Review

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Is Urethral Pain Syndrome Really Part of Bladder Pain Syndrome?

Sung Tae Cho

Department of Urology, Hallym University Kangnam Sacred Heart Hospital, Seoul, Korea

Urethral pain syndrome is a symptom complex that includes dysuria, urinary urgency, frequency, nocturia, and persistent or intermittent urethral and/or pelvic pain in the absence of proven infection. Bladder pain syndrome is a clinical diagnosis, based primarily on chronic symptoms of pain from the bladder and/or pelvis associated with urinary urgency or frequency in the absence of identified cause for the symptoms. To date, the term, urethral pain syndrome, remains to be unclear in referring to a distinct subgroup of bladder pain syndrome. However, these two syndromes share many similarities, except the organ of pain. This review is intended to summarize the current state of literature with regard to similar pathophysiology and possible interrelations between urethral pain syndrome and bladder pain syndrome.

Keywords: Cystitis, interstitial; Urinary bladder; Urethra

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Correspondence to: Sung Tae Cho
http://orcid.org/0000-0002-4691-6159
Department of Urology, Hallym University Kangnam Sacred Heart Hospital, Hallym University College of Medicine, 1 Singil-ro, Yeongdeungpo-gu, Seoul 07441, Korea
Tel: +82-2-829-5198, Fax: +82-2-846-5198
E-mail: cst326@paran.com

INTRODUCTION

The term "urethral syndrome" was used in 1965 by Gallagher et al. [1]. In 2002, the term "urethral pain syndrome" was implemented by the International Continence Society (ICS) to delineate the occurrence of recurrent episodic urethral pain, usually on voiding, with daytime frequency and nocturia, in the absence of proven infection. It is often common for dyspareunia to also be described. Regardless of the symptoms, the lack of evidence of urinary tract infection or other obvious pathologies is essential [2]. Due to these nonspecific symptoms, there are often overlaps with disease pictures, such as interstitial cystitis/bladder pain syndrome (IC/BPS) or the overactive bladder (OAB). As such, some authors describe the urethral syndrome as an early form of IC [3]. In the current guidelines of the European Association of Urology (EAU), urethral pain syndrome is considered to be a part of the complex of chronic pelvic pain [4].

Urethral pain syndrome and BPS have a lot in common, except the organ of pain. To aid in understanding the possible relationship between these two syndromes, we summarized both syndromes and presented evidence-based information on whether additional similarities with regard to pathophysiology exist between these two syndromes.

URETHRAL PAIN SYNDROME

Urethral pain syndrome is a symptom complex that includes dysuria, urinary urgency, frequency, nocturia, and persistent or intermittent urethral and/or pelvic pain in the absence of proven infection [2]. The diagnosis implies a specific duration of symptoms, a minimum of six months [5]. The exact etiology is unknown; however, infectious and psychogenic factors, urethral spasms, early IC, hypoestrogenism, squamous metaplasia, as well as gynecological

risk factors are discussed [6]. There is now evidence that the microscopic paraurethral glands connected to the distal third of the urethra in the prevaginal space are homologous to the prostate. They stain histologically for prostate-specific antigen and, like the prostate, are subject to infection and cancer. Some researchers have theorized that inflammation of the female prostate (Skene glands and the paraurethral glands) may explain the causes of urethral pain syndrome [7].

The diagnosis is mainly based on symptoms. However, it is important to rule out other conditions, including paraurethral pathology, bladder cancer, atrophic urethral changes, and vaginitis [5]. The incidence and prevalence of this condition is not well known thus far due to the lack of consensus in the method of diagnoses. In several studies, 15-30% of women who presented with lower urinary tract symptoms (LUTS) were diagnosed with urethral pain syndrome [8,9]. Most of these patients are women aged 20 to 30 years and 50 to 60 years. Contrary to the earlier definition, urethral pain syndrome may also occur in men, but less frequently [6,10]. This condition is more common in Caucasians than other races [5]. As a result of these nonspecific symptoms, patients with urethral pain syndrome often enter into urological care after long-term suffering and repeated treatment [6,11].

