The Relationship Between Sexual Abuse and Interstitial Cystitis/Painful Bladder Syndrome

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Interstitial cystitis/painful bladder syndrome (IC/PBS) is a chronic syndrome characterized by irritative voiding symptoms and pelvic pain or discomfort. IC/PBS represents localized bladder pathophysiologic changes and central nervous system upregulation. Patients exhibit bladder hyperalgesia and allodynia. Childhood sexual abuse occurs in up to 27% of females in the United States. Adults with a prior history of abuse or traumatization demonstrate hypothalamic-pituitary-adrenal (HPA) axis abnormalities, similar to IC/PBS patients. Childhood sexual abuse and physical traumatization are associated with subsequent lifelong risks of chronic pain syndromes. IC/PBS patients have increased rates of sexual abuse or physical traumatization histories compared with controls. IC/PBS patients with abuse histories tend to have greater pain intensity and lesser irritative voiding symptoms compared with nonabused IC/PBS patients. This article reviews the relationship between sexual abuse, HPA axis abnormalities, IC/PBS pathophysiology, and the role of sexual abuse on subsequent IC/PBS.

Introduction

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a chronic and often debilitating pain syndrome. IC/PBS encompasses a spectrum of disease characterized by irritative voiding symptoms such as urinary urgency, frequency, nocturia, and dysuria, and is often associated with bladder, urethral, or pelvic pain or discomfort in the setting of sterile urine and in the absence of other bladder pathology [1–5]. Symptoms are often increased by holding urine and relieved by voiding [1,2]. Symptoms are commonly aggravated by menstruation, sexual intercourse, stress, or certain foods [5–8]. The symptoms of IC/PBS negatively affect all aspects of daily life, including family, work, sleep, interpersonal relationships, and sexual functioning [9•,10]. The current literature supports the hypothesis that IC/PBS represents bladder hypersensitivity and allodynia, whereby normal bladder sensations of filling, urgency, and capacity are perceived at lower threshold volumes than normal, and sensations normally perceived as nonpainful (urgency, bladder filling, capacity, intercourse) are perceived as painful [5,11]. Patients present to clinicians in various ways [6,12•,13,14]. Despite considerable research efforts and advancements since IC was described by Hunner [15] in 1915, a considerable amount about the disease and its etiology still remains unknown.

Although the definition of sexual abuse varies, the estimated prevalence of childhood sexual abuse ranges from 13% to 27% for females, and 4% to 16% for males [9•,16•,17]. Recent studies on the health effects of sexual abuse and domestic violence show that such traumatized victims are at an increased lifetime risk of multiple chronic pain disorders, including vulvodynia, irritable bowel syndrome, abdominal pain, and IC/PBS [3,6,18,19]. Some evidence implicates changes in the hypothalamic-pituitary-adrenal (HPA) axis in these sexually and physically traumatized victims. This article reviews the role of sexual abuse and physical traumatization on subsequent development of IC/PBS.

Prevalence of IC/PBS

Prevalence estimates for patients diagnosed with IC/PBS vary significantly, as there is no accepted universal definition and the diagnosis is often delayed or missed. Several recent studies have shown that the prevalence is higher than previously thought. The Nurses I study estimated a prevalence of 1.7% in those younger than 65 years of age and increasing to 4% in those 80 years of age or older [20,21], with recent estimates suggesting a prevalence of approximately 3% to 6% for US women 18 years of age or older [22]. The ratio of women to men affected is typically 5:1 to 10:1. The actual gender distribution may be inaccurate, however, as men with symptoms suggestive of IC/PBS

are more likely to be misclassified into other vague disease entities such as chronic pelvic pain syndrome, chronic nonbacterial prostatitis, or prostadynia [2,14]. The reported prevalence of IC/PBS in the United States is believed to be three times that of Europe [1,21]. Even using the most conservative prevalence estimates, it is clear that IC/PBS is a common disorder with potentially severe adverse health and lifestyle consequences for patients.

