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Original Article

Urodynamic characteristics might be variable in bladder pain syndrome/interstitial cystitis patients with different non-bladder co-morbid conditions

Wei-Ming Cheng [a,c,d], Yu-Hua Fan [b,c,d,*], Alex T.L. Lin [b,c,d]

[a] *Division of Urology, Department of Surgery, Taipei City Hospital, Zhongxiao Branch, Taipei, Taiwan, ROC*
[b] *Department of Urology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[c] *Department of Urology, School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC*
[d] *Shu-Tien Urological Science Research Center, Taipei, Taiwan, ROC*

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Abstract

Background: The aim of the study was to identify the impact of non-bladder co-morbid conditions on the urodynamic characteristics of patients with bladder pain syndrome/interstitial cystitis.
Methods: Patients with bladder pain syndrome/interstitial cystitis completed the screening questionnaires for chronic fatigue syndrome, irritable bowel syndrome, fibromyalgia, temporo-mandibular disorders, multiple chemical sensitivities, tension/migraine headache, and localized myofascial pain disorder. They underwent either conventional pressure-flow urodynamic studies or video-urodynamic studies. Urodynamic variables were compared between patients with and those without co-morbid conditions.
Results: Of 111 patients (16 males and 95 females) with bladder pain syndrome/interstitial cystitis, 87 (78.4%) had at least one co-morbid condition (62% males vs 82% females, $p = 0.005$). Those with concomitant irritable bowel syndrome were younger and had urodynamic characteristics of smaller catheter-free voided volume, lower catheter-free average flow rate, smaller bladder volume on the first desire to void, and more prevalent dysfunctional voiding than those without irritable bowel syndrome. Patients with concomitant localized myofascial pain disorder also had larger bladder volume at the first desire to void and lower pressure at maximum flow than those without co-morbid myofascial pain disorder. There were no significant differences in urodynamic parameters between bladder pain syndrome/interstitial cystitis patients with and those without other co-morbidities.
Conclusion: Bladder pain syndrome/interstitial cystitis patients, especially females, are more likely to have non-bladder co-morbidities, especially tension/migraine headache and localized myofascial pain. Bladder pain syndrome/interstitial cystitis Patients with co-morbid irritable bowel syndrome are younger and more likely to have abnormal urodynamic findings.

Keywords: Interstitial cystitis; Irritable bowel syndrome; Myofascial pain syndrome; Tension-type headache; Urodynamics

1. Introduction

Bladder pain syndrome/interstitial cystitis (BPS/IC) includes symptoms of variable combinations of pain referable to the bladder and increased frequency and urgency of urination. It is associated with other regional and systemic pain syndromes, particularly irritable bowel syndrome (IBS), fibromyalgia (FM), and chronic fatigue syndrome (CFS).[1] Its

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* Corresponding author. Dr. Yu-Hua Fan, Department of Urology, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC.
E-mail address: yhfan2@gmail.com (Y.-H. Fan).

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etiology as well as those of other non-bladder conditions remain elusive and co-morbid conditions may complicate its clinical presentation and treatment.

A previous case–control study has shown that patients with BPS/IC are more likely to have multiple non-bladder conditions, which correlate to the severity of BPS/IC symptoms.[2] Although urodynamic studies are not essential for diagnosing BPS/IC, several studies report certain associated urodynamic characteristics, including smaller cystometric capacity, lower bladder compliance, and lower maximum flow rate.[3–6] However, the impact of these non-bladder conditions on the urodynamic characteristics of patients with BPS/IC has not yet been reported.

This study aimed to identify the differences of urodynamic characteristics between BPS/IC patients with and those without co-morbid conditions. The findings might improve the treatment of BPS/IC.

2. Methods

Patients diagnosed with non-ulcer type BPS/IC according to the 1987 National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases (NIDDK) criteria between January 2007 and July 2011 were prospectively recruited. All patients underwent hydrodistention of the urinary bladder under general anesthesia to 80 cm of water pressure for 3 min, to make sure that they had non-ulcer type PBS/IC. The ethics committee of Taipei Veterans General Hospital in Taipei, Taiwan approved the study protocol and all of the participants provided informed consent.