INTERSTITIAL CYSTITIS

The first known modern documentation of a condition resembling IC appeared in the early 19th century. Philip Syng Physick described an inflammatory condition of the bladder with an "ulcer" producing the same symptoms as a bladder stone in 1808 [12]. He expanded this concept to include chronic frequency, urgency, and pain syndrome, occurring in the absence of demonstrable etiology, which was called the 'tic douloureux of the bladder' in 1836 [12,13]. This may represent the first description of IC. Fifty years later, Skene used the term IC to describe an inflammation that had "destroyed the mucous membrane partly or wholly and extended to the muscular parietes" in 1887 [14]. However, because of the distinctive clinical characterization of the syndrome, the physician who is always remembered and quoted is Guy Hunner [13]. Early in the 20th century, he described a symptom complex of bladder pain associated with distinguishing cystoscopic feature of mucosal lesions as the "elusive ulcer," which was later termed Hunner's ulcer. For several years, this finding was the hallmark of IC, and urologists would look for ulcers but failed to make the diagnosis in their absence [13].

The Interstitial Cystitis Association (ICA), established in 1984, succeeded in gaining the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)'s interest in the research for this field [15]. In an effort to define IC, the NIDDK held a workshop in August 1987, at which point in time, the consensus diagnostic criteria were established for the diagnosis of IC [16]. After the pilot studies to test for the criteria, they were revised at the follow-up NIDDK workshop in 1988 [15,16]. These criteria were specifically designed for the basic and clinical research purposes, but not as a diagnostic tool for the clinician (Table 1) [17].

PAINFUL BLADDER SYNDROME

The ICS has been standardizing the terminology of lower urinary tract diseases. In 2002, for the first time, the ICS defined IC, calling it a painful bladder syndrome (PBS), delineating it as: "the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms, such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology [18,19]." The ICS reserves the diagnosis of IC as a "specific diagnosis that requires confirmation by typical cystoscopic and histological features." This definition may miss 36% of patients, primarily because it confines the pain to a suprapubic location and mandates a relationship of pain to bladder filling [18]. This disorder, despite confusion, came to be known as PBS/IC or IC/PBS.

BLADDER PAIN SYNDROME

The European Society for the Study of Interstitial Cystitis (ESSIC) proposed a new definition and another name change from IC/PBS to BPS alone. The ESSIC paper, published in 2008, proposed the following definition: "Chronic (six months or more) pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like persistent urge to void or urinary frequency. Confusable diseases as the cause of the symptoms must be excluded [20]."

ESSIC also introduced a new classification system of BPS types and a list of confusable diseases. BPS is indicated

Table 1. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) revised the criteria for interstitial cystitis in 1988

To be included as IC, patients must have either glomerulations on cystoscopic examination or a classic Hunner's ulcer, and they must have either pain associated with the bladder or urinary urgency. Examination for glomerulations should occur after distension of the bladder under anesthesia to 80-100 cmH_2O for 1-2 min. The bladder may be distended up to two times before evaluation. The glomerulations must be diffuse–present in at least 3 quadrants of the bladder –and there must be at least 10 glomerulations per quadrant. The glomerulations must not be along the path of the cystoscope (to eliminate artifact from contact instrumentation).

The presence of any one of the following will exclude the diagnosis of interstitial cystitis:

1. Bladder capacity of greater than 350 ml on awake cystometry using either a gas or liquid filling medium
2. Absence of an intense urge to void with the bladder filled to 100 ml of gas or 150 ml of water during cystometry, using a fill rate of 30-100 ml/min
3. The demonstration of phasic involuntary bladder contractions on cystometry using the fill rate described above
4. Duration of symptoms less than 9 months
5. Absence of nocturia
6. Symptoms relieved by antimicrobials, urinary antiseptics, anticholinergics, or antispasmodics
7. A frequency of urination while awake of less than eight times per day
8. A diagnosis of bacterial cystitis or prostatitis within a 3-month period
9. Bladder or lower ureteral calculi
10. Active genital herpes
11. Uterine, cervical, vaginal, or urethral cancer
12. Urethral diverticulum
13. Cyclophosphamide or any type of chemical cystitis
14. Tuberculous cystitis
15. Radiation cystitis
16. Benign or malignant bladder tumors
17. Vaginitis
18. Age less than 18 years

