General

The Implications of Mental Health and Trauma in Interstitial Cystitis

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This review aims to assess the relationship between interstitial cystitis (IC) and significant traumatic events or PTSD. It was shown that there is a strong correlation between past trauma and the development of interstitial cystitis, as well as a much higher incidence of PTSD in patients diagnosed with IC. It was also established that for individuals with early traumatic experiences, the more likely the development of IC later in life, and with more severe symptoms and adverse effects on quality of life. We describe three distinct hypotheses for the possible physiologic mechanism for development of IC with relation to mental health and trauma, although definitive evidence in this area is still lacking, which poses interesting avenues for further research. This review also revealed an apparent lack of, and need for, trauma informed care and screening for PTSD in patients diagnosed with IC or other chronic pain syndromes.

INTRODUCTION

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a progressive and chronic disorder of the lower urinary tract primarily in women, characterized clinically by flares of bladder pain, urinary frequency and urgency, and impaired quality of life secondary to persistent symptoms.[1] Discomfort typically involves the suprapubic and pelvic area including the vagina, urethra, and the perineum.[2,3] While an underlying etiology is unclear, the pathogenesis of the disease involves neurogenic inflammation, urothelial mast cell dysfunction, and likely an autoimmune response to urothelial components.[4,5] IC can be diagnosed via cystoscopy with hydrodistention of the bladder paired with a urothelial biopsy, but can also be diagnosed in the absence of physical or microscopic findings, typically following exclusion and evaluation for more prevalent urologic conditions.[4] Symptom severity and presentation in IC varies with cycles of flares and remissions, which are often associated with emotional and hormonal stressors.[6] Treatment usually involves patient education, physical therapy and pain management, as well as oral and intravesical pharmacologic agents to relieve symptoms.[6]

Both an increased prevalence and severity of IC/PBS symptoms have been observed in patients with comorbid PTSD. In fact, several studies have shown a five-fold increase in PTSD prevalence among IC/PBS patients.[7,8] IC is part of the "Widespread Pain Phenotype (WPP)" syndromes, which is a classified group of disorders that are somatic in nature, where the underlying pathophysiology is attributed to a long term mental and emotional stressor, rather than solely an underlying anatomic, biochemical, functional, or infectious pathology. WPP presents in many bodily systems, but commonly manifests as IBS, fibromyalgia, chronic fatigue syndrome, chronic pelvic pain, IC, and migraines.[9] The WPP syndromes, and specifically IC, are associated with lower pain threshold and higher depression levels, after controlling for known confounding factors.[9,10] A history of PTSD appears to increase the severity of IC/PBS symptoms, the WPP is more likely in this patient population. However, the results of this review point to three possible pathophysiologic mechanisms to explain a molecu-

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lar connection between physical and emotional pain. While the etiology is likely a combination of these hypotheses, it is important to understand them in their separate intricacies. This review focuses on the relationship between PTSD and interstitial cystitis, however these three mechanisms have also been noted in explanation of other WPP syndromes.[7,11,12]

POSSIBLE MECHANISMS OF ASSOCIATION

One basis for a proposed mechanism of physical injury is via the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis controls typical reactions to stress and affects how pain is perceived. Early trauma, neglect, or abuse has been demonstrated to permanently alter the HPA axis's ability to function, resulting in dysfunctional hypothalamic and pituitary reactions to stress and pain.[11,13] This process occurs due to sensitization and upregulation of the stress response mediated by the HPA axis following past traumatic events or adverse childhood experiences. This sensitization of the HPA axis is proposed to be a permanent artifact caused by significant emotional trauma on a maturing brain. One downstream effect of HPA axis dysfunction and sensitization is exacerbation of functional pain disorders that affect the genitourinary and gastrointestinal systems.[13] A proposed bladder-gut-brain axis (BGBA) has been used to explain the phenomenon in which a dysfunctional stress response by a sensitized central nervous system may lead to aberrant perception of pain, contributing to bladder and gut functional disorders through a process called 'alarm falsification.'[13,14] Implicated in this process is the overactivation of mast cells, which are highly responsive to HPA axis activation, expressing abundant receptors for major HPA axis products like corticotropin releasing factor (CRF).[11] Past trauma and adverse childhood experiences have been linked to increased expression and aberrant production of CRF, potentially inducing a cascade of mast cell activation in response to stress.[11] This resulting mast cell overactivation leads to local inflammatory changes in mucosal tissue as described below.