All of the study participants completed the screening questionnaires for CFS, IBS, temporo-mandibular disorder (TMD), multiple chemical sensitivities (MCS), tension/migraine headache, localized myofascial pain disorder (LMP), and FM prior to hydrodistention (Tables 1 and 2).[7] The diagnostic criteria for these co-morbidities were based on the 1994 Centers for Disease Control and Prevention criteria for CFS,[8] the Rome II criteria for IBS,[9] the 1992 Research Diagnostic criteria for TMD,[10] the 1999 consensus by Bartha et al. for MCS,[11] 1988 International Headache Society criteria for headache disorders,[12] 1986 International Association for the Study of Pain criteria for chronic pain syndromes,[13] and the London Fibromyalgia Epidemiology Study Screening Questionnaire.[14]

Table 1
Screening questions for co-morbid disorders.[7–13]

Chronic fatigue syndrome
Q: Unexplained, persistent, or relapsing fatigue for >6 months?
Irritable bowel syndrome
Q: Abdominal discomfort or pain accompanied or affected by constipation or diarrhea for >3 months in the past year?
Temporo-mandibular disorders
Q: Recurrent facial/jaw pain and/or limitation in jaw opening occurring in the past 6 months?
Multiple chemical sensitivities
Q: Symptoms in multiple organ systems reliably occurring on exposure on multiple unrelated chemicals?
Tension and migraine headache
Q: Recurrent headache (>5 for migraine, >10 for tension-type) lasting >30 min occurring in the past 6 months?
Localized myofascial pain disorder
Q: Localized muscle pain for > 3 months?

Table 2
The London Fibromyalgia Epidemiology Study Screening Questionnaire.[14]

Pain criteria
In the past 3 months
1. Have you had pain in muscles, bones, or joints, lasting at least one week?
2. Have you had pain in your shoulders, arms, or hands? On which side? Right, left, or both?
3. Have you had pain in your legs or feet? On which side? Right, left, or both?
4. Have you had pain in your neck, chest, or back?
Fatigue criteria
5. Over the past 3 months, do you often feel tired or fatigued?
6. Does tiredness or fatigue significantly limit your activities?

A positive screen was defined as a positive response to the item of the questionnaire, excluding the London Fibromyalgia Epidemiology Study Screening Questionnaire, which included pain and fatigue criteria. Meeting the pain criteria required "yes" responses to all four pain items and either (i) both a right- and left-side positive response or (ii) one response positive on both sides. Screening positive for chronic, debilitating fatigue required a "yes" response to both fatigue items. When patients met the pain criteria alone or both the pain and fatigue criteria, this was a total positive response.

Urodynamic study is not essential for diagnosis of BPS/IC, and all of the patients underwent conventional pressure-flow urodynamic studies or video-urodynamic studies before hydrodistention for research purpose. Free uroflowmetry was also done as part of urodynamic studies. Video-urodynamic study was performed on patients with concomitant voiding symptoms and low urinary flow rate. Compliance value <20 ml/cmH_2O was considered an impairment according to Stohrer et al.[15] The diagnosis of dysfunctional voiding was based on radiographic evidence of obstruction at the mid-urethra in women or membranous urethra in men, with sustained detrusor contraction and dyssynergic sphincter contraction in neurologically normal individuals.[16]

For statistical analysis, Pearson chi-square test and Fisher exact test were used for categorical variables. Simple T test was used for continuous variables of CFS, IBS, tension/migraine headache, and LMP while Mann–Whitney test was used for continuous variables of TMD, MCS, and FM. Statistical significance was set at $p < 0.05$.

3. Results

A consecutive 111 participants, including 16 males and 95 females were included. Their mean age at enrollment was 48.6 ± 14.8 years. Among the BPS/IC patients, 97 underwent video-urodynamic studies while the rest underwent conventional pressure-flow studies. 87 (78.4%) patients met the diagnostic criteria for at least one co-morbid condition, including 10 men (62.5% of male patients) and 77 women (81.1% of female patients). Non-bladder conditions were more

prevalent in females ($p = 0.005$). The BPS/IC patients with IBS were younger than those without IBS (44.3 ± 15.5 vs. 51.6 ± 13.6 years, $p = 0.013$). Female BPS/IC patients were more prone to have co-morbid tension/migraine headache (37.9% vs. 6.3%, $p = 0.019$) and LMP (46.3% vs. 0%, $p = 0.0002$). There was no tendency towards age or sex in other co-morbid conditions (Tables 3 and 4).

