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Clinical Evidence of a Neurogenic Mechanism for the Co-existence of Urinary and Bowel Symptoms in Women with Bladder Pain Syndrome

Lori Cory[1], **Heidi S. Harvie**[2], **Gina Northington**[3], **Anna Malykhina**[4], **Kristene Whitmore**[5], and **Lily Arya**[3]

[1]University of Pennsylvania School of Medicine, Philadelphia, PA, United States

[2]Gynecology, Chestnut Hill Hospital, Philadelphia, PA, United States

[3]Obstetrics and Gynecology, University of Pennsylvania, Philadelphia, PA, United States

[4]Surgery, University of Pennsylvania, Philadelphia, PA, United States

[5]The Pelvic and Sexual Health Institute, Philadelphia, PA, United States

Abstract

Purpose—The aim of our study is to determine if urinary and bowel symptoms are associated with the presence of neuropathic pain in women with bladder pain syndrome.

Materials and Methods—Female patients with a known diagnosis of bladder pain syndrome completed validated questionnaires to assess neuropathic pain, urinary and bowel symptoms, quality of life and pain catastrophizing. Women were dichotomized into neuropathic pain and non-neuropathic pain groups. Urinary and bowel symptoms, pain catastrophizing and quality of life scores were compared between the two groups using parametric and non-parametric tests.

Results—Of 150 women with bladder pain syndrome, 40 (27%) women had neuropathic pain while 110 (73%) did not. Women with neuropathic pain had significantly worse urinary symptom (13.1 ± 4.1 vs. 9.9 ± 4.0, $p<0.001$), bowel symptom (22.9 ± 10.0 vs. 14.1 ± 7.8, $p<0.001$), quality of life (12.2 ± 5.5 vs. 9.8 ± 3.8, $p<0.001$), and higher pain catastrophizing (32.2 ± 12.4 vs. 23.1 ± 14.3, $p<0.001$) scores than women without neuropathic pain. The severity of urinary symptoms was significantly correlated with the severity of bowel symptoms ($r = 0.13$, $p=0.001$). After adjusting for neuropathic pain, the significant relationship between urinary and bowel symptom scores disappeared ($r = 0.08$, $p=0.07$).

Conclusions—In women with bladder pain syndrome, the presence of neuropathic pain is significantly associated with the severity of bladder and bowel symptoms, quality of life and pain catastrophizing. A neurogenic mechanism may explain the co-existence of urinary and bowel symptoms in women with bladder pain syndrome.

Keywords

Cystitis; Interstitial; Neuralgia; Catastrophization; Irritable Bowel Syndrome; Questionnaires

Introduction

Bladder pain syndrome (BPS), formerly known as painful bladder syndrome/interstitial cystitis, is defined as a clinical syndrome of chronic pain, pressure or discomfort that is perceived by the patient to originate from the bladder and is associated with other urinary symptoms such as frequency or urgency.[1] Though BPS has a significant negative impact on patient well-being and quality of life,[2, 3] little is known about the pathogenesis of this disorder. A neurogenic mechanism for BPS has been implicated and subjects with BPS report site-specific pain with neuropathic characteristics such as burning pain and hypersensitivity to touch in the lower abdomen, urethra, lower back, rectum and vagina.[4, 5]

Studies in animal models[6-8] suggest that cross-sensitization among pelvic viscera may result in BPS. Visceral pain is transmitted centrally for processing via the spinothalamic tract via "silent," unmyelinated C-fibers.[9] C-fibers are abundant in the bladder[10] and may undergo electrophysiologic changes that result in the perpetuation of an acute insult into chronic pain.[9] Ultimately, these findings suggest that afferent hypersensitivity may occur secondary to inflammation in other pelvic viscera (i.e. urinary tract infection, endometriosis, irritable bowel syndrome)[6, 7, 11, 12] and later lead to chronic pain as seen in BPS.[9] However, clinical evidence of neurologic sensitization in women with BPS is lacking.

Neuropathic pain is clinically characterized by the presence of a variety of sensory symptoms and pain qualities. Using cluster analysis, prior studies have demonstrated a characteristic sensory profile and a typical constellation of neuropathic symptoms, such as radiating pain, pain attacks, and hypersensitivity to touch, in subjects reporting neuropathic pain.[13, 14] These symptoms can be reliably captured using questionnaires and patient reported instruments used to distinguish neuropathic from nociceptive pain have been validated.[14-16]

The aim of our study is to determine if urinary and bowel symptoms are associated with the presence of neuropathic pain in women with BPS. Our hypothesis is that in women with BPS, the presence of neuropathic pain is associated with more severe urinary and bowel symptoms and worse quality of life than in women without neuropathic pain.

