses. Basic research and therapeutic trials for these syndromes have historically taken two separate paths. However, mounting evidence suggests that significant overlap may exist between them in epidemiology, pathophysiology, and even therapy. This discussion reviews some of the common features of these clinical problems and makes a case that they might in fact represent different manifestations of the same disease process.

Introduction

Epidemiology

Interstitial cystitis (IC) and male chronic pelvic pain syndrome (MCPPS) are highly prevalent in the general population. Recent epidemiologic studies suggest that approximately 700,000 females in the United States are afflicted with IC [1••]. If males were considered, this estimate might be as high as 1 million! National Ambulatory Medical Care Surveys demonstrate nearly 2 million physician visits per year with prostatitis listed as the diagnosis, the vast majority of those encounters likely due to National Institutes of Health (NIH) category IIIA MCPPS. Prostatitis was listed as a diagnosis in 8% and 1% of urologic and primary care visits, respectively [2••]. In addition, 16% of 31,681 health care professionals surveyed in the United States (all without prostate cancer) self-reported a history of prostatitis [3••].

Impact on the quality of life

Perhaps more significant than the high prevalence of IC and MCPPS is the often devastating impact that these conditions have on the quality of life. Chronic pain and irritative voiding symptoms can have a profound impact on employment status, sexuality, and activities of daily living. In 1987, Held *et al.* [4] reported that patients with IC were three to four times more likely to report thoughts of suicide than the general population. Additionally, patients with IC were five times more likely to have been treated for emotional problems. Quality-of-life evaluations were rated lower for these patients than patients receiving hemodialysis for end-stage renal disease. In a 1993 study by Koziol *et al.* [5], 93.4% of patients with IC found it difficult or impossible to travel. Leisure activities, sleep, and employment were adversely affected in 89.9%, 88.2%, and 84.4% of patients, respectively. Family relationships and responsibilities were adversely affected in 69.7% of patients. The National IC Database Study (sponsored by the National Institute of Diabetes, Digestive, and Kidney Diseases [NIDDK]) found interference with work and social activities in 54% and 71.7% of respondents, respectively [6]. Unfortunately, less attention has been given to the patient with MCPPS with regard to its impact on quality of life, however, completed studies have showed startling disturbances. In 1996, Wenninger *et al.* [7] noted that "sickness impact profiles" of patients with prostatitis were comparable with those of patients suffering from myocardial infarction, angina, or Crohn's disease. Quality-of-life scores related to mental health have been found to be lower in patients with MCPPS than in patients with severe congestive heart failure and diabetes mellitus [8•].

Theories of Pathogenesis

A review of literature compiled over the past 20 years demonstrates that investigations related to IC and MCCPS IIIA have taken separate but parallel paths. Interestingly, in many instances these paths have led to similar theories of etiology and pathogenesis, ranging from "atypical organisms" to aberrant neuronal function. Some investigated findings are discussed below.

Occult infection

Although Category IIIA MCPPS is not characteristically associated with bacteria found within expressed prostatic secretions (EPS), urine voided after prostatic massage, or semen, infection with "atypical" or fastidious organisms has been proposed by numerous investigators [9–12]. Krieger *et al.* [13] demonstrated bacterial DNA sequences