Etiology of IC/PBS

The etiology of IC/PBS remains controversial. Current theories for the pathogenesis of IC/PBS include abnormalities in urothelial permeability, mast cell activation, neuroplasticity of the peripheral and central nervous system, and infectious etiologies [6,11,23–25]. Much data have been published on urothelial permeability [24,26]. Changes in the urothelial mucin (glycosaminoglycan) layer are implicated in solute permeability across the urothelium with submucosal injury and depolarization of sensory nerves [24]. In this paradigm, urothelial mucin dysfunction leads to solute permeability, submucosal inflammation, mast cell activation, and depolarization of sensory nerves by potassium and mast cell–derived substance P. Another paradigm asserts that mast cell activation occurs first and produces urothelial dysfunction [23,27]. Saban et al. [25] showed in an animal model that various inciting factors (bacterial-derived lipopolysaccharide, antigen, or chemical injury) all produce many common changes in bladder submucosa and dorsal root ganglia. It is likely that IC/PBS represents a final common pathway for a diverse set of inciting factors that lead to local bladder inflammation, peripheral and central neural upregulation, alterations in the HPA axis, and changes in central appraisal and processing of nociceptive stimuli [12•]. Sexual abuse or domestic violence is associated with a number of lifelong changes in central appraisal and processing of nociceptive stimuli. It is proposed that subjects with a history of such traumatization may have enhanced sensitization to visceral pain; thus, subsequent development of bladder discomfort or pain from IC/PBS may be magnified.

Associated Comorbidities of IC/PBS

Various diseases have been shown to be associated with the diagnosis of IC/PBS. Alagiri et al. [19] studied a population of patients diagnosed with IC/PBS and compared the incidence of concomitant diagnoses in this population to the incidence within the general population. They, and others, have found an increased incidence of allergies, irritable bowel syndrome, skin hypersensitivity, dyspareunia, endometriosis, and fibromyalgia [3,19,28]. IC/PBS also has been linked to other pelvic pain syndromes such as vulvodynia, with one study demonstrating that more than half of patients diagnosed with IC/PBS had a concomitant diagnosis of vulvodynia [18]. Approximately three quarters of women seeing a gynecologist for complaints of chronic pelvic pain have symptoms of urgency, frequency, or other irritative voiding symptoms [6], demonstrating the obvious overlap between the diagnosis of IC/PBS and chronic pelvic pain [28].

Sexual Abuse and Correlation With IC/PBS

Physical and sexual abuse against women and children is an extremely common occurrence, and it may result in detrimental health outcomes for those involved. The study of prevalence rates in any form of abuse is problematic, as there is a tendency toward underreporting of events in the general population. The estimated prevalence of childhood sexual abuse ranges from 13% to 27% for females and 4% to 16% for males [9•,16•,17], with some estimates of up to 40% lifetime prevalence of physical or sexual violence [29]. This experience of abuse has a direct correlation with future health and has been linked to diseases such as irritable bowel syndrome, chronic diarrhea, chronic constipation, dysmenorrhea, dyspareunia, and chronic pelvic pain [9•,30,31]. Individuals who report a history of childhood abuse report a fourfold greater incidence of chronic pain, headache, gastrointestinal and respiratory illnesses, gynecological complaints, neurological symptoms, overall physical health problems, and increased visits to health care providers [30,32,33]. There is an increased incidence of sexual and/or physical abuse in patients with chronic pelvic pain [30,31,34,35]. Lampe et al. [35], in a structured interview of 36 women with chronic pelvic pain, found a significant association with sexual victimization before age 15 and later development of chronic pelvic pain compared with patients with either chronic headaches or normal controls. Walling et al. [34] similarly demonstrated a relationship between sexual abuse and chronic pelvic pain compared with those with chronic headache and normal controls. They reported a prevalence of sexual abuse of 56% in a population of women with chronic pelvic pain.