The next proposed mechanism, an extension of the HPA axis, to explain the relationship between PTSD and IC is mast cell activation and degranulation.[13] Mast cells are a heterogeneous population of granulocytic cells of the immune system, and play an important role in neuroimmunologic signaling, as they act both centrally and peripherally.[15] It has been shown that an increase in CRF release in the setting of chronic stress triggers urothelial mast cell activation.[15] Although currently theoretical in human subjects, activation of mast cells in the bladder as a response to stress has been studied in a mice model.[16] In one investigation mice were placed under non-traumatic immobilization to simulate stress before the bladder was removed for analysis. Results showed activation of over 70% of bladder mast cells within 30 minutes of stress induction.[16] This study also demonstrated a decrease in mast cell activation when mice were treated neonatally with capsaicin, suggesting involvement of a neuropeptide, like substance P, in the pathogenesis of IC and other inflammatory diseases involving mast cell activation.[16] Likewise, also in a mouse model, mast cell activation was linked to anxiety-like behavior. Mice were put in an 'elevated plus maze' and 'open field arena,' and anxiety related behavior was measured via "stress induced defecation." In this study, animals pretreated with sodium cromoglycate, an inhibitor of mast cell degranulation, exhibited less anxiety-like behavior when compared to controls.[15] Thus, these studies indicate that mast cell activation may not only function in causing physical changes in the cellular components of the bladder, but also increase anxiety levels. Although preliminary and not yet studied in human subjects, these studies pose interesting and pertinent avenues for further research.

The final compelling hypothesis is known as the post-traumatic oxytocin dysregulation disorder theory. It integrates attention to psychological and physical comorbidities and could account for the increased incidence of these disorders among females specifically.[17] Like the HPA axis, this phenomenon has also been identified as part of the hypothetical bladder-gut-brain axis (BGBA).[13] Oxytocin is "a neuropeptide that, as both a neurotransmitter and paracrine hormone, regulates multiple normative psychological, social, and physical functions: attachment and affiliation, including maternal behavior and pair bonding; stress regulation and memory under stressful conditions; and smooth muscle contractility for digestive, sexual, reproductive, and lactation processes."[17] At a most basic level, oxytocin is a major regulator of smooth muscle contraction. It is common knowledge that excessive nervousness, anxiety, or upsetting situations can often cause GI symptoms. Oxytocin regulation operates as a feedback mechanism, a loop between the brain and body where smooth muscle receptors in the GI and GU tract react to output from the brain. Increased oxytocin levels produce increased GI and GU peristalsis resulting in nausea, reflux, diarrhea, hyperemesis gravidarum,[18] increased bladder contraction leading to incontinence, and uterine contraction that can manifest as physical discomfort or even preterm labor.[17] Data from recent studies of psychopathology also suggest that trauma,[19] severe PTSD,[18] and depression[20] are associated with very high or more pulsatile oxytocin levels.[17] In this light, it has been shown that anything which impacts the delicate balance between brain and genitourinary, reproductive, and gastrointestinal systems can re-trigger PTSD or post-traumatic symptoms. For example, GI upset after eating spoiled food, breastfeeding, medical or illicit drug use, or simply a hug from a close friend can disrupt the oxytocin balance, and thus trigger the experience of a past traumatic event as the fluctuations in endogenous hormone levels mimic hormonal imbalance caused by the trauma. These symptoms can be mitigated with counseling, meditation, exercise, and CBT, but this hinges on the ability of providers to recognize this association.