to be significantly more common in the prostate biopsy tissue of patients with chronic prostatitis/chronic pelvic pain syndrome (46.4%) versus patients with prostate cancer (19.6%). Using 16S rRNA polymerase chain reaction (PCR) technique, Shoskes and Shahed [14] found bacterial DNA in as many as 70% of EPS specimens from patients with MCPPS IIIA. Fifty-one percent of those patients were also found to have gram-positive–bacteria EPS cultures, bacteria that are often assumed to be commensals. Only 14% of those patients without prostatic inflammation (NIH MCPPS IIB) had bacterial DNA in their EPS. Interestingly, 57% of the total patients who had PCR positive for bacterial DNA improved with antibiotic therapy, while no patient with a negative PCR for bacterial DNA improved on antibiotic therapy. This study certainly suggests that PCR may aid in selecting patients for antibiotic therapy, but also suggests that occult bacteria may participate in the genesis of patient symptoms in a subpopulation of patients with MCPPS IIIA. These findings have prompted treatment algorithms to include an initial trial of antibiotic therapy without laboratory evidence of overt infection [15••,16]. In contrast to these studies, Keay *et al.* [17] demonstrated bacterial DNA to be present in the transperineal biopsies of 89% of patients diagnosed with prostate cancer, a higher percentage than seen in the MCPPS IIIA groups of other studies. These conflicting data, difficulties in the determination of commensal versus virulent organisms, the focal nature of prostatitis, and the added variable of "bacterial protection" in the form of prostatic calculi and biofilms continue to impair investigative efforts.

Similar controversies exist regarding an infectious etiology for IC. Sophisticated culture techniques that identify fastidious or unusual bacterial forms, *Mycoplasma* species, fungi, and viruses have failed to consistently demonstrate a causative organism [18]. Likewise, PCR technique has failed to demonstrate differences in bacterial forms between bladder biopsies of patients with IC and control subjects [19,20]. Interestingly, occasional reports are published that stir up conventional wisdom. Such a study was published in 2000 by Potts *et al.* [21] who identified *Ureaplasma urealyticum* in 48% of patients: patients who would have been otherwise diagnosed with IC. Ninety-one percent of these patients treated with antibiotics had improvement in their symptoms. Many patients with IC have had a documented urinary tract infection with consequent chronic bladder-based symptoms. This has lead many investigators to speculate that the episode of cystitis might have caused permanent "bladder injury" and the subsequent development of irritative voiding symptoms [22]. This scenario certainly might fit the patient with prostatitis as well.

"Leaky epithelium"

The healthy bladder surface is coated by a thin mucinous substance, termed bladder surface mucin (BSM), which is composed of numerous sulfonated glycosaminoglycans and glycoproteins. BSM is thought to function as a "bladder protectant," decreasing the ability of organisms to bind to the underlying urothelial cells. Qualitative changes have been noted in BSM between IC patients and control subjects, and in some animal models of IC [23–26]. It has been speculated that these qualitative changes in BSM may cause permeability alterations, with the permeability changes ultimately resulting in bladder inflammation and/or hyperalgesia [25]. Although prostatic acini are lined by columnar epithelium rather than transitional cells, the prostatic surface does elaborate mucus [27,28]. Could changes of the prostatic epithelial surface or its elaborated mucin, when exposed to the common occurrence of intraprostatic urinary reflux [29••], be responsible for patient symptoms in MCPPS?

The potassium sensitivity test was developed by Parsons [30] as a relatively simple office procedure to help diagnose patients with IC. Patients with IC will typically have a worsening of pelvic pain and/or irritative voiding symptoms after the instillation of a potassium chloride solution, presumably due to enhanced absorption of the salt through a "defective" bladder surface. Preliminary data collected by Parsons (Personal communication) demonstrated that 84% of 43 patients (18% with increased frequency only) with MCPPS IIIA tested positive with the potassium sensitivity test, thereby suggesting a common etiology for symptoms between the IC and MCPPS groups. Pentosan polysulfate sodium (PPS) is a common medication used for the treatment of IC. Its presumed mechanism of action is its binding to the urothelial surface, thereby augmenting an abnormally permeable bladder surface. Recent preliminary uncontrolled studies suggest that this medication may improve the symptoms of patients suffering from MCPPS IIIA [31]. Although further studies are clearly needed to determine the efficacy of PPS for the treatment of MCPPS, perhaps this similarity in clinical response reflects similarities in pathogenesis.