Prior to 2007, no studies in the English literature had attempted to measure the relationship between IC/PBS and sexual abuse. Peters et al. [16•] conducted a 100-question validated mailed survey of 215 women diagnosed with IC/PBS compared with 464 symptom-free, age-matched controls in the United States. They found a prevalence of abuse of any type in women with IC/PBS of 38% compared with 24% of controls. When divided into physical abuse, emotional abuse, and sexual abuse, they found a prevalence of 17.2% versus 8%, 31.6% versus 18.5%, and 17.7% versus 8.2%, respectively, compared with controls. Goldstein et al. [9•] studied the relationship between a history of abuse and the development of IC/PBS in a survey of 141 women who presented to a single center specializing in pelvic floor disorders. Using a validated mailed questionnaire format, they reported a prevalence of sexual abuse of 36% in patients diagnosed with IC/PBS using the NIDDK (National Institute of Diabetes and Digestive and Kidney Diseases) criteria, a statistically significant

increase over control women in that study. When a subset of the women with IC/PBS were seen in the clinic setting and interviewed directly, the incidence of abuse increased to 49%. As stated by Goldstein et al. [9•], the discovery that IC/PBS patients reported more abuse than the general population proves only an association and not a causal relationship between the two. However, it generates the hypothesis that triggers such as trauma, abuse, pelvic surgeries, or other life stressors may stimulate or mediate the inflammatory cascade that leads to IC/PBS symptoms. It may also mediate the experience of symptomatology, and patients with IC/PBS have been found to experience greater pain intensity in the setting of previous sexual abuse compared with controls [12•].

Pathophysiology of IC/PBS

Much of the research and hypotheses about the effects of sexual abuse have been presented in the context of chronic pelvic pain, with very few theories applying solely to IC/PBS. Because the two conditions have been shown to be related, it is possible that the pathophysiologic mechanisms resulting in chronic pelvic pain may be applicable to both conditions.

Stress

The link between psychological trauma and somatic symptomatology has been known since the late 1800s, beginning with studies of the effects of wartime stress on the hearts of soldiers [36]. An association exists between childhood or adult history of physical and/or sexual abuse and the development of chronic pain syndromes, including chronic pelvic pain [3,37]. Other studies have shown a high rate of traumatic life experiences in patients with chronic pelvic pain or other chronic gastrointestinal disorders [30,37]. Heim et al. [38] demonstrated an increased rate of abuse in patients with chronic pelvic pain that was associated with an alteration in the HPA axis, in keeping with other stress-related disorders such as posttraumatic stress disorder (PTSD). Studies of familial-linked panic disorder have found an increased incidence of IC/PBS [23].

Stress is known to aggravate symptoms of patients with IC/PBS [39]. Stress also aggravates other chronic disease states such as irritable bowel syndrome, rheumatoid arthritis, and psoriasis [11]. Stress activates the HPA axis, which through cortisol secretion, activation of the sympathetic nervous system, and increased mast cell activity leads to inflammation and a state of hypervigilance [11,38,39]. Corticotropin-releasing hormone (CRH) is secreted from the hypothalamus under conditions of stress and is also expressed in peripheral sites, including the spinal cord, dorsal root ganglia, sympathetic root ganglia, and mast cells [23,38]. CRH in these peripheral sites is thought to lead to a proinflammatory state and activation of mast cells. Thus, stress directly increases neurogenic inflammation mediated by mast cells [23], which has been demonstrated in animal models subjected to cold stress that resulted in increased number and activity of mast cells within the bladder [40]. This increase in mast cell activity also occurs in other chronic disease states such as irritable bowel syndrome [23]. A common pathophysiologic mechanism may be mast cell activation resulting in neurogenic inflammation and augmented central processing of nociceptive signals.

