Review Article

Int Neurourol J 2016;20 Suppl 2:S95-104
https://doi.org/10.5213/inj.1632712.356
pISSN 2093-4777 · eISSN 2093-6931

INTERNATIONAL NEUROUROLOGY JOURNAL
INJ
OPEN ACCESS

Pathomechanism of Interstitial Cystitis/Bladder Pain Syndrome and Mapping the Heterogeneity of Disease

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is a heterogeneous syndrome which is usually characterized by urinary frequency, nocturia, and bladder pain. Several pathomechanisms have been proposed, including uroepithelial dysfunction, mast cell activation, neurogenic inflammation, autoimmunity, and occult urinary tract infections. It is possible that an inflammatory process alters regulation of urothelial homeostasis and results in dysfunction of the bladder epithelium. Different phenotypes of IC/BPS have been explored including Hunner and non-Hunner type IC, hypersensitive bladder, and bladder pain both with and without functional somatic syndrome. Different gene expressions have also been found in different IC phenotypes. Abnormal expressions of uroplakin, chondroitin sulfate and adhesive protein E-cadherin, tight junction protein zonula occludens-1 in IC/BPS bladder suggest abnormal epithelial differentiation in this bladder disease. Analysis of inflammatory proteins, or cytokines in the urine or serum provides another diagnostic foundation forIC/BPS subtypes. The involvement of IC/BPS in systemic functional somatic syndrome and other pelvic organ diseases might also subdivide subtypes of IC/BPS. Chronic inflammation, increased urothelial apoptosis, and abnormal urothelial function are closely associated in IC bladders. This article reviews recent research on the pathomechanisms of IC, which might help us in mapping the heterogeneity of the disease.

Keywords: Lower Urinary Tract Symptoms; Cystitis; Bladder Pain; Biomarkers; Urotheliuim

• **Conflict of Interest:** No potential conflict of interest relevant to this article was reported.

INTRODUCTION

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic bladder condition which is characterized by bladder pain, urinary frequency, and nocturia. IC/BPS had been considered a progressive disease that may evolve from early to late stage. Patients might have an inflammatory reaction both in the bladder as well as in the central nervous system (CNS) after insults to the bladder, which produce early IC/BPS symptoms such as urinary frequency and nocturia. Patients may experience spontaneous symptom relief after the body's defense mechanism solves the inflammation in the bladder. However, the inflammation also might increase and cause permanent inflammatory imprinting in the bladder as well as in the CNS if the bladder insults persist. The current article reviews the recent research on the pathogenesis of IC/BPS with different clinical characteristics. Through histopathological study, urothelial barrier dysfunction and sensory protein expressions, and serum and urinary biomarker studies, we will combine clinical and basic data to map the heterogeneity of IC/BPS.

CLINICAL CHARACTERISTICS WITH BLADDER HISTOPATHOLOGY IN IC/BPS

Most urologists suggest the cause of IC/BPS might result from long-standing inflammation of the bladder [1]. However, the

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Submitted: August 11, 2016 / **Accepted after revision:** September 30, 2016

actual pathophysiology is still unclear. The most common clinical presentations of IC/PBS are bladder and lower abdominal pain, glomerulation hemorrhage after cystoscopic hydrodistention, or denudation or thinning of the urothelium. Clinical findings suggest bladder inflammation and urothelial dysfunction [2,3]. Urothelial dysfunction, chronic inflammation, impaired bladder circulation, neurogenic hyperactivity, and systemic functional disorders have been linked to IC/BPS and presumably interact in forming IC/BPS [4].

Denudation or thinning of the epithelium is the most common histopathological finding of IC/BPS [1]. Increased levels of urothelial cell apoptosis and decreased proliferation have been noted, suggesting an altered homeostasis in IC/BPS urothelium [5]. Abnormal expression of tight junction protein zonula occludens-1 (ZO-1), uroplakin and chondroitin sulfate have been found in IC/BPS bladders [6-8]. An increased antiproliferative factor and lower expression of interleukin (IL)-8 have been found in IC/BPS bladders, which may contribute to IC/BPS pathophysiology [9-12]. Altered urothelial differentiation might result in increased permeability and decreased protective function of the bladder urothelium [13]. The increased urothelial permeability could result in a leaky urothelium and generate hypersensitive bladder symptoms [14]. Increased lymphocyte infiltration in the bladder interstitium and urothelial ulceration in chronic IC might limit the distention of the bladder, resulting in small functional bladder capacity and urination frequency-urgency symptoms. Increased sensory afferent activity including pain associated C-fibers in chronic IC will further cause bladder pain with a full bladder, especially in ulcer type IC/BPS [15].