Neurogenic inflammation

Neurogenic inflammation is a well-described phenomenon that occurs in the patient with IC. In this paradigm, sensory nerves may secrete inflammatory mediators, resulting in local inflammation and/or hyperalgesia. A central component of this process is Substance P, a short chain peptide that functions as a nociceptive neurotransmitter in the central and peripheral nervous system, as well as an inflammatory mediator. When released by peripheral nerves (C-fibers or fibers associated with pain transmission) an inflammatory cascade occurs that results in processes such as mast cell degranulation and the activation of nearby nerve terminals. Supporting this pathogenic mechanism is the finding of increased numbers of substance P-containing nerves in the bladders of IC patients [32,33]. Additionally, increased concentrations of substance P have been found in the urine of patients with IC, the concentration of substance P being affected by the patient's degree of

pain [34]. No investigations have yet been performed to detail the role of neurogenic inflammation in MCPPS IIIA, however, symptomatic improvements observed in patients after intravesicular instillation of dimethyl sulfoxide [35], a "gold standard" therapy for IC and a depleter of substance P [36], suggest that neurogenic inflammation may play a role in symptom exacerbation in some patients. Additionally, an animal model of "spontaneous" nonbacterial prostatitis has demonstrated an increased number of sensory C-fibers with progression of inflammation [37].

Mast cell activation

Mast cells contain cytoplasmic granules, which themselves contain substances such as histamine, leukotrienes, prostaglandins, and tryptases: all of these agents are capable of stimulating inflammation. These granules may be released into the interstitium (degranulation) as part of an immunoglobulin E-mediated hypersensitivity reaction or in response to multiple other stimuli including neurotransmitters (substance P), cytokines, anaphylatoxins (complement: C3a, 4a, 5a), bacterial toxins, hypoxia, physical factors, lectins, various allergens, toxins, stress, and others [38–41]. Mastocytosis has been reported in the bladders of 30% to 65% of patients with IC [42,43]. This is probably an underestimation due to technical difficulties in identifying mast cells that have already degranulated (become "activated") [44]. Indirect evidence of the mast cell as an active participant in the pathogenesis of IC comes from increased levels of histamine found in the bladder walls of patients with IC [45] and increased urinary excretion of 1,4-methyl-imidazole-acetic-acid, a histamine metabolite [46,47], by these same patients.

Although little work has been conducted to determine the role of the mast cell in MCPPS IIIA, case reports such as that submitted by Theoharides *et al.* [48] suggest that mastocytosis and elevated urinary histamine levels might be observed in some patients with prostatitis. This correlates well with an estrogen-induced model of prostatitis where increased numbers of degranulated mast cells were noted [49]. Increasing mast cell degranulation appeared in the previously discussed rat model of spontaneous prostatitis with prostatitis progression [37].

Autoimmunity

The interest in autoimmunity as a possible cause of IC dates back to 1938, when Fister [50] noted similarities between IC and systemic lupus erythematosus. Indeed, IC has many of the features of an autoimmune disease: symptom chronicity with exacerbations and remissions; frequent organ-specific mononuclear cell infiltrates; the lack of a clearly defined pathogen; occasional clinical response to steroids or other immunosuppressants [51]; the high prevalence of antinuclear antibodies; and associations with well-described autoimmune syndromes. Further studies investigating the role of autoimmunity in IC are far from conclusive and often conflicting. High levels of bladder-specific autoantigens have been identified in some patients [52], however, this has not been a consistent finding [53,54]. In fact, some investigators suggest that this phenomenon is simply an indirect response to local cellular damage [38]. The same type of controversy exists for autoimmunity in the patient with MCPPS. Evidence suggests that autoimmunity may be responsible for symptoms in some patients suffering from MCPPS III. Alexander *et al.* [55] demonstrated that three of 10 men with MCPPS had an autoimmune response to prostatic proteins, as evidenced by a T lymphocytic response to seminal plasma. Although some patients with MCPPS appear to have evidence of autoimmunity-related pathogenesis, autoimmunity may also be present in conditions as common as benign prostatic hyperplasia (BPH) [56].