The urodynamic characteristics among BPS/IC patients co-morbid with various non-bladder conditions (Tables 5 and 6) revealed that BPS/IC patients with IBS showed smaller catheter-free voided volume, lower catheter-free average flow rate, smaller bladder volume on the first desire to void, and more prevalent dysfunctional voiding than those without IBS. Nevertheless, significantly higher catheter-free maximum flow rate was observed in BPS/IC patients co-morbid with CFS and tension/migraine headache. Those with co-morbid LMP exhibited larger catheter-free voided volume and lower pressure at maximum flow. Stress incontinence was more prevalent in BPS/IC patients with TMD on urodynamic studies. There were no significant differences in urodynamic parameters among BPS/IC patients with TMD, MCS, or FM and those without. We also evaluated urodynamic differences between PBS/IC patients with two or more non-bladder conditions and those without, but no statistical differences could be identified (data not shown).

4. Discussion

Patients with BPS/IC have been reported to be co-morbid with other non-bladder conditions (Table 7).[17–22] The prevalence of IBS, tension/migraine headache, and FM in the present study is comparable to those in previous literature. Nevertheless, there is a high prevalence (53.2%) of CFS in BPS/IC patients. Similar prevalences of CFS in BPS/IC patients have been reported by Chelimsky et al. Other studies, however, note much lower prevalences (4–15%). Different diagnostic criteria for CFS may play an important role in the discrepancy. While Chelimsky used the same screening questionnaire for CFS as that in the present study, in other studies, the diagnosis of CFS was based on the past medical history.

As BPS/IC is more prevalent in female patients, most studies on non-bladder conditions in BPS/IC patients have excluded male patients.[17–21] The present study includes male patients with BPS/IC but still reveals a female predominance of tension/migraine headache and LMP among BPS/IC patients. Lai et al. have shown that female patients with BPS/IC are more likely to report non-pain and pain symptoms outside the pelvis than females without BPS/IC. In contrast, male patients with BPS/IC and chronic prostatitis or chronic pelvic pain syndrome do not report more extra-pelvic pain than male controls.[23]

A survey conducted in 17 countries reveals that the prevalence of any chronic pain is higher among females than in males, including tension/migraine headache and localized musculoskeletal pain.[24] Estrogen and progesterone may regulate pain sensitization by modulating the expression of nociceptive mediators, as well as processing pain-related stimuli in the brain.[25] Various psychosocial factors like pain coping strategies and stereotypical gender roles may contribute to differences in pain expression in this study.[26]

In the present study, BPS/IC patients with IBS are younger than those without. Clemens et al. report that BPS/IC and IBS have a similar age of symptoms onset (32.4 and 32.1 years, respectively), which is younger than those of CFS and FM (35.4 and 37.5 years, respectively). Clemens hypothesizes that the age differences may hint of the pathophysiology of BPS/IC. Patients may represent a regional pain syndrome that develops initially in the pelvis and progresses bi-directionally between adjacent organs (bowel or urinary bladder). Later, the regional pain syndrome advances to systemic symptoms such as CFS or FM.[21] This may explain the similar temporal conditions as the present study.

Moreover, BPS/IC is a clinical diagnosis characterized by complaints of supra-pubic pain related to urinary bladder filling. They may be other symptoms, including daytime frequency, nocturia, and urgency. Several studies report that patients with BPS/IC may possessed certain urodynamic characteristics, such as smaller bladder volume on the first

Table 3
The prevalence of non-bladder conditions in male and female patients.