DISCUSSION

While interstitial cystitis and PTSD are both well-defined syndromes, they present distinctly and uniquely depending on the individual patient, making them not only difficult

to diagnose but also to quantitatively analyze studies and trends. This in part is due to the highly variable patient response to trauma. In PTSD, patient outcomes are multifaceted and dependent upon many factors; including type of trauma, pre-traumatic health condition, social status, mental health history, familial and living situations, prior level of function, personal processing of the patient, mental and emotional resilience, and patient age and maturity level.[21, 22] Also, PTSD is underdiagnosed and oftentimes overlooked for decades too long, allowing ample time for mental health disorders to manifest as physical dysfunction.

As part of the WPP phenomenon, IC is often a diagnosis of exclusion, a name given to a characteristic group of symptoms where a functional problem is not serious enough to account for all symptoms. Inherently, these diagnoses are often delayed in order to exhaust all medical tests, while physical and mental health symptoms progressively decline. "Patients with co-occurring interstitial cystitis and PTSD report higher levels of current pain, anxiety/depressive symptoms and worse quality of life compared to counterparts w/o co-occurring PTSD."[23] Thus, the underdiagnosis of PTSD not only leads to debilitating physical symptoms, but concurrently adds to the deterioration of mental and physical health. Compared to controls, patients with IC reported significantly more pain (total, sensory and affective), worse physical quality of life, increased sleep dysfunction, depression, suicidal ideation,[24] catastrophizing, anxiety, stress and moderately more sexual/social function problems.[25] Even after diagnosis, treatment modalities for WPP syndromes are sparse and not often curative.

Likewise, the treatment of chronic pain patients often strains the doctor-patient relationship. Characteristically, these patients are seen as having a lower pain tolerance and are seen more frequently by physicians. This adds to the stress of the patient, stress on the healthcare system and provider, and can lead to sub-par treatment of individuals by physicians. In 2008 economists from John Hopkins University calculated the annual cost of diagnosing, treating, and managing chronic pain in the United States to be 630 billion dollars. This was more than the annual cost of heart disease and diabetes combined by almost thirty percent.[26] Likewise, Western health systems tend to divide care of the mind and body into separate clinical domains. Many of the "medically unexplained" or "idiopathic" diagnoses are attributed to physical pain conditions, and are treated in medical settings usually without attention to their potential comorbidity with posttraumatic psychiatric conditions.[27] It has been shown that patients with diagnosed PTSD are ninety times more likely to have a somatic symptom disorder than those without PTSD.[8] Thus, it is vital that in treating patients with symptomatologies consistent with any widespread pain phenotype, physicians employ "trauma informed care,"[12] and promptly screen for and treat PTSD, trauma, and mental health disorders. There still exists a stigmatization of mental health in this country that perpetuates the problem of chronic pain and mistreatment of patients.[21]

CONCLUSION

While this review revealed many understudied areas in the realms of PTSD, mental health, chronic pain, and mechanisms of their linkage, it did undeniably show that in a virtually cyclical relationship, childhood or past trauma poses a risk for developing IC,[28,29] and that diagnosed IC is linearly correlated to previous trauma or previous diagnosis of PTSD.[23,30] While there are many theories and specifics for this mechanism, it is clear that mental health and urologic pain disorders are interrelated. The major takeaway from this review is the lack of and thus necessity for physician education in trauma informed care when faced with chronic pain patients. It has been detailed that one-time, universal screening for history of trauma/abuse does not encourage patients to disclose such sensitive information.[30] Instead, physicians must first focus on the establishment of an authentic relationship with their patients while also offering recurring opportunities for their patients to share details of past trauma.[31] This has been confirmed via patient-centered surveys and requires more widespread implementation into patient care.[31] Doing so presents a unique challenge as each individual will have particular preferences to how this process of disclosure should occur. Making such a variable process also a standardized one is undoubtedly difficult but entirely necessary to ensure optimal, holistic care of IC and other trauma-related pathologies.

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