CRH also induces pituitary secretion of adrenocorticotropic hormone, which in turn leads to increased cortisol secretion from the adrenal cortex [38]. Circulating levels of cortisol regulate the HPA axis via a negative feedback loop. In acute periods of stress, elevated cortisol levels provide a protective effect to organisms by increasing metabolic energy supply and reducing inflammatory reactions through inhibition of lymphocytes, macrophages, and inflammatory mediator release. Cortisol also suppresses the synthesis of inflammatory leukotrienes and prostaglandins. This process results in an overall immune suppression, protecting from the toxic effects of the acute stress response [38]. Chronic or traumatic stress is hypothesized to promote specific alterations in the HPA axis characterized by decreased adrenal activity and an overall hypocortisol state. As reviewed by Heim et al. [38], PTSD studies of Vietnam veterans and Holocaust survivors demonstrated decreased adrenal activity, a finding duplicated in patients with other chronic stress–related disorders, including chronic fatigue syndrome, idiopathic chronic pain syndromes, fibromyalgia, and rheumatoid arthritis. Adrenal suppression occurs in women with chronic pelvic pain, with studies showing decreased salivary cortisol levels and a pronounced suppression of cortisol secretion in response to a CRH stimulation test [38]. This hypocortisol state fails to provide the protective anti-inflammatory milieu and may result in an increased vulnerability to stress-related disorders.

Psychosocial factors

To fully study IC/PBS, one must also look at the psychosocial factors that contribute to the disease. As stated by Moore and Kennedy [3], mechanical pain may contribute to the acute experience of disease, but the psychological assessment as to the significance of the pain may contribute to continuing disability and chronic pain. This psychological assessment may lead to increasing levels of stress, increased muscle tension, and propagation of the inflammatory and visceral motor response. Women with chronic pelvic pain have increased incidence of depression, anxiety disorders, somatization, substance abuse, and sexual dysfunction [38,41]. Furthermore, women with chronic pelvic pain report more major life events, and the onset of symptoms of chronic pelvic pain has been linked to stressful life events [38]. Depression has been linked to multiple comorbidities, including IC/PBS and other chronic pain syndromes, and depression is the most common symptom reported by survivors of sexual abuse [33]. Goldstein et al. [9•], demonstrated more severe and higher rates of depression in patients with IC/PBS versus

controls; however, whether chronic pain leads to depression or depression leads to the experience of chronic pain is less well understood.

Lesserman et al. [32] reported that sexual abuse may produce feelings of guilt and shame, and may lead to maladaptive and ineffective coping strategies and be manifest through physical pain and suffering with increased reporting of pain. Some have hypothesized that the inability to self-regulate emotions leads to an increased perception of threat and an increase in the "fight or flight" sympathetic response [30]. Previous sexual abuse has been linked to other psychiatric diagnoses such as PTSD. In a German study of women with chronic pelvic pain, of those who reported a history of sexual abuse, 40% met the diagnostic criteria for PTSD [38]. Survivors of childhood abuse have a greater neuroendocrine response to stressful situations, implying a physiologic sensitization to stress and thus an increased susceptibility to stress-related illnesses [42]. Importantly, it seems that the increased rate of chronic pain experienced by those with a history of sexual abuse persists even after controlling for concurrent depression [12•]. Exposure to abuse in childhood results in disturbances in emotional, physiological, behavioral, and social functioning, likely contributing to the experience of chronic pain in adulthood and acting as a significant barrier in the treatment of such problems [30]. Likewise, some IC/PBS patients tend to catastrophize their symptoms and fare worse than IC/PBS patients who do not [43].