	Male	Female	Total	*p*
Patients number	16	95	111	
At least one co-morbid conditions	10 (62.5%)	77 (81.1%)	87 (78.4%)	0.005*
Chronic fatigue syndrome	6 (37.5%)	53 (55.8%)	59 (53.2%)	0.189
Irritable bowel syndrome	5 (31.3%)	36 (37.9%)	41 (36.9%)	0.781
Temporo-mandibular disorder	1 (6.3%)	10 (10.5%)	11 (9.9%)	1.000
Multiple chemical sensitivity	1 (6.3%)	11 (11.6%)	13 (11.7%)	1.000
Tension/migraine headache	1 (6.3%)	36 (37.9%)	37 (33.3%)	0.019*
Localized myofascial pain	0 (0%)	44 (46.3%)	44 (39.6%)	0.0002*
Fibromyalgia	0 (0%)	10 (10.5%)	10 (9.0%)	0.352

*$p < 0.05$.

Table 4
The urodynamic characteristics of BPS/IC male and female patients.

	Male	Female	Total
Patient numbers	16 (14.4%)	95 (85.6%)	111 (100%)
Age (years)	48.9 ± 16.9	48.3 ± 14.3	48.4 ± 14.7
Uroflowmetry			
Volume (ml)	219.6 ± 123.8	223.0 ± 154.5	222.5 ± 150.4
Maximum flow rate (ml/s)	12.6 ± 3.9	16.7 ± 8.9	16.1 ± 8.5
Average flow rate (ml/s)	6.7 ± 2.8	8.6 ± 5.3	8.3 ± 5.0
Filling cystometry			
Volume at first desire (ml)	117.8 ± 76.8	126.1 ± 81.9	124.9 ± 81.2
Cystometric capacity (ml)	197.5 ± 80.0	240.2 ± 109.7	234.4 ± 107.2
Detrusor pressure at maximum flow rate (cmH_2O)	8.9 ± 5.2	12.9 ± 6.7	12.5 ± 6.7
Detrusor over-activity	5 (35.7%)	14 (15.4%)	19 (18.1%)
Detrusor under-activity	3 (21.4%)	12 (13.2%)	15 (14.3%)
Acontractile detrusor	1 (7.1%)	17 (18.7%)	18 (17.1%)
Impaired compliance	0 (0%)	0 (0%)	0 (0%)
Dysfunctional voiding	3 (18.8%)	45 (47.4%)	48 (43.2%)
Urodynamic stress incontinence	0 (0%)	5 (5.3%)	5 (4.5%)

Table 5
The urodynamic characteristics of BPS/IC patients co-morbid with various non-bladder conditions.

Co-morbidity	Chronic fatigue syndrome		p	Irritable bowel syndrome		p	Temporo-mandibular disorder		p[a]
	With	Without		With	Without		With	Without	
Patient numbers	59 (53.2%)	49 (44.6%)		41 (36.9%)	67 (60.4%)		11 (9.9%)	98 (88.3%)	
Age (years)	47.7 ± 14.8	50.2 ± 14.6	0.365	44.3 ± 15.5	51.6 ± 13.6	0.013*	48.8 ± 12.8	48.8 ± 14.8	0.993
Uroflowmetry									
Volume (ml)	246.7 ± 172.7	199.4 ± 117.8	0.108	183.5 ± 120.0	249.2 ± 162.6	0.028*	225.4 ± 182.6	222.1 ± 147.8	0.948
Maximum flow rate (ml/s)	17.9 ± 10.0	14.2 ± 6.2	0.026*	14.4 ± 7.3	17.5 ± 9.2	0.074	16.2 ± 8.8	16.2 ± 8.6	0.996
Average flow rate (ml/s)	9.0 ± 5.9	7.5 ± 3.9	0.133	7.0 ± 3.6	9.2 ± 5.7	0.018*	8.8 ± 5.9	8.3 ± 5.0	0.758
Filling cystometry									
Volume at first desire (ml)	131.7 ± 94.3	120.6 ± 69.3	0.546	95.4 ± 59.5	141.7 ± 89.5	0.012*	71.7 ± 40.1	130.1 ± 83.4	0.072
Cystometric capacity (ml)	238.2 ± 120.5	237.2 ± 90.3	0.961	209 ± 91.3	251.1 ± 114.1	0.055	196.9 ± 101.2	237.9 ± 107.2	0.274
Detrusor pressure at maximum flow rate (cmH_2O)	23.6 ± 13.2	22.9 ± 13.9	0.75	25.2 ± 15.0	21.4 ± 11.9	0.242	21.8 ± 16.5	23.3 ± 13.2	0.801
Detrusor over-activity	9 (15.8%)	9 (19.6%)	0.122	8 (20.5%)	11 (17.2%)	0.921	3 (33.3%)	16 (16.8%)	0.802
Detrusor under-activity	4 (14.8%)	9 (19.6%)		4 (21.1%)	8 (14.8%)		1 (9.1%)	13 (13.3%)	
Acontractile detrusor	13 (22.8%)	5 (10.9%)		6 (15.4%)	12 (18.8%)		1 (11.1%)	17 (17.9%)	
Impaired compliance	1 (1.8%)	0 (0%)		0 (0%)	1 (1.6%)		0 (0%)	1 (1.1%)	
Dysfunctional voiding	26 (42.6%)	22 (41.5%)	0.904	24 (55.8%)	22 (31%)	0.011*	2 (18.2%)	45 (43.3%)	0.195
Urodynamic stress incontinence	3 (4.9%)	2 (3.8%)	0.766	3 (7%)	2 (2.8%)	0.293	2 (18.2%)	2 (2.9%)	0.018*

