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REVIEW ARTICLE

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How can we improve the diagnosis and management of bladder pain syndrome? Part 1: ICI-RS 2018

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Abstract

Background: This paper summarizes the discussion in a think tank at the ICI-RS 2018 about the diagnosis of bladder pain syndrome (BPS).

Aims: To review the guidelines, investigations and subtypes of BPS.

Materials and Methods: Review of literature in the light of the think tank discussion.

Results: All guidelines recommend completing history, physical examination, urine analysis, urine culture, and urine cytology to define the BPS phenotype but there are differences on further investigations. In those guidelines which recommend cystoscopy, the identification of Hunner's lesions (HLs) is recommended as this changes the treatment plan and outcome.

Conclusion: We propose that the differentiation of Hunner's ulcers is an important step in the assessment of these patients. Further suggestions for research are suggested.

KEYWORDS

cystoscopy, imaging, investigation, magnetic resonance imaging, painful bladder syndrome, urinary frequency

1 | INTRODUCTION

This paper summarizes the discussion in a think tank at the ICI-RS 2018 about the diagnosis of bladder pain syndrome (BPS). It defines a condition which has an unknown etiology and pathophysiology. Sometimes, particularly in the United States, BPS is referred to as BPS/IC (interstitial cystitis). Thus, according to the organization defining the syndrome, both the syndrome's name and the diagnosis can vary. Pain is considered a key feature of BPS by the EAU,[1] AUA,[2] ICI,[3] CUA,[4] ICS,[5] RCOG,[6] and ESSIC[7]; however, urinary frequency and

urgency are the predominant complaints (along with pressure or discomfort) in the East Asian guideline definition of BPS.[8] This may suggest a geographic difference in clinical presentation.

All guidelines recommend completing history, physical examination, urine analysis, urine culture, and urine cytology to define the BPS phenotype. Yet, the different guidelines diverge as to whether frequency volume charts, urodynamics, cystoscopy, hydrodistension (HD), and bladder biopsy are recommended. In those guidelines which recommend cystoscopy, the identification of Hunner's lesions (HLs) is recommended as this changes the treatment plan and outcome.[9-11] We have focused on the application of magnetic resonance imaging (MRI) and cystoscopy as these investigations have been applied in a research setting and cystoscopy is a key part of the diagnostic pathway for BPS.

2 | DIAGNOSTICS

2.1 | Magnetic resonance imaging

There is need to better phenotype BPS as the present treatments have varying outcomes probably because different pathologies are classified within the syndrome. One attempt to subclassify patients as BPS/IC with or without HL is with MRI. The use of MRI to phenotype BPS/IC has been investigated in two recent papers.

Ackerman and Rodriguez published a prospective study comparing 15 women with non-HL BPS/IC and 15 age-matched controls with no pain or menorrhagia.[12] All patients underwent 1.5 T pelvic MRI using a T2 weighted sequence. Cystoscopy was reported normal in all patients. Axial and sagittal images were reviewed by two blinded radiologists that measured the H line, the distance from the inferior pubic ramus to posterior margin of rectum. Also, levator width, levator length, and posterior puborectalis angle were all measured. All MRI measures and clinical factors (age, parity, and duration of symptoms) were compared between the two groups using a paired, two-tailed *t* test. There were no differences in clinical factors between the groups, non-HL BPS/IC exhibited shorter levator muscles, a wider posterior puborectalis angle, and a shorter H line compared to controls, $P < .02$. In summary, this study identified objective findings of pelvic muscle hypertonicity on MRI in patients with BPS/IC, as measured by shortened levator muscles, increased posterior puborectalis angle, and a smaller levator hiatus (shorter H line).

Tyagi and Chermansky published a study in BPS/IC patients evaluating the clinical safety and feasibility of MRI enhanced with intravesical novel contrast mixture (NCM).[13] Six women between ages 25 and 78 submitted to 3 T MRI before and after intravesical NCM. This cohort consisted of two controls (no bladder symptoms), two with non-HL BPS/IC, and two with HL BPS/IC. Cystoscopy was performed in all patients. NCM 50 mL was freshly prepared by diluting gadobutrol 1:250 and ferumoxytol 1:104 in sterile water for injection, and NCM was instilled through a urethral catheter and retained within the bladder during the MRI with a catheter plug. Quantitative T1 measurements were calculated by taking differences in signal intensity of 20 pixels in pre-contrast and post-contrast images of bladder wall. T1 measurements resolve well the different layers of the bladder wall because of the signal-to-noise ratio is higher than with T2 measurements.[14]

Post-contrast bladder wall T1 values of HL BPS/IC women were reduced from pre-contrast values by 44% compared to 18% for controls and non-HL BPS/IC patients, $P < .0001$. BPS/IC patients with HL had more gadobutrol diffusion into bladder wall compared to non-HL IC patients (Figure 1). NCM enhanced-MRI increased fourfold in all subjects the bladder wall contrast-to-noise ratio of the post-contrast images compared to pre-contrast images. NCM instillation did not evoke pain or discomfort. In summary, NCM enhanced-MRI achieved differential contrast and detected enhanced gadobutrol uptake within the bladder wall of BPS/IC patients with HL.