Neuropathologic changes

IC/PBS has sometimes been referred to as a type of complex regional pain syndrome (CRPS), or reflex sympathetic dystrophy of the bladder [1]. Butrick [6] reported that the multiple etiologies of IC/PBS may be understood as the neuropathology that results from any prolonged inflammatory or noxious event and can result in a self-perpetuating chronic pain syndrome. Pain is an essential adaptive response to signal tissue damage. Tissue damage results in the release of inflammatory cytokines, which in turn activates A-δ and C-fiber afferent neurons that carry the pain signal from the periphery to the dorsal horn of the spinal cord. Within the spinal cord, the sensory neurons terminate upon second-order neurons, including interneurons, which eventually transduce the signal to the cerebral cortex for processing and conscious perception of bladder events [11]. From here, there is activation of efferent pathways back to the bladder and other pelvic sites, some of which prove to be maladaptive (discussed below). A second group of sensory C-fibers, known as the "silent" C-fiber afferents, make up 30% to 80% of all afferent sensory neurons from the viscera and have the potential to transmit pain but are only activated by prolonged noxious stimuli [6]. Activation of these silent C-fiber afferents is thought to play a role in the upregulation of the dorsal horn. This process may contribute to the pathologic neuroplastic changes of IC/PBS, as the bladder has been shown to be rich in silent C-fiber afferent innervation [44]. The fact that most IC/PBS patients report pain at low bladder volumes suggests that there is an abnormality in the sensory afferent nerves and their processing of bladder sensation [11].

In CRPS, sympathetic overactivity contributes to the chronic debilitating pain [12•]. There is an increase in nerve fiber density in the bladders of IC/PBS patients [11], including an increase in sympathetic innervation [45,46]. Urinary catecholamine levels in the bladders of patients with IC/PBS are elevated [47]. Interestingly, the number of sympathetic nerves decreases after anesthetic hydrodistention, possibly explaining part of its therapeutic benefit for some patients [1]. As reviewed by Lutgendorf et al. [45], in addition to evidence of increased sympathetic innervation and activity in the periphery, increased tyrosine kinase activity occurs in the locus coeruleus of cats with IC/PBS. The locus coeruleus is the most important source of norepinephrine in the central nervous system, and it plays a role in autonomic responses to stress including regulation of heart rate and blood pressure. In their laboratory stress model in which patients with IC/PBS were subjected to mental stress challenges, the authors demonstrated baseline autonomic dysfunction in the form of increased baseline heart rate in patients with IC/PBS, consistent with increased sympathetic activity as a factor in the development and exacerbation of symptoms of IC/PBS [45].

The classic neuropathic changes that occur as an acute pain episode develops into a chronic pain syndrome are thought to involve an alteration in the threshold of the nociceptive neurons. Similarly, one of the key features of bladder afferents is that organ insult and organ dysfunction can lead to sensitization of the bladder afferent nerves and the sensation of increased pain [11]. Within the dorsal horn, the *N*-methyl-D-aspartate receptors are activated, leading to loss of inhibitory signals to dorsal horn neurons, resulting in a lowered action potential threshold within the afferent neurons [6]. The clinical consequence is allodynia, or the perception of pain from a usually non-noxious stimulus. Lesserman et al. [32] proposed that traumatic stimulation of the genitals may downregulate the sensation thresholds of visceral nociceptors, thereby increasing sensitivity to abdominal/pelvic pain or other symptoms.

The pain experienced in IC/PBS involves both hyperalgesia and allodynia, with the pain often experienced out of proportion and across a greater area than would be expected by the tissue pathology itself. Neurogenic inflammation is believed to play a role in the initiation or propagation of pain in IC/PBS [6,11,16•]. With upregulation of the dorsal horn, there is reflexive firing of afferent sensory nerves antidromically [6]. This results in the peripheral release of potent inflammatory cytokines such as nerve growth factor and substance P, which in turn cause mast cell degranulation within the bladder urothelium resulting in propagation of the inflammatory response, manifested by the sensation of cystitis, vaginal pain, or vulvodynia [25]. Pathologically, this is characterized by lymphocytes seen penetrating the perineural

tissue with the nerves having lost their sheaths [11]. The resulting sensation can characteristically be spread across pelvic organs that share innervations, thus producing a type of pelvic crosstalk affecting the nonirritated organs, explaining in part why many of the pelvic pain syndromes appear to be linked [6,16•].