Adapted from Bladder pain syndrome (Interstitial Cystitis) and related disorders. In: Campbell-Walsh urology. 10th ed. Philadelphia: Saunders; 2012. p. 334-70 [17].

by two symbols: The first corresponds to cystoscopy with hydrodistention (CHD) findings (1, 2, or 3, indicating increasing grade of severity), and the second to biopsy findings (A, B, and C, indicating increasing grade of pathologic severity) [20]. Although neither CHD nor bladder biopsy was prescribed as an essential part of the evaluation, categorizing patients in terms of whether they have undergone the procedure with results, made it possible to follow patients with similar findings and study each identified cohort to compare the natural history, prognosis, and response to therapy [20]. The definition of ESSIC is a clinically useful one, and changes made since its original iteration have likely made it more sensitive and inclusive [21].

The panel of the Society for Urodynamics and Female Urology (SUFU) produced a slightly different definition for IC/BPS in 2008: "An unpleasant sensation (pain, pressure, discomfort), perceived to be related to the urinary bladder, associated with LUTS for more than six weeks, in the absence of infection or other identifiable causes" [22]. The SUFU definition was adopted in the guidelines of the American Urological Association (AUA) in 2011, along with the nomenclature IC/BPS, without differentiating between the two [23].

HYPERSENSITIVE BLADDER SYNDROME

Homma [24] proposed that frequency/urgency syndrome is characterized by frequency (frequent voiding) and urgency (strong desire to void). It is an inclusive term that incorporates OAB, hypersensitive bladder syndrome (HBS), and other conditions that are associated with frequency and urgency. Urgency in OAB is characterized by a sudden onset and/or fear of leakage, while urgency in HBS is characterized by persistent nature and is associated with the fear of pain. OAB-wet is a subgroup of OAB, while PBS is a subgroup of HBS with pain. IC is one of the diseases manifested by frequency/urgency and overlapping with HBS and PBS [24,25].

A clinical guideline and algorism for IC and HBS has been developed by a group of East Asian (Japan, Korea, and Taiwan) urologists as a revised form of the Japanese guideline for IC [26]. This East-Asian guideline defines IC as a disease of the urinary bladder diagnosed by three following conditions: 1) a characteristic complex of LUTS, 2) bladder pathology, such as Hunner's ulcer and bladder bleeding after overdistention, and 3) exclusions of confusable diseases. The characteristic symptom complex is termed, HBS, which is defined as bladder hypersensitivity, usually associated with urinary frequency, with or without

bladder pain. For the definite diagnosis of IC, cystoscopy or hydrodistention is crucial; HBS is the diagnosis when IC is suspected, but not confirmed by the 3 requirements.

NEW PARADIGM

The paradigm change has resulted in altering what was originally considered a bladder disease (IC) to a chronic pain syndrome (BPS). IC/BPS is now viewed not only through the paradigm of chronic pain syndrome manifesting through bladder-related symptoms, but as a syndrome that may not only isolated to the bladder alone [17]. There may be many causes of chronic pelvic pain. When a cause cannot be determined, the condition is characterized as pelvic pain syndrome. If it can be distinguished as urologic, it is further categorized by the organ system. A urologic pain syndrome can sometimes be further differentiated based on the site of perceived pain. These pain syndromes include bladder, urethra, prostate, testicular, and epididymal pain syndromes. The types of BPS can be further defined as IC or simply categorized by ESSIC criteria [17,22].

URETHRA AND BLADDER PATHOPHYSIOLOGY IN PAIN SYNDROME

IC/BPS is a chronic disease characterized by prolonged duration of symptoms of pelvic or perineal pain, thinning of the bladder epithelium, and various voiding symptoms, such as nocturia, increased urinary frequency, and urgency. In terms of pain, suprapubic or bladder pain is prominent. However, many patients report different and/or additional sites, particularly in the urethra, genitalia, and lower back [27,28]. Although the cause of BPS is usually unknown, there is a body of evidence supporting the involvement of bladder urothelial abnormalities in these illnesses [29,30]. Parsons showed that a leaky dysfunctional epithelium and subsequent diffusion of potassium into the tissue may be responsible for the pelvic pain [10]. These altered the paradigms in the generation of frequency, urgency, and pelvic pain. After all, urethral pain syndrome and BPS have all been shown to have epithelial leak and potassium sensitivity, uniting these syndromes into one disease, lower urinary tract dysfunction epithelium (LUDE) [10,31].