Materials and methods

This was a prospective cross-sectional study of 150 consecutive women presenting to a urology practice (K. Whitmore) between July and September 2010 with a diagnosis of BPS. Institutional Review Board approval was obtained from the University of Pennsylvania.

Study Participants

Patients eighteen years or older with a known diagnosis of BPS as defined by the Bladder Pain Syndrome International Consultation on Incontinence[17] were eligible for the study. Diagnostic criteria for inclusion in this study were chronic (>6 months) pelvic pain, pressure or discomfort perceived to be related to the urinary bladder and accompanied by at least one other urinary symptom (i.e. urgency or frequency).[17] All women had documented negative urine culture at the time of diagnosis. Women who had undergone cystoscopy were included

only if cystoscopy findings were negative for tumors, stones, polyps and foreign bodies. Exclusion criteria were failure to meet the Bladder Pain Syndrome International Consultation on Incontinence diagnostic criteria[17], known neurologic disorders (multiple sclerosis, Parkinson's disease, spina bifida, spinal cord injury/trauma), diabetes mellitus, history of a pelvic floor malignancy treated with chemotherapy and/or radiation and recent pregnancy.

Measures

Following informed consent, demographic data on medications, allergies, co-existent medical conditions and prior pelvic surgeries were collected. All women completed the following validated questionnaires: O'Leary-Sant Interstitial Cystitis Symptom and Problem Indices, PainDETECT neuropathic pain questionnaire, Birmingham Irritable Bowel Syndrome symptom questionnaire and Pain Catastrophizing Scale.

PainDETECT is a validated 9-item instrument used as a screening tool for the detection of neuropathic pain.[13] One item characterizes the course of pain (persistent pain with slight fluctuations, persistent pain with pain attacks, pain attacks without pain between them, pain attacks with pain between them), one item assesses radiation and seven items evaluate the quality of pain (burning sensation, paresthesias, pain induced by light touch, pain with characteristics mimicking electric shocks, thermal hyperalgesia, numbness and pain induced by light pressure). Total scores range from -1 to 38 with scores ≥ 19 indicating presence of a neuropathic component (>90% probability). In a validation study comparing patients with neuropathic and nociceptive pain, PainDETECT was shown to have a sensitivity and specificity of 85% and 80%, respectively for the diagnosis of neuropathic pain.[13]

The ***O'Leary-Sant questionnaire***, comprised of the Interstitial Cystitis Symptom Index and the Interstitial Cystitis Problem Index,[18] was used to measure the severity of urinary symptoms and their impact on quality of life. Each index contains four items assessing lower urinary tract symptoms (urgency, frequency, nocturia and pain associated with the bladder). Index scores range from 0 to 20 and 0 to 16 for the Interstitial Cystitis Symptom Index and the Interstitial Cystitis Problem Index, respectively.[18]

The Birmingham Irritable Bowel Syndrome symptom questionnaire was used to characterize bowel symptoms. This questionnaire consists of eleven items assessing three internal dimensions (abdominal pain, diarrhea and constipation) and has been validated for the evaluation of irritable bowel syndrome symptoms.[19] Scores for each dimension range from 0 to 15 for the pain and constipation dimensions and 0 to 25 for the diarrhea dimension. There is no cut off score for the diagnosis of irritable bowel syndrome. A summary score is calculated as the sum of the three dimension scores with a range from 0 to 55.

The Pain Catastrophizing Scale was utilized to identify subjects with a tendency to catastrophize in response to perceived pain. The scale consists of 13 questions within three components: rumination, magnification and helplessness. Individual questions are scored from 0 to 4 with total scores ranging from 0 to 52. Increased pain catastrophization is seen with higher scores. In validation studies, the instruments showed high internal consistency

with coefficient alphas of 0.87, 0.60 and 0.79 for the rumination, magnification and helplessness components, respectively.[20]

Analysis

Based on the PainDETECT score, women were divided into two groups: neuropathic pain (score ≥ 19) and non-neuropathic pain (score < 19).[16] Demographic data are presented as percentages, medians or as means ± standard deviation. Categorical data were compared between women with and without neuropathic pain using the Pearson Chi-square and Fisher's exact tests as appropriate. Continuous variables (scores of validated instruments) were compared between the two groups using parametric and non-parametric t-tests for independent samples as appropriate. We assessed relationships of urinary, bowel and pain catastrophizing scores with neuropathic pain scores using Spearman correlation coefficients. We analyzed the relationships of urinary symptom scores (dependant variable) with bowel and pain catastrophizing scores using linear regression. To determine the effect of neuropathic pain on these associations, we performed regression while adjusting for neuropathic pain scores and reported the 95% confidence intervals of the beta coefficient.

