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Review Article

The role of urodynamic study in evaluation of interstitial cystitis/painful bladder syndrome

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ABSTRACT

The current paradigm of diagnosing interstitial cystitis/painful bladder syndrome (IC/PBS) focuses largely on the exclusion of other pathology and symptoms of urinary frequency, urgency, and pain, pressure, or discomfort with bladder filling, and places less emphasis on diagnostic tests. Consequently, many experts have suggested that urodynamic study (UDS) is not recommended for routine clinical use to establish IC/PBS diagnosis. However, recent studies have demonstrated the correlations of UDS variables with clinical symptoms, the results of a potassium sensitivity test, severity of glomerulations, and maximal bladder capacity during cystoscopic hydrodistention. Moreover, a combination of UDS and potassium sensitivity test has been shown to aid in differentiating IC/PBS in women with increased bladder sensation. All of these facts suggest that there might be a role for UDS in the diagnosis of IC/PBS.

1. Introduction

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a clinical diagnosis based on symptoms including urinary frequency, urgency, and bladder pain, pressure, and/or discomfort in the absence of other pathological findings [1–5]. Since diseases that cause similar symptoms need to be excluded, patients with IC/PBS are often diagnosed years after the onset of their symptoms [1,2,4]. Development of objective tests, including urodynamic study (UDS), in the evaluation of patients with irritative voiding symptoms may be beneficial in the early diagnosis and, therefore, treatment of IC/PBS. There is currently a paucity of literature addressing urodynamics and its role in IC/PBS.

In the United States, IC/PBS affects about nine times as many women as men [6]. Estimates of the prevalence rates of IC/PBS vary widely, from 67 to 230 per 100,000 women having clinically confirmed disease [7,8]. Since IC/PBS cannot be cured, the goal of treatment is largely based on symptomatic relief at present. A certain percentage of patients treated have successful results for a short time, but most patients experience symptom relapse in long-term follow-up and need continual treatment with several different therapeutic modalities [9].

The aim of this article is to provide a topical review from the recent literature focusing on the role of UDS in the evaluation of IC/PBS.

2. Definition of interstitial cystitis/painful bladder syndrome

According to the most recent American Urology Association (AUA) guidelines, the definition of IC/PBS is: “An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks’ duration, in the absence of infection or other identifiable causes” [10].

3. Pathophysiology of interstitial cystitis/painful bladder syndrome

Although there are numerous hypotheses regarding the primary cause of IC/PBS, no single etiology has been established, and most experts believe it is a multifactorial process that starts with one of several urological insults, such as immune-mediated injury, chronic inflammation, deficient bladder defenses, or obstruction of vascular or lymphatic vessels [11]. The natural history of IC/PBS then involves a cascade of events, in which bladder insult leads to epithelial layer dysfunction, C-nerve fiber activation, and the proliferation of mast cells [12]. Without appropriate treatment,

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these processes become aggravated over time, leading to a vicious cycle of progressively worsening tissue damage, scarring, and fibrosis [13].

3.1. Glycosaminoglycan layer defect

A key concept currently accepted for describing the defect underlying the observed pathophysiologies in IC/PBS is based on the belief that breakdown of the glycosaminoglycan (GAG) layer (the semipermeable protective coating that covers the bladder epithelium and protects against leakage of urinary irritants such as potassium and urea into the bladder wall) is the primary trigger of the cascade. In a healthy bladder, this mucous layer acts as a barrier that prevents damage to the underlying nerves and muscles and impedes bacterial adherence. If the GAG layer is impaired or inefficient, the irritants in the urine are able to penetrate the bladder wall, initiate the pathological cascade, damage tissue, cause pain, and disrupt the normal reparative process of the GAG layer. Addressing this altered permeability of the bladder epithelium has become a focus for IC/PBS treatment strategies.

3.2. Neurogenic inflammation and spinal windup

Also contributing to this disease process is the concept of spinal cord "windup", the repetitive stimulation of C fibers in the dorsal horn and upregulation of sensory nerves in the bladder that cause the characteristic pain of IC/PBS [12,14]. The ability to perceive pain from internal organs is a function of the afferent sensory system, which in some organs projects to the central nervous system, thereby linking the viscera to the pain centers of the brain [15]. The bladder has the highest neural density of tissues within the pelvis [14]. A large group of visceral nerves are "silent" until a prolonged noxious stimulus, such as inflammation, causes them to become activated [15]. With ongoing stimulation from inflammation, during which there is prolonged release of neurotransmitters such as substance P, the threshold for neuronal stimulation decreases (allodynia) so that the amount of stimulation required to send a signal to the cerebral cortex is reduced [14].