Another outcome of the pathologic neuroplastic changes that occurs in the setting of chronic pain appears to center around the development of a visceromuscular reflex. It is thought that a state of hypercontracted pelvic floor musculature results in pelvic floor instability and the development of myofascial trigger points [6,16•]. Myofascial dysfunction and hypertonic pelvic floor occur in as many as 85% of patients with IC/PBS and/or chronic pelvic pain syndromes [6]. These hypertonic pelvic floor muscles then become a source of pain even if the local inflammatory process within the bladder is treated. Fenton [48] described a process he termed *limbic-associated pelvic pain*. The limbic pain pathway involves the anterior cingulate cortex, in interaction with the amygdala, either to suppress or promote pain [49]. The experience of pain relies on somatosensory transmission of pain stimuli, integrated with limbic system processing of the anticipatory, fearful, and affective quality of the pain. Fenton hypothesized that abuse leads to limbic dysfunction in the anterior cingulate cortex, hippocampus, and amygdala, in which the limbic system mediates a cycle of hypervigilance for pain sensation from pelvic organs, leading to descending induction of pathologic changes in pelvic organs, typically manifest by muscle contraction. The pelvic organ dysfunction in turn leads to transmission of a chronic nociceptive signal registered by the limbic system perpetuating the cycle.

Clinical manifestations

Our study of sexual abuse and IC/PBS showed differences in IC/PBS patients with and without a history of prior sexual abuse [12•]. IC/PBS patients with prior history of abuse tend to have less irritative voiding complaints (fewer voids per day, larger voided volumes, less nocturia) than IC/PBS patients without a prior history of sexual abuse. Likewise, abuse patients tend to have more severe pain manifestations. Upon examination, abuse patients tend to have more tender areas to abdominal, vaginal, and rectal palpation. We infer that IC/PBS patients with an abuse history have central sensitization more often than nonabuse patients. If substantiated by other data, these findings may have important clinical consequences. It may represent a more "severe" form of IC/PBS when abused patients present with IC/PBS, as they have both "localized" and "centralized" IC/PBS. Bladder-focused treatments in these patients may not be adequate. It may also pose a diagnostic challenge for clinicians. An abused patient that presents primarily with pelvic pain and modest (or no) irritative voiding symptoms may not raise suspicion of IC/PBS [50]. Further, the IC/PBS literature prior to the recent understanding of sexual abuse and physical traumatization implies that IC/PBS most likely represents a heterogenous patient population of abuse and nonabuse patients. Outcomes of therapies may have been confounded by inclusion of patients with central sensitization. It may be instructive for future studies to subset patients more appropriately.

Conclusions

IC/PBS is a visceral pain syndrome with associated central and peripheral neuropathic changes. The study of chronic pain conditions and sexual abuse is difficult due to methodological shortcomings stemming from non-uniform definitions of disease and abuse, as well as difficulties with underreporting and retrospective recall bias [35]. Nonetheless, there appears to be an increased prevalence of sexual abuse reported in patients with IC/PBS. It may be that sexual abuse alters the HPA axis and the manner in which nociceptive signals are transmitted for central processing. The experience of trauma somehow changes a patient's ability to cope physically and psychologically with subsequent stressors and leaves them vulnerable to development of a chronic pain syndrome. As the organ-centric focus of IC/PBS is shifted toward an understanding of the neuropathological and psychological changes associated with this chronic debilitating condition, multimodal therapy aimed at both the inciting event and the central propagation of pathologic neurological changes may be more successful at relieving the symptoms of IC/PBS patients. More research is needed to ascertain how the timing and types of abuse are directly related to the development of IC/PBS symptoms. It may be advised that all patients presenting for evaluation of symptoms consistent with IC/PBS be screened for evidence of sexual or physical abuse such that they may be referred to the appropriate resources for multidisciplinary treatment of this complex disease.

Disclosure

Dr. Joel M. H. Teichman has served as a scientific advisor for Ortho Women's Health & Urology. He owns stock in Urigen Pharmaceuticals, Inc.

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