LUDE can affect the bladder, urethra, labia or vaginal introitus in women, and the prostatic ducts and urethra in men. Because patients with LUDE may experience pain in one or more locations throughout the pelvis in any combination, it is important for physicians to avoid making a diagnosis solely based on the site of pain. A useful diagnostic tool is the intravesical potassium sensitivity test, which detects the abnormal epithelial permeability of LUDE [32].

There is also evidence that the urothelium in the region of the urethra may play a role in continence and sensation. It has been suggested that symptoms of pain that arise from the lower urinary tract might originate principally from the bladder neck and proximal urethra [33]. The bladder neck and proximal urethral contain the largest density of bladder nerves, and the epithelial cells that line the surface show neuronal-like properties [34]. Thus urethral epithelial-neural interactions could lead to a "urethral instability" influencing the storage and voiding reflexes, and resulting in symptoms of urgency and pain [34,35].

CONCLUSIONS

Urethral pain syndrome is an occurrence of recurrent episodic urethral pain usually on voiding with frequency and nocturia. BPS is chronic pelvic pain, pressure, or discomfort often exacerbated by bladder filling, and associated with urinary frequency. Seemingly, two different syndromes that would usually seem nothing like one another have much in common when it comes to the new paradigm and pathophysiology.

Chronic pelvic pain can have multiple causes, including many types of urologic pain syndromes. In broad terms, urologic pain syndrome encompasses urethral pain syndrome and BPS. Pain arising from the lower urinary tract may originate from the bladder neck and proximal urethra, and LUDE can affect tissues of the bladder and urethra. Even if controversies still remain, urethral pain syndrome can be a part of BPS. Further basic science and clinical research in this area is needed to better understand the pathophysiology of these syndromes.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Gallagher DJ, Montgomerie JZ, North JD. Acute infections of the urinary tract and the urethral syndrome in general practice. Br Med J 1965;1:622-6.
2. Abrams P, Cardozo L, Fall M, Grifftihs D, Rosier P, Ulmsten U, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology 2003;61:37-49.
3. Stamm WE, Running K, McKevitt M, Counts GW, Turck M, Holmes KK. Treatment of the acute urethral syndrome. N Engl J Med 1981;304:956-8.
4. Engeler DS, Baranowski AP, Dinis-Oliveira P, Elneil S, Hughes J, Messelink EJ, et al. The 2013 EAU guidelines on chronic pelvic pain: is management of chronic pelvic pain a habit, a philosophy, or a science? 10 years of development. Eur Urol 2013;64:431-9.
5. Kaur H, Arunkalaivanan AS. Urethral pain syndrome and its management. Obstet Gynecol Surv 2007;62:348-51; quiz 353-4.
6. Dreger NM, Degener S, Roth S, Brandt AS, Lazica DA. [Urethral pain syndrome: fact or fiction--an update]. Urologe A 2015;54:1248-55. German.
7. Gittes RF, Nakamura RM. Female urethral syndrome. A female prostatitis? West J Med 1996;164:435-8.
8. Gurel H, Gurel SA, Atilla MK. Urethral syndrome and associated risk factors related to obstetrics and gynecology. Eur J Obstet Gynecol Reprod Biol 1999;83:5-7.
9. Tait J, Peddie BA, Bailey RR, Arnold EP, Russell GL, Bishop VA, et al. Urethral syndrome (abacterial cystitis)--search for a pathogen. Br J Urol 1985;57:552-6.
10. Parsons CL. The role of a leaky epithelium and potassium in the generation of bladder symptoms in interstitial cystitis/overactive bladder, urethral syndrome, prostatitis and gynaecological chronic pelvic pain. BJU Int 2011;107:370-5.