As the neurological stimulation escalates because of hyperalgesia and allodynia, conditions of widespread pain and discomfort begin, and there may be progressive damage to the pelvic floor or gastrointestinal organs, as well as gynecological and urinary symptoms. Based on the duration and severity of these alterations taking place within the dorsal horn, the changes can become permanent; a process known as centralization. With this neural upregulation, patients begin to experience exaggerated reflex output and viscero-visceral hyperalgesia, and muscle spasticity [14]. In these circumstances, the pain threshold is reduced so that minimal contact can induce a response. In addition, pain in one organ will cause discomfort in a neighboring organ because of their shared innervation, leading to multiple pain generators and a self-perpetuating cycle of pain. This progressive and variable regional pain syndrome with multiorgan presentation complicates the diagnosis of IC/PBS.

4. Evaluation of interstitial cystitis/painful bladder syndrome

Although the characteristic symptoms of IC/PBS are well documented, the substantial overlap with features of other disorders mandates a focused screening and thorough differential diagnosis to rule out other potential causes of urgency/frequency and/or pelvic pain symptoms that characterize this condition. In addition to a history and physical examination, urinalysis and urine culture are the first steps in ruling out disorders that mimic IC/PBS, such as urinary tract infection and bladder cancer. The absence of bacteria or blood cells in a voided urine specimen is characteristic of IC/PBS. Other specialized examinations aiding in the diagnosis of IC/PBS include a potassium sensitivity test (PST), cystoscopy with bladder hydrodistention, and UDS.

Screening tools for IC/PBS include the Pelvic Pain and Urgency/Frequency Patient Symptom Scale and O'Leary-Sant IC Symptom Index and IC Problem Index, which may describe the nature and severity of the disease. However, none of these has been shown to be of value for diagnosis [16,17].

4.1. Potassium sensitivity test

The PST is a sensitive indicator of bladder dysfunction that can be performed in a clinician's office [18]. The PST is based on the premise that, unlike healthy bladder walls, the altered GAG epithelium in IC/PBS will allow potassium [instilled directly into the bladder as a 0.4 M potassium chloride (KCl) solution] to pass into the bladder. If it is able to pass through the bladder wall, the potassium, which is an irritant, will trigger a pain response and/or a sense of urgency. Up to 90% of patients diagnosed with IC/PBS have positive PSTs, as do 81% of gynecological patients with pelvic pain; less than 2% of healthy women experience pain or urgency symptoms during a PST [16,19]. However, a PST cannot, on its own, reliably distinguish IC/PBS from other disorders of bladder origin [18].

4.2. Cystoscopy with bladder hydrodistention

The cystoscopic findings in IC/PBS consist of glomerulations, maximal bladder capacity under anesthesia, or Hunner's ulcers. Although the presence of submucosal hemorrhages or glomerulations on cystoscopy is part of the National Institute of Diabetes and Digestive and Kidney Diseases research parameters for the diagnosis of IC/PBS, it is not predictive of pathology and does not correlate with symptoms; a biopsy is not diagnostic of IC/PBS and the presence of glomerulations is not specific for IC/PBS [20]. The primary indication for cystoscopy in the assessment of pelvic pain is to rule out malignancy in patients with hematuria and/or abnormal urinary cytology. Cystoscopy is no longer widely used as a standard diagnostic procedure in suspected IC/PBS.

4.3. Biomarkers

Interest in the mechanism of bladder repair from tissue damage has led to the identification of several potential biological markers that might prove valuable for identifying IC/PBS from urine samples. Although the list of urinary factors tested as biomarkers of IC/PBS is relatively long—including norepinephrine, substance P, kallikrein, GAG, and mast cell mediators—the most likely current candidates to establish a diagnosis of IC/PBS early in the course of the disorder are antiproliferative factor [21], nerve growth factor [22], and glycoprotein-51 [23].