Histopathological inflammation is a characteristic feature of the IC bladder [1]. Patients with Hunner ulcer IC/BPS show increased expression of T- and B-cell markers in the submucosa [16]. Overexpression of some proinflammatory genes has also been found in IC/BPS bladder [17-19]. It has been suggested that immunological reaction occurs in IC/BPS bladders [8]. A subset of IC/BPS patients might have an elevated serum IgE level [20]. However, no one pathogenic etiology can be adapted to fit all IC patients. It is apparent that IC is a heterogeneous syndrome resulting from different etiology and pathogenesis. Therefore, ex-

Table 1. Potential bladder tissue biomarkers for the diagnosis of IC/BPS

Protein	Source	Evidence of activity	Reference
Pro-nociceptive inflammatory proteins	Bladder	Increased expression of TRPV1, 2, 4, ASIC1, NGF, CXCL9, and TRPM2 in IC/BPS	17
PDECGF/TP	Bladder	Highly associated with glomerulations during cystoscopic hydrodistention	39
VEGF	Bladder	Increased VEGF was associated with bladder inflammation and smaller functional bladder capacity in IC/BPS	41
HIF-1α	Bladder	Increased expression of HIF-1α and VEGF associated with glomerulations in IC/BPS	37
Apoptotic signaling molecules	Bladder	Bad, Bax, and cleaved caspase-3, were increased in the IC/BPS	24
Urothelial barrier protein	Bladder	E-cadherin and ZO-1 expression was only decreased in IC/BPS	5, 8, 29, 30
Differentiation related proteins	Bladder cell line	A switch from a cytokeratin (CK)13(lo)/CK14(hi) to a CK13(hi)/CK14(lo) phenotype, expression of claudin 3, 4, and 5 proteins, and induction of uroplakin gene transcription	6
Proteoglycan core proteins	Bladder	Abnormal expression of keratin 18 and 20 and biglycan, decorin, perlecan, and syndecan-1 are found in IC/BPS	8
Uroplakin III	Bladder	Over expression of uroplakin III-delta4 in nonulcerative type IC/BPS	7
IL-8	Bladder	Lower IL-8 expression levels in IC/BPS bladder	12
NGF	Bladder	Increase of NGF level in IC/BPS	58, 59
Chemokines	Bladder	Increased mRNA expression of CXCR3 binding chemokines (CXCL9, 10, and 11) and TNFSF14 (LIGHT) in ulcer type IC/BPS	19

IC/BPS, interstitial cystitis/bladder pain syndrome; TRPV, TRP vanilloid; ASIC, acid sensing ion channel; NGF, nerve growth factor; CXCL9, chemokine (C-X-C motif) ligand 9; TRPM, TRP melastatin; PDECGF/TP, platelet derived endothelial cell growth factor/thymidine phosphorylase; VEGF, vascular endothelial growth factor; HIF-1α, hypoxia-inducible factor-1-α; ZO-1, zonula occludens-1; IL, interleukin; CXCR, CXC chemokine receptor; TNFSF14, tumor necrosis factor ligand superfamily member 14 .

ploring the histopathological features in different inflammatory cells and bladder histopathology, and correlating these pathological findings with clinical characteristics might help us understand the possible pathomechanism of IC/BPS (Table 1).

THE UROTHELIAL DYSFUNCTION IN IC/BPS

The urothelium of the urinary bladder is considered to be a barrier between urine and the underlying bladder. Bladder surface mucus also plays an important role in this barrier function [6,21]. Failure of urothelial cytodifferentiation may contribute to the clinical features of IC/BPS [6]. Urothelial barrier dysfunction may lead to abnormal urinary solutes migration, such as potassium, which depolarizes muscle and nerves, and then causes tissue injury and bladder pain [9,10].

Histopathological studies of IC/BPS bladder have confirmed the involvement of macrophages, eosinophils, and mast cells in the urothelium. Involvement of eosinophils is also supported by increasing urinary eosinophil cationic protein in the urine cytology [22]. In the ESSIC type 3C IC/BPS patients, increased expression of B- and T-cell markers, decreased expression of urothelial markers, focal lymphoid aggregates in the submucosa and higher urinary immunoglobulin concentration were found [16]. This evidence demonstrates that chronic inflammation could be a fundamental cause of the urothelial dysfunction in IC/BPS.