Similarities in Presentation Between Interstitial Cystitis and Male Chronic Pelvic Pain Syndrome

A significant overlap of presenting signs and symptoms exists between IC and MCPPS. In some instances, this overlap can be so impressive as to make the distinction between these two entities quite "blurry." Additionally, confusion and misdiagnosis between IC, MCPPS category IIIA, MCPPS category II (chronic bacterial prostatitis), and BPH [57] is very common. In 1969, Hanash and Pool [58] reported that 55% of 123 male patients had undergone at least one transurethral resection of the prostate (TURP) before being diagnosed with IC. In 1977, DeJuana and Everett [59] reported on 11 male patients with IC, five of whom underwent TURP and two who underwent open prostatectomy prior to their final diagnosis. Incorrect surgical procedures are performed less frequently today, most likely because of an increased awareness of the potential for sensory dysfunction and a more widespread use of urodynamic evaluation. Nevertheless, the diagnosis of IC can be confounded by the fact that only 7% of patients initially present with the entire complement of symptoms that they will ultimately develop. Driscoll and Teichman [60••] reported that the median time for total symptom manifestation was 2 years, and not all patients manifest the entire spectrum of described complaints. It is quite likely that this same progression of symptoms is occurring in the patient with MCPPS, a condition whose symptoms may afflict up to 9.7% of the total community [61].

Typical symptoms of IC include urinary frequency, urinary urgency, and pelvic pain. Pain is typically worsened with bladder filling. Urethral syndrome, a condition thought by many to be an IC variant, is often diagnosed when dysuria is associated with other irritative voiding symptoms. Common complaints associated with prostatitis parallel those of IC, but may also include dysuria, perineal or penile pain, and pain with ejaculation. Pain with bladder filling, a classic feature of IC, is described in 45% of patients with MCPPS. This is consistent with a

report by Mayo *et al.* [62] who found bladder hypersensitivity in 30% of patients with MCPPS.

Detrusor instability is relatively uncommon in the patient with IC, present between 0% and 14.6% of patients [63–66]: this condition is seen in 3% of our patient population. A high prevalence of instability (30%) was noted in only one study that selected out patients with relatively severe inflammatory disease [67]. Although few large studies are available for review, bladder instability like IC appears to be uncommon in the patient with MCPPS [62].

A common complaint among patients with IC and MCPPS is that of urinary hesitancy. The National IC Database Study noted this symptom in 78% of patients [66]. This, in addition to complaints of poor urinary flow rates, constipation, dyspareunia, and generalized pelvic pain, have been attributed to associated pelvic floor pseudodyssynergia or spasm, broadly termed "pelvic floor dysfunction" [65,68,69,70••]. We retrospectively reviewed the charts of 100 consecutive female patients meeting NIDDK criteria for IC, noting other associated complaints including decreased force of the urinary stream (75%), urinary hesitancy (75%), a sensation of incomplete voiding (73%), the need to strain with urination (70%), and dyspareunia (45%). Likewise, voiding dysfunction in the patient with MCPPS appears to be quite common. Although Mayo *et al.* [62] found little evidence of pseudodyssynergia in MCPPS, most literature has demonstrated a high incidence of bladder neck and/or pelvic floor spasm associated with this condition, particularly within the MCPPS IIIB variant (prostatodynia) [71,72,73•]. This similarity between MCPPS IIIB and IC is seen again in studies where both groups have been found to develop significant glomerulations (petechial hemorrhages of the bladder surface) upon bladder hydrodistention [74].

Conclusions

In 1987, Messing [75] suggested that many men who initially received a diagnosis of nonbacterial prostatitis or prostatodynia might actually have had IC. This thought was based upon often striking similarities in clinical presentation between these syndromes. Supporting this hypotheses, other investigators noted the frequent misdiagnosis of IC as MCPPS [73,60••]. Although no direct comparative studies have been performed, further investigations detailing similar epidemiology, pathophysiology, and even response to various therapies for IC and MCPPS begs the question whether these two syndromes are in fact different points in a spectrum of the same disease.

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