5. Urodynamic study and interstitial cystitis/painful bladder syndrome

UDS is a group of tests under fluoroscopy used to assess the function and morphology of the urinary tract by measuring various aspects of urine storage and evacuation. UDS has been widely used to aid in understanding the physiological mechanisms of lower urinary tract dysfunction [24]. However, there is a paucity of current literature addressing urodynamics and its role in IC/PBS. The current paradigm for IC/PBS diagnosis relies mainly on a history and physical examination and places less emphasis on diagnostic

tests [25]. Consequently, the AUA guidelines do not recommend UDS for routine clinical use to establish a diagnosis of IC/PBS [10].

The characteristic UDS findings in IC/PBS patients include an early first sensation of filling (FSF) and small cystometric bladder capacity (CBC) [26–28]. Although the findings of UDS are not pathognomonic for IC/PBS, they may provide information regarding concomitant voiding dysfunction in IC/PBS patients and can aid in detection of bladder outlet obstruction, poor detrusor contractility, and other conditions that could explain why patients are initially refractory to first-line therapy [10]. In addition, UDS variables have been shown to be correlated with clinical symptoms, the results of PST, and cystoscopic findings in IC/PBS patients.

5.1. Correlation between urodynamic study parameters and clinical symptoms

Kirkemo et al evaluated the association of symptoms and cystometric findings in the ICDB study [29]. They found that the first sensation to void and maximal cystometric capacity correlated with frequency, urgency, and nocturia as measured by voiding diaries, visual analog scales (VAS), and a quality-of-life questionnaire. A recent study by Kuo et al showed in detail that UDS parameters, such as the FSF, first desire to void (FD), strong desire to void (SD), CBC, and voided volume (VV) were significantly associated with the severity of clinical symptoms measured by the IC symptom index and IC problem index [28].

5.2. Correlation between urodynamic study parameters and potassium sensitivity test

Although previous studies failed to find a relationship between cystometric parameters and a positive PST in IC/PBS patients [30,31], a recent study evaluating 214 IC/PBS patients demonstrated that subjects with a positive PST had lower mean volumes at SD, CBC, and VV, and thus a low maximum flow rate (Q_{max}) [28]. Although a positive PST may be rendered in conditions other than IC/PBS [32], it can still indicate more severe urothelial dysfunction that is more susceptive to the stimulation of KCl, thus resulting in volume reduction of the bladder in IC/PBS patients [28].

5.3. Correlation between urodynamic study parameters and cystoscopic hydrodistention

Nigro et al reported that the volume at maximum capacity on urodynamics was positively associated with the volume during hydrodistention [33]. Recently the study reported by Kuo et al not only supported their findings, but also identified other UDS parameters (FSF, FD, SD, Q_{max}, and VV) that were positively correlated with anesthetic maximal bladder capacity [28]. Furthermore, their study also implied the severity of glomerulations is negatively correlated with the bladder volume measured objectively as UDS parameters (FSF, FD, SD, CBC, and VV). More advanced disease progression involving *neovascularization*and possible neurogenic inflammation of the bladder may lead to an unpleasant sensation during bladder filling and thus limit bladder capacity [28]. The mechanism of glomerulations and its correlation with IC/PBS are not, however, fully understood and need investigation.

5.4. Combined urodynamic study and potassium sensitivity test may help in the diagnosis of interstitial cystitis/painful bladder syndrome in female patients

Our recent study consisting of 405 women with increased bladder sensation and 272 symptomatic controls [34] demonstrated that a diagnosis of definite IC/PBS could be highly suspected in women with frequency urgency and pain symptoms, a small CBC of less than 350 mL on UDS, and a positive PST, especially when the PST response of pain was $\geq$2 on a VAS. A positive predictive value of 100% can be achieved if we choose women for cystoscopic hydrodistention based on these clinical findings; even when the pain response was $\geq$1 on a VAS, the positive predictive value was 91.2% [34].

6. Conclusion

Although the value of UDS in the diagnosis of IC/PBS remains inconclusive, previous studies have demonstrated correlations of UDS parameters with clinical symptoms, the results of PST, severity of glomerulations, and maximal bladder capacity during cystoscopic hydrodistention. In addition, a recent study showed that a combination of UDS and PST may aid in differentiating IC/PBS in women with increased bladder sensation. All of these results suggest that there might be a role for UDS in the diagnosis of IC/PBS.

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