These two MRI studies in patients with non-HL and HL BPS/IC are small and lack the power to detect unrelated confounders. In a more recent large study of 106 patients with 82 patients fulfilling the criteria of BPS/IC and 24 who did not. Diffusion-weighted MRI was used to differentiate between these two categories. In the BPS/IC group the bladder wall had a high intensity signal with a sensitivity of 28% and a specificity of 88%.

Although no signal intensity of the bladder wall was related to the absence of a BPS/IC with a sensitivity of 96% and a specificity of 29%.[15]

The use of MRI for BPS is in its infancy and will need more studies to show its reliability and ease of applicability. Future prospective studies are needed to determine the utility of MRI in better understanding BPS/IC phenotypes. Proof of concept testing is needed with repeat MRI imaging after successful treatment of BPS/IC with or without HLs. Finally, comparing the cost of pelvic MRI with the costs associated with inappropriate therapies and/or delay in correct BPS/IC diagnosis could support the clinical use of this imaging.

2.2 | Cystoscopy

The role of cystoscopy in the diagnosis and classification of BPS/IC is a matter of debate. ESSIC has highlighted the importance of excluding confusable diseases (such as

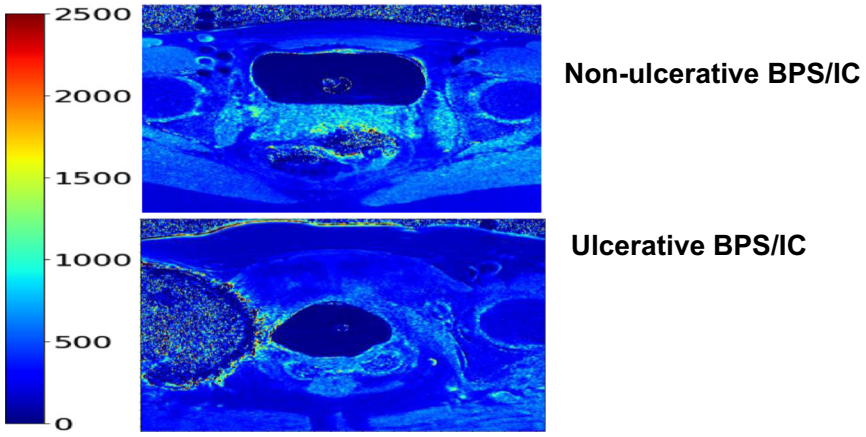

FIGURE 1 T1 measurement of bladder wall in BPS/IC. T1 values for each pixel are illustrated by color bar. T1 in the dark blue pixel is 0 ms, and T1 in the dark red pixel is 2500 ms. More blue and green pixels are seen within bladder walls of patients with ulcerative BPS/IC, demonstrating a greater reduction in T1 relaxation time and more gadobutrol diffusion into the bladder wall. BPS, bladder pain syndrome; IC, interstitial cystitis

carcinoma in situ) and indicated cystoscopy under anesthesia with HD and eventual biopsy as diagnostically essential.[7] Furthermore, cystoscopic and histopathological findings enable further documentation and classification of BPS/IC. European Association of Urology,[1] conjoint expert opinions from East Asia,[8] and the Bladder Pain Syndrome Committee of the ICI[3] follow the recommendations of ESSIC. Conversely, AUA guidelines do not indicate cystoscopy as an integral part of the initial diagnostic work-up for BPS/IC.[2]

According to ESSIC, cystoscopy and HD with biopsy is an integral part of the diagnostic evaluation for BPS/IC. Cystoscopic findings suggestive of BPS/IC are: glomerulation grades 2 to 3 or HL or both. Infiltration of inflammatory cells and/or formation of granulation tissue and/or overexpression of mast cells and/or intrafascicular fibrotic changes represent the histopathological findings that are interpreted in favor of BPS/IC.[7] BPS/IC subtypes are described on the basis of cystoscopic and histopathological findings (Table 1). Transurethral resection of HL have been associated with symptomatic improvement rates in the range of 90%.[16,17] HL-directed endoscopic treatment options were further enriched by studies investigating the potential utility of Nd:YAG laser, electrocoagulation, and instillation of triamcinolone[11,18,19] all of which reported improvement rates ranging from 70% to 90%.