CHRONIC INFLAMMATION AND APOPTOSIS

Increased apoptosis cells and decreased proliferative cells were noted in IC bladder urothelium compared with the control group [5]. P38 mitogen-activated protein kinase might be an important mediator of the antiproliferative factor in the bladder urothelial cells [23]. Increased levels of the apoptotic signaling molecules, including Bax, cleaved caspase-3, and Bad were elevated in the IC/BPS bladder tissues [24]. The apoptosis in IC/BPS bladders might be due to upregulation of inflammatory signals. Chronic inflammation in the suburothelium may inhibit normal urothelial basal cell proliferation and affect apical urothelium function. Acute bladder irritation such as bacterial infection increases afferent nerve activity and results in long-term plasticity, and then lowers the threshold for nociceptive and mechanoceptive sensation [25,26]. A rise in bladder nerve growth factor (NGF) after any insult to the bladder initiates signals that are transported to the dorsal root ganglion or spinal cord [27,28].

A previous study revealed abnormal differentiation in the urothelium of IC/BPS bladders with loss of E-cadherin and altered differentiation markers [8]. E-cadherin concentration in the IC/BPS bladder urothelium is significantly lower than that of healthy controls [29]. ZO-1 and E-cadherin expression was only decreased in IC/BPS, but not in patients with overactive bladder (OAB), suggesting the barrier function of urothelium was prominent in IC/BPS but not altered in the OAB bladders [30]. However, decrease of E-cadherin expression is also associated with recurrent urinary tract infections in women [30-32]. These pathological differences between IC/BPS and other hypersensitive bladder diseases might result in distinct urothelial protein production. The pathophysiology of IC/BPS urothelium involves an aberrant differentiation program that results in altered synthesis of proteoglycans, tight junction proteins, cell adhesive proteins, and bacterial defense molecules such as GP51 [33-35]. Therefore, replacement therapy such as intravesical glycosaminoglycan instillation has been effectively used for treatment of IC/BPS [36].

GLOMERULATIONS OF BLADDER UROTHELIUM IN IC/BPS

IC bladders showed characteristic changes after hydrodistention under a certain pressure. Aberrant urothelial cells disrupt the permeability barrier, endothelial cell injury results in glomerulation bleeding, and degenerative change of nerves and regenerative features are frequently encountered in IC/BPS bladders [37,38]. Several inflammatory proteins were associated with increased angiogenesis and glomerulations in IC/BPS, including vascular endothelial growth factor (VEGF) [39], hypoxia-inducible factor-1-alpha [40], and platelet derived endothelial cell growth factor/thymidine phosphorylase [37]. Increased VEGF expression in the urothelium was associated with bladder inflammation and smaller bladder capacity in IC/BPS patients. Down-regulation of VEGF in IC.BPS bladder tissue has been noted after repeated botulinum toxin A (BoNT-A) injections [41]. Measuring these angiogenic growth factors concentrations in the urine may be a new and useful method for the diagnosis of IC/BPS.

Previous studies have revealed that repeated intravesical BoNT-A injections could reduce bladder pain in patients with IC/BPS [42,43]. The elevated NGF levels in the IC/BPS bladder tissue significantly decreased to the normal range after BoNT-

A treatment [44]. Repeated BoNT-A injections plus cystoscopic hydrodistention provide better therapeutic outcomes in treating IC/BPS than a single treatment [45]. Since repeated BoNT-A injections could increase bladder capacity and relieve bladder pain in responders, the results provide evidence of urothelial repair and suburothelial inflammation reduction in the IC/BPS responders to BoNT-A. Chronic suburothelial inflammation might damage the urothelial function and cell differentiation, and repeated BoNT-A injections may gradually reduce the urothelium inflammation, thereby improving the symptoms in patients with IC/BPS [46].

CENTRAL NERVOUS SENSITIZATION IN IC/BPS

Recent evidence revealed neurogenic inflammation may play an essential role in the pathogenesis of several diseases, including arthritis, migraines, asthma, and possibly, IC/BPS [47]. Preliminary studies have shown the levels of immunoreactive substance P and NGF increase in the bladder tissue and urine of IC/BPS patients [48,49]. Increase of urinary adenosine triphosphate (ATP) and increased stretch-activated ATP release by bladder urothelial cells have been found in IC/BPS patients, suggesting augmented purinergic signaling in IC/BPS bladders [50]. Insult to the bladder wall or urothelium might induce inflammatory reactions and subsequently produce painful inflammation, such as in IC/BPS [51].