In a previous study on adults with neuropathic pain, the mean visual analogue score of average intensity of neuropathic pain was 5.5 ± 2.0.[21] We fixed alpha at 0.05 and power at 90%. Based on these assumptions, we estimated that we needed 40 women with neuropathic pain to detect a difference of 25% in the mean pain score of women with and without neuropathic pain. Given that the prevalence of neuropathic pain has been previously reported as 25-30% in women with interstitial cystitis,[4, 5] we planned to identify 150 women with BPS. All reported p-values were two-sided and p-values < 0.05 were considered statistically significant. All statistical analysis was done using Stata version 10.0 (StatCorp, College Station, TX).

Results

Of the 172 women who met the inclusion criteria, 150 women agreed to participate and were enrolled. Of those enrolled, 133 women (89%) had undergone cystoscopy at the time of diagnosis. Based on responses to the neuropathic pain questionnaire, 40 women (27%) were included in the neuropathic pain group (score ≥ 19).

There was no significant difference in age, parity, body mass index or current treatment between women with neuropathic pain and those without neuropathic pain (Table 1). The rate of fibromyalgia was significantly greater in women with neuropathic pain than women without neuropathic pain. Women with neuropathic pain were more likely to have undergone hysterectomy and other abdominal or pelvic surgical procedures than women without neuropathic pain, but these differences did not reach significant levels. Subjects with neuropathic pain scored significantly higher on the Pain Catastrophizing Scale.

Women with neuropathic pain had significantly worse total urinary symptom and quality of life scores than women without neuropathic pain (Table 2) and reported significantly greater severity of individual urinary symptoms including urgency, frequency and pain/burning in the bladder than women without neuropathic pain. The severity of nocturia was similar

between the two groups. The total irritable bowel syndrome symptom score for women with neuropathic pain was significantly higher than for women without neuropathic pain (Table 3). Individual dimension scores for abdominal pain, diarrhea and constipation were also significantly higher in women with neuropathic pain than in women without neuropathic pain.

The neuropathic pain score was significantly correlated to the total urinary symptom, bowel symptom and quality of life scores (Table 4). These correlations remained significant after controlling for prior surgery and pain items on the three instruments (Interstitial Cystitis Symptom and Problem Indices and Birmingham Irritable Bowel Syndrome symptom questionnaire).

On regression analysis, the total urinary symptom score was significantly associated with the total bowel symptom, the quality of life and the pain catastrophizing scale scores (Table 5). After adjusting for the neuropathic pain score, the significant relationship of the urinary symptom score with the bowel symptom score disappeared. The relationship of the urinary symptom score with the quality of life and pain catastrophizing scale scores became weaker after adjusting for the neuropathic pain score, but remained statistically significant.

Discussion

Interstitial cystitis (BPS), irritable bowel syndrome, and other chronic pelvic pain disorders often occur concomitantly.[22-24] Afferent sensitization of pelvic viscera due to convergent neural input has been postulated to play a role in the overlap of chronic pelvic pain disorders.[6, 12] However, clinical evidence of neuropathic abnormalities in women with BPS is lacking. We report significant associations between neuropathic pain and urinary and bowel symptoms in women with BPS. Urinary and bowel symptoms and quality of life were significantly worse in women with BPS and neuropathic pain than in women with BPS and no neuropathic pain. The total urinary symptom score as well as the severity of specific urinary symptoms such as urgency, frequency and bladder pain were significantly worse in women with neuropathic pain than in women without neuropathic pain. Similarly, the total bowel symptom score and the severity of diarrhea and constipation dimension scores were significantly worse in women with neuropathic pain than in women without neuropathic pain. The observed correlations between neuropathic pain, urinary and bowel symptom scores remained significant after controlling for pain items on the instruments suggesting that neuropathic pain correlates directly with the severity of visceral symptoms, both bladder and bowel (Table 4). Finally, urinary symptom scores were significantly associated with bowel symptoms scores (Table 5) and this relationship disappeared after adjusting for the neuropathic pain score, suggesting that a neurogenic mechanism may explain the association between urinary and bowel symptoms in women with BPS.