Recent studies have shown that patients with HL are more symptomatic than the patients without. Patients with type 3C disease were older (62 vs 42 years, $P < 0.001$) with a lower average maximal voided volume (206 vs 289 mL, $P < .001$) and a lower average bladder capacity under anesthesia (459 vs 743 mL, $P < .001$)[20] and HL were associated with more frequency and lower maximum bladder capacities.[21] They have suggested that endoscopic evaluation of the bladder should be offered to the patients with a strong desire to void volume ≤210 mL or an MBC ≤236 mL. In the UPOINT classification, Nickel et al[22] categorized BPS/IC patients into six domains with the urinary domain including patients with bothersome lower urinary tract symptoms, the psychosocial domain being characterized by patients with clinical depression, or an identifiable maladaptive coping mechanism, the organ-specific domain being comprised mainly of patients suffering from the typical cyclic pain provoked by bladder filling and temporary relief with voiding and/or demonstrating positive cystoscopy + biopsy findings, the infection domain being consisted of patients with urine culture-documented urinary tract infections within the last 2 years which have provoked/exacerbated baseline symptoms, the neurological/systemic domain hallmark of which being prior diagnoses of disorders involving some degree of neuropathy or neural upregulation (such as of irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, vulvodynia), and the tenderness domain patients of which demonstrate trigger point tenderness during physical examination (Table 2).[22] Doiron et al[23] investigated the utility of the UPOINT phenotype comparing HL and non-HL disease which does

TABLE 1 Classification of types of BPS/IC according to findings at cystoscopy with hydrodistension (HD) and bladder biopsies

	Cystoscopy with HD			
Biopsy	**Not done**	**Normal**	**Glomerulations**	**Hunner lesion**
Not done	XX	1X	2X	3X
Normal	XA	1A	2A	3A
Inconclusive	XB	1B	2B	3B
Positive	XC	1C	2C	3C

TABLE 2 UPOINT schema: treatment options which can be recommended based upon the predominant clinical phenotype of the patients with BPS/IC

Clinical phenotype	Treatment options
Urinary	Behavioral treatments, antimuscarinic drugs, intravesical treatment (heparin, DMSO, HA, CS, PPS), HD, botulinum toxin A, sacral neuromodulation, radical surgery
Psychosocial	Stress management and psychosocial support
Organ-specific	
Hunner lesion (−)	Amitriptyline, cimetidine, hydroxyzine, PPS, quercetin, intravesical treatment (DMSO, heparin, HA, CS, alkalinized lidocaine, PPS), HD, botulinum toxin A, radical surgery
Hunner lesion (+)	Cyclosporin A, endoscopic treatment (fulguration, laser ablation, resection, steroid injection), hyperbaric oxygen, radical surgery
Infectious	Antibiotics
Neurological/systemic	Gabapentanoids, cimetidine, hydroxyzine, sacral neuromodulation
Tenderness	Pelvic floor physiotherapy, massage therapy, acupuncture, trigger point injections

Abbreviations: CS, chondroitin sulfate; DMSO, dimethylsulfoxide; HA, hyaluronic acid; HD, hydrodistension; PPS, pentosan polysulfate.

respond differently to treatment and there was no statistical significance in the number and distribution of UPOINT phenotypes. The authors suggest that patients with HL cannot be identified by clinical phenotyping only and cystoscopy is necessary. This has been further supported by a further study which shows women with HLs responding to fulguration or cyclosporine which further validates HLs as a differentiating phenotype.[24] Pentosan polysulfate was effective in randomised controlled trials (RCTs) from the early 1990s which focused on ulcerative disease (IC) while the randomized controlled trial by Nickel et al[25] including any BPS regardless of the presence or not of HLs ended up being a negative trial.

3 | DISCUSSION

There are minimal data to support the use of noninvasive tests such as symptoms or imaging to differentiate between different types of BPS and certainly these need to be validated against treatment response in the future. There are emerging studies supporting two separate pathologies with and without HLs. This is based on treatment response but characterization of the phenotype is a feature which has not yet been perfected.

4 | CONCLUSION

In BPS patients cystoscopy excludes other pathologies. Identification of the patients who demonstrate positive cystoscopic signs and histopathologic alterations in favor of BPS might have implications regarding treatment outcome because lesion-targeted endoscopic treatment has shown promising results. HL BPS patients tend to be older with a more severe symptomatology in terms of pain and lower urinary tract symptoms when compared to non-HL BPS patients. Clinical phenotyping needs to be defined carefully to individualized treatment.

5 | FUTURE RESEARCH QUESTIONS

- The various phenotypes of PBS need to be defined as a single treatment will fail if inappropriately targeted. Methods of phenotyping may include defining pain in different ways and assessing its relationship to the pathology, new biomarkers in blood, urine, or bladder biopsy. The place of new noninvasive methods such as MRI.

- We need standardization of the histopathology reporting. The histopathologist need to be familiar with ESSIC and ICI findings about BPS/IC.
- Standardized investigation, research protocol of BPS/IC patients independent of the speciality as BPS appears to be a systemic disease associated with fibromyalgia.

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