The chronic pain in IC/PBS may also result from CNS sensitization and persisting activation of the afferent sensory system in the urinary bladder [52]. Central c-fos expression was increased in the rat models of neurogenic detrusor overactivity and chronic inflammation [53]. Suppressing the NGF levels in spinal cord dorsal root ganglia could suppress bladder hyperreflexia [54]. Mechanical stimulus in IC/BPS patients induced a significantly higher stimulus-response curve, and a segmental hyperalgesia was noted, suggesting spinal central sensitization was involved in the IC/BPS pathophysiology [55]. If the neurogenic inflammation in the DGR or CNS can be reduced gradually after treatment, the visceral pain in IC/PBS may be relieved.

PROTEOMICS INVESTIGATION OF THE POTENTIAL SERUM AND URINARY BIOMARKERS

In recent years, the lamina propria of the bladder has been found to play a crucial role in transmitting the bladder sensation in response to chemical stimuli and inflammation of the bladder [56,57]. Increased NGF levels in the urothelium and urine have been reported in patients with IC/BPS [58,59]. However, urinary NGF levels are also elevated in several lower urinary tract diseases such as bladder outlet obstruction, urinary tract stones, OAB, and urinary tract infection [59]. Nevertheless, the level of urinary NGF is closely related to the visual analog pain scale and decreases in responders to conventional treatment for IC/BPS [60]. Urinary NGF levels were significantly decreased in and associated with greater pain improvement and a successful response to intravesical BoNT-A injections, suggesting urinary NGF, and although not specific to IC/BPS, might be a useful biomarker for measuring the bladder condition severity in IC/BPS patients.

In addition, abnormal cell differentiation in the IC/BPS bladder urothelium was remarkable, which causes alteration of several barrier proteins and junction protein production. It is possible to search for possible urinary biomarkers for early detection of IC/BPS in patients with frequency urgency syndrome [61]. A previous study showed the urinary levels of inflammatory cytokines were elevated in patients with IC/BPS, including IL-2, IL-6, and IL-8 [62], but not specific to National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) defined IC/BPS patients [63]. Although cytokine urinary level alone might not be useful to make a diagnosis of IC/BPS, a combination of several different urinary cytokines might raise the diagnostic rate of IC/BPS (Table 2).

Bladder biopsies from IC/BPS patients have confirmed the presence of macrophages and eosinophils in the urothelium and increased mast cell count in the detrusor [1,37]. In cyclophosphamide cystitis rats, elevated levels of chemokines and activation of mast cells were noted [64]. The most important inflammatory mediators causing chemotactic migration of mast cells, eosinophils and macrophages include MCP-1 (CCL2), macrophage inflammatory protein (MIP-1β) (CCL4), and eotaxin (CCL11) [65-67]. Chemokines may also directly trigger these target cells in the bladder and thereby induce the inflammatory changes in IC/BPS. Analysis of multiple proteins from a urine sample is a convenient approach to measuring the activation of inflammatory cells in the bladder tissue [68].

Elevated serum C-reactive protein (CRP) has been noted in IC/BPS patients [69]. Serum CRP levels might be used to distinguish patients with IC/BPS from bladder hypersensitivity disorders. A previous study also revealed that the serum NGF level was elevated in IC/BPS patients [70]. However, there was