Our findings that a neurogenic mechanism is responsible for the co-existence of urinary and bowel symptoms in women with BPS is supported by other studies. Animal studies have shown that afferent irritation of one pelvic organ may adversely influence and sensitize another organ via neural interactions or altered sensory processing.[6, 12] Ness et al. have reported that subjects with interstitial cystitis have significantly lower threshold related to

pressure, ischemia and bladder than healthy controls.[25] Prospective studies will be required to determine if neuropathic pain in women with urinary symptoms can lead to the development of bowel symptoms and vice versa.

Can neural interactions also explain pain catastrophizing in women with BPS? It is possible that afferent sensitization of the central pain pathways results in increased perception of pain in women with BPS. Alternatively, pain catastrophizing may simply be present in women with worse symptoms. In our study, urinary symptom scores were significantly associated with pain catastrophizing and quality of life scores. After adjusting for the neuropathic pain score, the association of urinary symptoms with pain catastrophizing and quality of life became weaker, but remained statistically significant (Table 5). This finding suggests that in our population, pain catastrophizing was associated with worse symptom severity and that neuropathic pain was not a significant mediator for pain catastrophizing. Prior brain MRI studies in subjects with chronic low back pain[26] and irritable bowel syndrome[27] have demonstrated augmented central pain processing and abnormal central affective processing of painful sensory input, respectively. An inability to activate a sensory modulation system may predispose subjects with chronic back pain to poor coping.[28] Functional MRI studies will be needed to determine if similar abnormal central processing is present in women with BPS also.

Strengths of our study include the enrollment of women with well-defined BPS using established diagnostic criteria[17], use of validated questionnaires to capture patient reported symptoms and adequate sample size. Limitations of our study should also be considered. Our study is cross-sectional in design and cannot determine the causal role of neuropathic pain. Misclassification of women with neuropathic pain is another potential limitation. We dichotomized women into two groups with and without neuropathic pain based on a cut off score of 19 as described in the original validation study. However, subjects with scores ranging from 13 to 18 may have some components of neuropathic pain.[13] Therefore, some women with neuropathic pain may have been included in the non-neuropathic pain group resulting in bias towards the null hypothesis. Since we observed significant differences in urinary and bowel symptoms and quality of life data between women with and without neuropathic pain, such misclassification likely did not occur. Using patient reported instruments, our study provides compelling clinical evidence that a neurogenic mechanism plays a significant role in the co-existence of urinary and bowel symptoms in women with BPS.

Conclusions

In women with bladder pain syndrome, the presence of neuropathic pain is significantly associated with the severity of bladder and bowel symptoms, quality of life and pain catastrophizing. This study provides clinical evidence of a neurogenic mechanism for the co-existence of urinary and bowel symptoms in women with bladder pain syndrome.

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Table 1

Demographics

	Neuropathic Pain† N = 40	Non-neuropathic Pain‡ N = 110	p-value
Mean Age (years)	40.1 ± 13.5	45.0 ± 14.8	0.07
Median Parity (range)	1 (0-4)	1 (0-7)	0.26[1]
Mean BMI (kg/m^2)	26.1 ± 5.6	25.1 ± 5.1	0.29
Current Treatment(s):			
Pentosan polysulfate sodium	12 (30.0%)	50 (45.5%)	0.09
TCA	5 (12.5%)	13 (11.8%)	1.00[2]
Hydroxyzine	3 (7.5%)	7 (6.4%)	0.73[2]
Gabapentin	5 (12.5%)	9 (8.2%)	0.53[2]
Narcotics	18 (45.0%)	33 (30.0%)	0.09
BZD	17 (42.5%)	49 (44.6%)	0.82
Bladder instillation*	1 (2.5%)	11 (10.0%)	0.18[2]
Sacral neuromodulation	2 (5.0%)	2 (1.8%)	0.29[2]
Past Surgical History:			
Hysterectomy	10 (25.0%)	15 (13.6%)	0.10
Caesarean section	9 (22.5%)	14 (12.7%)	0.14
Appendectomy	7 (17.5%)	12 (10.9%)	0.28
Ovarian cyst removal	2 (5.0%)	2 (1.8%)	0.29[2]
Anti-incontinence/prolapse procedure	2 (5.0%)	1 (0.9%)	0.17[2]
Past Medical History:			
Endometriosis	4 (10.0%)	16 (14.6%)	0.59[2]
Irritable bowel syndrome	10 (25.0%)	22 (20.0%)	0.51
Migraines	7 (17.5%)	20 (18.2%)	0.92
Fibromyalgia	17 (42.5%)	15 (13.6%)	**<0.001**
Chronic fatigue syndrome	4 (10.0%)	5 (4.6%)	0.25[2]
Depression	4 (10.0%)	9 (8.2%)	0.75[2]
Anxiety	2 (5.0%)	10 (9.1%)	0.52[2]
Pain Catastrophizing Scale	32.2 ± 12.4	23.1 ± 14.3	**<0.001** [3]