11. Burkhard FC, Blick N, Hochreiter WW, Studer UE. Urinary urgency and frequency, and chronic urethral and/or pelvic pain in females. Can doxycycline help? J Urol 2004;172:232-5.
12. Parsons JK, Parsons CL. The historical origins of interstitial cystitis. J Urol 2004;171:20-2.
13. Fall M, Logadottir Y, Peeker R. Interstitial cystitis is bladder pain syndrome with Hunner's lesion. Int J Urol 2014;21 Suppl 1:79-82.
14. Skene AJC. Diseases of the bladder and urethra in women. 2nd ed. New York: William Wood; 1887.
15. Meijlink JM. Interstitial cystitis and the painful bladder: a brief history of nomenclature, definitions and criteria. Int J Urol 2014;21 Suppl 1:4-12.
16. Gillenwater JY, Wein AJ. Summary of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases Workshop on Interstitial Cystitis, National Institutes of Health, Bethesda, Maryland, August 28-29, 1987. J Urol 1988;140:203-6.
17. Hanno PM. Bladder pain syndrome (Interstitial Cystitis) and related disorders. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. Campbell-Walsh urology. 10th ed. Philadelphia: Saunders; 2012. p. 334-70.
18. Warren JW, Meyer WA, Greenberg P, Horne L, Diggs C, Tracy JK. Using the International Continence Society's definition of painful bladder syndrome. Urology 2006;67:1138-42; discussion 1142-3.
19. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002;21:167-78.
20. van de Merwe JP, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. Eur Urol 2008;53:60-7.
21. Mouracade P, Lang H, Jacqmin D, Saussine C. [Using the intersititial cystitis new diagnostic criteria in daily practice: about 156 patients]. Prog Urol 2008;18:674-7. French.
22. Hanno P, Dmochowski R. Status of international consensus on interstitial cystitis/bladder pain syndrome/painful bladder syndrome: 2008 snapshot. Neurourol Urodyn 2009;28:274-86.
23. Hanno PM, Burks DA, Clemens JQ, Dmochowski RR, Erickson D, Fitzgerald MP, et al. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. J Urol 2011;185:2162-70.
24. Homma Y. Lower urinary tract symptomatology: its definition and confusion. Int J Urol 2008;15:35-43.
25. Nordling J, Fall M, Hanno P. Global concepts of bladder pain syndrome (interstitial cystitis). World J Urol 2012;30:457-64.
26. Homma Y, Ueda T, Tomoe H, Lin AT, Kuo HC, Lee MH, et al. Clinical guidelines for interstitial cystitis and hypersensitive bladder syndrome. Int J Urol 2009;16:597-615.
27. Warren JW, Langenberg P, Greenberg P, Diggs C, Jacobs S, Wesselmann U. Sites of pain from interstitial cystitis/painful bladder syndrome. J Urol 2008;180:1373-7.
28. FitzGerald MP, Brensinger C, Brubaker L, Propert K; ICDB Study Group. What is the pain of interstitial cystitis like? Int Urogynecol J Pelvic Floor Dysfunct 2006;17:69-72.
29. Cho YS. Interstitial Cystitis/Bladder pain syndrome: a urologic mystery. Int Neurourol J 2016;20:3-4.
30. Keay SK, Birder LA, Chai TC. Evidence for bladder urothelial pathophysiology in functional bladder disorders. Biomed Res Int 2014;2014:865463.
31. Parsons CL, Bullen M, Kahn BS, Stanford EJ, Willems JJ. Gynecologic presentation of interstitial cystitis as detected by intravesical potassium sensitivity. Obstet Gynecol 2001;98: 127-32.
32. Parsons CL. Interstitial cystitis and lower urinary tract symptoms in males and females-the combined role of potassium and epithelial dysfunction. Rev Urol 2002;4 Suppl 1:S49-55.

33. Birder LA, Andersson KE, Kanai AJ, Hanna-Mitchell AT, Fry CH. Urothelial mucosal signaling and the overactive bladder-ICI-RS 2013. Neurourol Urodyn 2014;33:597-601.
34. Birder LA, de Wachter S, Gillespie J, Wyndaele JJ. Urethral sensation: basic mechanisms and clinical expressions. Int J Urol 2014;21 Suppl 1:13-6.
35. McLennan MT, Melick C, Bent AE. Urethral instability: clinical and urodynamic characteristics. Neurourol Urodyn 2001;20: 653-60.