*$p < 0.05$.
[a] Mann–Whitney test was used instead of simple T test.

desire, lower bladder compliance, smaller cystometric capacity, and slower catheter-free maximum flow rate.[3] The urodynamic characteristics of BPS/IC patients co-morbid with other non-bladder conditions may help unravel the underlying pathophysiology of these chronic pain syndromes.

Patients with BPS/IC and IBS show smaller catheter-free voided volume, lower catheter-free average flow rate, and smaller bladder volume on the first desire to void. Change of serotonin receptor function due to molecular defect in the human gut may lead to the development of IBS.[27] Serotonin also plays a role in suppressing voiding and the urge to void. Mbaki et al. note that the activation of 5-HT_{2A} in female rats leads to the facilitation of the micturition reflex and increased urethral smooth muscle tone.[28] The relationship between lower urinary tract function and colonic irritation and serotonin may explain the urodynamic findings in BPS/IC patients with IBS.

Moreover, patients with BPS/IC and IBS have more frequent dysfunctional voiding on urodynamic study. According to Prott et al., about 90% patients with non-diarrhea IBS had symptoms of pelvic floor dyssynergia, including straining and incomplete evacuation. On anorectal function testing, 91% showed absent relaxation or paradoxical contraction of the anal sphincter on straining.[29] There may be a viscero-muscular reflex whereby the insult originates from the bowel and/or the bladder, resulting in hypertonic contraction of the pelvic floor muscles. Dysfunctional voiding could only be confirmed by video urodynamic studies; therefore, if BPS/IC patients are suspected to have IBS, video urodynamic studies should be done to rule out the presence of dysfunctional voiding because treatment with alpha blockers or muscle relaxants may improve the lower urinary tract symptoms of these patients.

In this study, higher catheter-free maximum flow rate is observed in BPS/IC patients co-morbid with CFS or tension/migraine headache. Although many theories have been posited, the cause of IC is unknown. Inflammatory cytokines, including TNF-α, IL-1, IL-6, and TNF-γ, are released after various insults. These cytokines elicit the inducible nitric oxide synthase (NOS). Koskela et al. found higher inducible NOS expression and NO formation in BPS/IC patients.[30] Furthermore, NO and its potent oxidant peroxynitrite produce symptoms of CFS and migraine.[31] Therefore, NO may play a role in the pathogenesis of BPS/IC with CFS or tension/migraine headache. Ho et al. report that NO elicits a relaxation effect more on the bladder neck and urethra than on the detrusor muscle,[32] which may explain the higher catheter-free maximum flow rate in BPS/IC patients with CFS and tension/migraine headache.