*Contains gentamycin, heparin, sodium bicarbonate, marcaine and solucortef

†Score ≥ 19 on PainDETECT

‡Score < 19 on PainDETECT

[1]Equality of medians test

[2]Fisher's exact test

[3] Non-parametric t-test for independent samples

Table 2

Comparison of urinary symptoms and quality of life in women with and without neuropathic pain

	Neuropathic Pain† N=40	Non-neuropathic Pain‡ N=110	p-value*
Total urinary symptom score (ICSI)	13.1 ± 4.1	9.9 ± 4.0	**<0.001**
Urgency (ICSI, Question 1)	3.1 ± 1.4	2.1 ± 1.7	**<0.001**
Frequency (ICSI, Question 2)	4.0 ± 1.3	3.4 ± 1.6	**0.02**
Nocturia (ICSI, Question 3)	3.0 ± 1.7	2.5 ± 1.5	0.13
Pain/burning in the bladder (ICSI, Question 4)	3.0 ± 1.1	2.0 ± 1.3	**<0.001**
Total quality of life score (ICPI)	12.2 ± 5.5	9.8 ± 3.8	**<0.001**

ICSI = O'Leary-Sant Indices, **Interstitial Cystitis Symptom Index**

ICPI = O'Leary-Sant Indices, **Interstitial Cystitis Problem Index**

† Score ≥ 19 on PainDETECT

‡ Score < 19 on PainDETECT

* Parametric or non-parametric t-test for independent samples

Table 3

Comparison of bowel symptoms between women with and without neuropathic pain

	Neuropathic Pain† N=40	Non-neuropathic Pain‡ N=110	p-value*
Total bowel symptom score (IBS)	22.9 ± 10.0	14.1 ± 7.8	**<0.001**
Pain dimension score	8.8 ± 4.0	5.3 ± 3.6	**<0.001**
Diarrhea dimension score	7.8 ± 6.1	4.1 ± 4.3	**<0.001**
Constipation dimension score	6.4 ± 4.5	4.6 ± 4.1	**0.02**

IBS = Birmingham Irritable Bowel Syndrome Symptom questionnaire

† Score ≥ 19 on PainDETECT

‡ Score < 19 on PainDETECT

* Parametric or non-parametric t-test for independent samples

Table 4

Relationship of neuropathic pain to urinary and bowel symptoms and quality of life

	Total Neuropathic Pain Score [¥]	
	R value [*]	**p-value**
Total urinary symptom score (ICSI)	0.31	**<0.001** [†‡]
Total quality of life score (ICPI)	0.28	**<0.001** [†‡]
Total bowel symptom score (IBS)	0.49	**<0.001** [†‡]

ICSI = O'Leary-Sant Indices, **Interstitial Cystitis Symptom Index**

ICPI = O'Leary-Sant Indices, **Interstitial Cystitis Problem Index**

IBS = Birmingham Irritable Bowel Syndrome Symptom questionnaire

[*] Correlation – Spearman's

[†] Remains significant after adjusting for prior surgery

[‡] Remains significant after adjusting for pain items (either bladder or bowel)

[¥] As measured with PainDETECT

Table 5

Association of urinary symptom score with bowel symptom, quality of life and Pain Catastrophizing Scale scores

	Total urinary symptom score (ICSI)			
	Unadjusted		Adjusted for Neuropathic Pain Score ¥	
	Beta coefficient (95% CI)	p-value	Beta coefficient (95% CI) ‡	Adjusted P value ‡
Total bowel symptom score (IBS)	0.13 (0.06, 0.19)	**0.001**	0.08 (-0.01, 0.16)	0.07
Total quality of life score (ICPI)	0.89 (0.79, 0.99)	**<0.001**	0.86 (0.75, 0.97)	**<0.001**
Total Pain Catastrophizing Scale score	0.10 (0.05, 0.14)	**<0.001**	0.07 (0.02, 0.12)	**0.01**

ICSI = O'Leary-Sant Indices, **Interstitial Cystitis Symptom Index**

ICPI = O'Leary-Sant Indices, **Interstitial Cystitis Problem Index**

IBS = Birmingham Irritable Bowel Syndrome Symptom questionnaire

‡Adjusted for Neuropathic Pain score

¥As measured with PainDETECT