Table 2. Potential urine and serum biomarkers for the diagnosis of IC/BPS

Protein	Source	Evidence of activity	Reference
APF	Urine	APF altered the pattern of cellular gene expression toward a phenotype like IC/BPS.	9
		APF treatment decreased expression of tight junction proteins ZO-1 and occluding.	10, 11
HB-EGF	Urine	Urine HB-EGF levels were significantly lower in IC/BPS patients. APF and HB-EGF levels were similar in ulcerative and nonulcerative IC/BPS	10
EGF	Urine	EGF levels were significantly higher in IC/BPS	10
NGF	Urine	Increased NGF levels in IC/BPS and sensory urgency	59
NGF	Urine	A decrease of urinary NGF level was associated with greater pain reduction and a successful response to treatment	60
IL-2, IL-6, IL-8	Urine	Significant elevations in symptom scores and IL-2, IL-6, and IL-8 were found in active IC/BPS	62
ATP	Urine	Increased urinary ATP and increased stretch-activated ATP release by bladder urothelial cells	50
Chemokines	Urine	A significant fivefold to twentyfold increase in CXCL-10 and 1, IL-6 and NGF in ulcer IC	68
GP51	Urine	Low urine GP51 levels in IC/BPS patients compared to normal controls	35
CRP	Serum	Serum CRP levels were significantly higher in IC/BPS	69
IgE	Serum	Elevated serum IgE level in IC/BPS	20
NGF	Serum	Serum NGF was elevated in IC/BPS patients	70
IL-1β, IL-6, TNF-α, and IL-8	Serum	Serum proinflammatory cytokine and chemokine significantly higher in patients with IC/BPS than controls	71

IC/BPS, interstitial cystitis/bladder pain syndrome; APF, antiproliferative factor; ZO-1, zonula occludens-1; HB-EGF, heparin-binding epidermal growth factor; EGF, epidermal growth factor; NGF, nerve growth factor; IL, interleukin; ATP, adenosine triphosphate; CXCL, CXC chemokine ligand; GP51, glycoprotein 51; CRP, C-reactive protein; TNF-α, tumor necrosis factor-α.

no significant correlation between the urinary and serum NGF levels in patients with IC/BPS. The serum NGF levels are not significantly different between IC/BPS patients with different clinical characteristics and comorbidities [70]. Cytokines and chemokines have been demonstrated to play critical roles in the pathogenesis of many chronic inflammatory diseases. The upregulated serum tumor necrosis factor-α, IL-1β, IL-6, and IL-8 levels in IC/BPS patients may potentially have a prognostic role and might help physicians choose an appropriate therapeutic agent. One recent study revealed these serum proinflammatory cytokines and chemokine levels were significantly higher in IC/BPS patients than in the controls [71]. Increased expression of these proinflammatory cytokines and chemokine levels in the serum of IC/BPS patients suggests that not only mast cell activation, but also some other inflammatory mediators might play crucial roles in the pathogenesis of IC/BPS.

ULTRASTRUCTURE INVESTIGATION OF THE UROTHELIAL CELLS IN IC/BPS BLADDER

IC/BPS has been considered a disease of the bladder urothelium [72]. Urothelium leakage has been proposed as the cause which generates bladder symptoms of IC/BPS [14]. Bladder urothelium denudation and thinning, aberrant synthesis of proteoglycans, cell adhesive proteins and tight junction proteins, and bacterial defence molecules were found in the IC/BPS bladders [33-35].

Three important components involved in bladder permeability barrier function are: apical membrane, tight junctions, and an active trafficking mechanism [73,74]. Umbrella cells located at the apical surface of bladder mucosa are the main cell layer that maintains the barrier function. Mature umbrella cells form uroplakins and well-defined tight junctions [75]. Loss of umbrella cells cause exposure of intermediate cells and loss of barrier function and active trafficking mechanism of the bladder epithelium [74,76]. Therefore, leakage of urine solutes into the underlying suburothelial layer results in sensory receptor exposure, so patients might develop irritative bladder symptoms and small functional bladder capacity [77]. Bacterial cystitis, mechanical trauma, and exposure to noxious chemicals lead to disruption of the bladder permeability barrier in IC/BPS [76,77]. Although a rapid recovery process will take place after urotheli-

al damage, the maturation of the intermediate cells needs time and subsequent neurogenic inflammation might result in further damage to the bladder wall [78].

IC/BPS is a heterogeneous and progressive syndrome. Patients with IC/BPS have bladder pain, urinary frequency, and urgency to varied degrees. After cystoscopic hydrodistention, the glomerulations developed vary from a mild to severe haemorrhage in appearance. The maximal bladder capacity also varies greatly. However, diffused bladder wall thickening and hydronephrosis which are frequently seen in patients with severe ketamine cystitis are not observed in IC/BPS bladders [79]. In microscopic histopathological examination of IC/BPS bladders, the epithelium denudation, inflammation with or without granulation tissue formation may present in the bladders in different degrees of severity. The IC bladders might have very mild to severely inflamed urothelium which causes symptoms from mild urinary frequency-urgency to severe bladder pain [15]. Therefore, understanding the urothelial ultrastructure changes in different stages of IC/BPS is very important for urologists for screening IC/BPS bladder of those patients with bladder hypersensitivity.