BPS/IC patients with LMP present with larger catheter-free voided volume and lower pressure at maximum flow. Doggweiler-Wiygul et al. disclosed that BPS/IC symptoms and irritating voiding symptoms improve or resolve after treatments for myofascial trigger points in the pelvic floor muscles, as well as the gluteus, piriformis, infraspinatus, and supraspinatus muscles.[33] Weiss report that BPS/IC patients have moderate-to-marked improvement after manual physical therapy to the pelvic floor. Electromyography also show decreased resting pelvic floor tension after treatment,[34] hinting that trigger points in the pelvic floor muscles result in increased bladder outlet resistance due to excess pelvic floor tension.

However, in this study, patients with BPS/IC and LMP paradoxically present with larger catheter-free voided volume and lower pressure at maximum flow, indicating lower bladder outlet resistance. It can be speculated that the trigger points in these patients are located in muscles other than the pelvic floor, like the gluteus or piriformis muscles.

Stress incontinence was more prevalent in patients with BPS/IC and TMD. It is believed that the etiology of TMD is multifactorial, including both local insults and systemic conditions, such as generalized joint hypermobility.[35] In a study

Table 6
The urodynamic characteristics of BPS/IC patients co-morbid with various non-bladder conditions (continued).

Co-morbidity	Multiple chemical sensitivities		p[a]	Tension/migraine headache		p	Localized myofascial pain		p	Fibromyalgia		p[a]
	With	Without		With	Without		With	Without		With	Without	
Patient numbers	13 (11.7%)	96 (86.5%)		37 (33.3%)	71 (64.0%)		44 (39.6%)	67 (60.4%)		10 (9.0%)	96 (86.5%)	
Age (years)	47.9 ± 15.1	49.0 ± 14.7	0.803	46.6 ± 14.0	49.8 ± 14.9	0.266	51.3 ± 14.4	47.5 ± 14.8	0.170	46.6 ± 15.1	49.2 ± 14.6	0.628
Uroflowmetry												
Volume (ml)	250.1 ± 190.2	220.6 ± 145.5	0.511	250.5 ± 158.5	211.9 ± 147.0	0.214	247.8 ± 171.2	206.0 ± 135.3	0.181	269.6 ± 212.6	216.6 ± 139.7	0.483
Maximum flow rate (ml/s)	17.1 ± 6.4	16.1 ± 8.8	0.693	19.3 ± 10.4	14.7 ± 7.1	0.021*	17.6 ± 10.3	15.1 ± 7.1	0.172	19.8 ± 13.3	15.6 ± 7.5	0.373
Average flow rate (ml/s)	8.7 ± 3.4	8.3 ± 5.3	0.785	9.6 ± 5.4	7.8 ± 4.8	0.084	8.9 ± 5.7	7.9 ± 4.6	0.353	11.3 ± 8.1	8.0 ± 4.5	0.256
Filling cystometry												
Volume at first desire (ml)	108.5 ± 70.0	128.5 ± 83.9	0.457	126.8 ± 91.3	127.9 ± 77.2	0.955	156.6 ± 93.4	108.0 ± 68.7	0.007**	140.7 ± 102.3	119.3 ± 70.3	0.489
Cystometric capacity (ml)	195.3 ± 105.3	242.6 ± 106.8	0.152	232.7 ± 102.9	241.2 ± 109.6	0.709	268.1 ± 112.7	213.7 ± 99.6	0.011*	228.6 ± 126.0	235.8 ± 103.8	0.854
Detrusor pressure at maximum flow rate (cmH2O)	25.9 ± 11.2	22.9 ± 13.6	0.518	24.2 ± 12.9	22.9 ± 13.6	0.717	19.1 ± 11.5	25.7 ± 13.9	0.016*	25.0 ± 12.3	22.7 ± 13.8	0.758
Detrusor over-activity	5 (41.7%)	14 (15.2%)	0.155	5 (14.3%)	14 (20.6%)	0.101	4 (9.5%)	15 (23.1%)	0.172	2 (25%)	15 (15.6%)	0.245
Detrusor under-activity	0 (0%)	13 (13.5%)		1 (2.7%)	13 (20.3%)		5 (11.4%)	10 (14.9%)		0 (0%)	15 (15.6%)	
Acontractile detrusor	1 (8.3%)	17 (18.5%)		8 (22.9%)	9 (13.2%)		6 (14.3%)	12 (18.5%)		0 (0%)	18 (19.1%)	
Impaired compliance	0 (0%)	1 (1.1%)		0 (0%)	1 (1.5%)		0 (0%)	1 (1.5%)		0 (0%)	0 (0%)	
Dysfunctional voiding	5 (35.7%)	43 (42.6%)	0.775	15 (39.5%)	33 (43.4%)	0.841	18 (39.1%)	31 (43.1%)	0.705	4 (40%)	46 (42.2%)	1.000
Urodynamic stress incontinence	2 (14.3%)	3 (3%)	0.052	3 (7.9%)	2 (2.6%)	0.196	4 (8.7%)	1 (1.4%)	0.055	1 (10%)	4 (3.9%)	0.369