MAPPING THE HETEROGENEITY OF IC/BPS

IC/BPS is a clinical syndrome characterized by bladder pain, usually with urinary frequency, urgency, and nocturia. Different subtypes of IC/BPS have been identified, such as ulcer type and nonulcer type, which might have distinct clinical characteristics and underlying pathophysiology [80,81]. Pelvic pain is considered the hallmark symptom of IC/BPS patients, but patients with mild to moderate IC/BPS might only present with urinary frequency-urgency [82].

Classification of IC/BPS subtypes could be made with the findings of cystoscopy after hydrodistention and morphological findings in bladder biopsy [83]. This definition of IC/BPS by symptoms alone has been accepted by the American Urological Association [82], the European Association of Urology [83], as well as the International Consultation on Incontinence [84]. However, Asian urologists have proposed different diagnostic criteria of IC/BPS. For the definite diagnosis of IC/BPS, cystoscopy or hydrodistention is considered to be an essential diagnostic test by Eastern urologists, while hypersensitive bladder syndrome was used as the diagnosis if IC/BPS has not been confirmed by the required criteria [3,4].

The NIDDK developed the research criteria for IC/BPS since 1987 [85]. However, the criteria are too stringent for clinical use [86]. The severity of cystoscopic findings after hydrodistention was not found to be significantly correlated with the degree of bladder inflammation [87]. Erickson et al. [63] found similar urine markers and bladder biopsy findings between 2 groups. Recently, we have revisited the diagnostic roles of the potassium sensitivity test (PST) and cystoscopic hydrodistention [88]. Both PST and glomerulations after hydrodistention are found to be sensitive indicators of IC/BPS, but the specificity of glomerulations is lower than that of PST in the diagnosis of IC/BPS [88]. Therefore, construction of a diagnostic framework is needed for distinguishing IC/BPS from bladder disorders with similar symptoms. This diagnostic framework may facilitate early diagnosis and appropriate treatment of IC/BPS [89].

IC/BPS patients are also found to have higher odds of comorbid autoimmune or neurological diseases, such as rheumatological diseases and mental illnesses [90]. They also have higher risks of irritable bowel syndrome, fibromyalgia, general fatigue and functional somatic syndrome [91-94]. A distinct phenotype of IC/BPS patients with multiple sensitivities has been identified [95]. Pelvic morbidity is also related to symptom development. Women with IC/BPS often have a gynecologic disease history such as cesarean births, hysterectomy, miscarriage, stillbirth or abortion [92,96]. The symptoms in IC/BPS women are also likely affected by the menstruation cycle [97]. Myofascial pain is often demonstrated in IC/BPS and suggested for therapeutic implication [98]. In patients with concurrent IC/BPS and irritable bowel syndrome, bladder symptoms will improve after treating small-intestinal bacterial overgrowth with antibiotics [99]. Cross-talk in pelvic organs has been suggested as a possible pathomechanism by which uterine or bowel pathology modulates the IC/BPS symptoms [100].

Investigation of the potential biomarkers of IC/BPS according to the possible pathophysiology has progressed greatly in recent decades. However, clinically applicable biomarkers in urinary or serum have not yet been well developed in the diagnosis of IC/BPS. Measuring urinary proteins or serum cytokines is a possible convenient approach to monitoring the inflammatory cell activity in the bladder tissue. Differences in urinary or serum biomarkers could provide a diagnostic basis for IC/BPS subtypes and might be a useful tool for the differential diagnosis among IC/BPS, hypersensitive bladder, and OAB. In addition, the involvement of IC/BPS in systemic functional somatic syndrome and other pelvic organ diseases might also subdivide another subtype of IC/BPS. Mapping the heterogene-

ity of IC/BPS might also provide different treatment strategies and prognostic outcomes.

CONCLUSION

The pathophysiology of IC/BPS might involve chronic inflammation, increased apoptosis, urothelial dysfunction, and CNS sensitization. In addition, systemic involvement of IC/BPS with multiple comorbidities and functional somatic syndromes are also found together with increased sympathetic nervous system tonicity and increased serum proinflammatory proteins and cytokines. Through analyzing different presentations in bladder conditions, urothelial dysfunction, urinary biomarker production, and immunohistochemistry of the bladder wall, it is possible to map IC/BPS into different phenotypes and provide evidence for successful treatment.

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