*$p < 0.05$.
**$p < 0.01$.
[a] Mann–Whitney test was used instead of simple T test.

Table 7
Prevalence of non-bladder conditions in patients with BPS/IC.[17–22]

Reference	Sample description	Diagnostic methods for co-morbidities	No. of patients	Chronic fatigue syndrome	Irritable bowel syndrome	Temporo-mandibular disorder	Multiple chemical sensitivity	Tension/migraine headache	Localized myofascial pain	Fibromyalgia
Current study	Clinical cohort	Questionnaires	111	53.2%	36.9%	9.9%	11.7%	33.3%	39.6%	9.0%
Novi et al., 2005	Clinical cohort	Questionnaires	46		43%					
Clemens et al., 2006	Clinical cohort	Questionnaires	111		40%			32.1%		16.3%
Warren et al., 2009	Physician referral	Self-reported diagnosis	313	4.2%	27.5%			35.8%		9.3%
Nickel et al., 2010	Clinical cohort	Self-reported diagnosis	205	9.5%	38.8%			29.9%		17.7%
Clemens et al., 2012	Random, community sample	Self-reported diagnosis	534	14.8%	40%			24.8%		22.2%
Chelimsky et al., 2012	Clinical cohort	Questionnaire	58	53%	27%					

investigating lower urinary tract dysfunction in children with generalized joints hypermobility, daytime and nighttime urinary incontinence was more prevalent due to nonneurogenic bladder sphincter dysfunction.[36] It is reported that changes in matrix metalloproteinases activity may contributed to both TMD and stress incontinence, which resulting in higher stress incontinence rate in BPS/IC patients with TMD.[37,38]

The present study had some limitations. First, we depended on established case definitions that were designed to facilitate symptom-based diagnoses without confirmation of accuracy, especially those requiring physical examination findings or exclusion of specific medical disorders. Second, the study participants were all drawn from tertiary care clinics, hampering the generalizability of findings to primary care patients and to the general population. Third, the questionnaires were administrated in Chinese. Because of lack of funds, the questionnaires have not been validated in Chinese formally. We submitted the questionnaires to several BPS/IC patients to determine whether the questions were clear, understandable and in a logical order (face validity). Furthermore, the same patients and two experts in functional urology were asked to criticize the content of the questionnaire (content validity). We did not assess the internal consistency and the repeatability of the questionnaires. Fourth, only 16 male patients were enrolled and this might interfere with the analysis by sex in BPS/IC patients with various non-bladder conditions. Moreover, the number of patients with certain non-bladder co-morbid conditions (eg: TMD, MCS, and FM) is slightly too low to have a significant statistical differences in urodynamic parameters with strong power. Fifth, all the study participants were classified as non-ulcer type of BPS/IC. The relationship between non-bladder conditions and Hunner's ulcer could not be evaluated in the present study.

In conclusion, patients with BPS/IC, especially females, are more likely to have non-bladder related conditions, especially tension/migraine headache and LMP. Patients with BPS/IC and co-morbid IBS are younger and are more likely to have abnormal urodynamic findings, especially higher prevalence of dysfunctional voiding. Further investigation into the pathophysiology underlying the urodynamic characteristics in each specific co-morbid condition is warranted and may guide the proper management of these patients.

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