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Relationship of bladder pain with clinical and urinary markers of neuroinflammation in women with urinary urgency without urinary incontinence

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Abstract

PURPOSE: The pathogenesis of bladder pain is poorly understood. Our hypothesis is that in women with urinary urgency without incontinence, bladder pain is associated with the presence of neurogenic inflammation in the bladder wall and neuroinflammatory biomarkers in the urine.

METHODS: We conducted a prospective cross-sectional study of women with urinary urgency without incontinence. Urinary symptoms were measured using Female Genitourinary Pain Index. Neuropathic pain, a clinical biomarker of neuroinflammation, was measured using the PainDETECT questionnaire. Inflammatory neuropeptides measured in the urine included nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and osteopontin (Opn). Neuropathic pain scores and urinary neuropeptide levels were compared between patients with and without bladder pain using univariable and multivariable analysis.

RESULTS: In 101 women with urinary urgency without incontinence, 62 (61%) were in the bladder pain group (VAS ≤ 3) while 39 (39%) were in the no bladder pain group. Urinary symptom scores (5.0 +/−3.1 versus 3.5 +/−2.4, $p < .001$) and neuropathic pain scores (13.3 ± 8.6 versus 5.1 ± 4.8, $p < .001$) were significantly higher for the bladder pain group than for the no bladder pain group. On multivariable analysis after controlling for age, BMI, and severity of urinary urgency, bladder pain score was significantly associated with elevated urinary levels of VEGF ($p=0.04$) and Opn ($p=0.02$) while neuropathic pain score was significantly associated with an increased NGF level ($p=0.03$).

CONCLUSIONS: In women with urinary urgency without incontinence, bladder pain is associated with the presence of clinical and urinary biomarkers of neuroinflammation.

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Keywords

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INTRODUCTION

Urinary urgency, defined as a sudden compelling desire to urinate, may or may not be associated with incontinence. Of the over 40 million women in the United States with urinary urgency, 7-23% report urgency without incontinence.[1,2,3] Urinary urgency has a significant impact on quality of life even in the absence of incontinence.[1,4] Clinicians have long suspected that the urgency phenotype without incontinence is distinct from urgency urinary with incontinence, however, the majority of existing studies have focused on urinary urgency with incontinence, and the pathogenesis of urgency in the absence of incontinence remains poorly understood.

The presence of pain may be indicative of a different underlying etiology for the urgency phenotype compared to women with urgency without bladder pain. In animal models, visceral hypersensitivity conveyed by afferent Adelta and C fiber innervation of the urinary bladder, has been implicated in the pathogenesis of bladder pain.[5,6,7] Clinically, neuroinflammation is associated with the presence of neuropathic pain which is characterized by a typical constellation of sensory symptoms such as radiating pain, pain attacks and hypersensitivity to touch (allodynia).[8,9] PainDETECT is a 9-item questionnaire that has been validated to clinically measure neuropathic pain in a variety of conditions including fibromyalgia, post-herpetic neuralgia, and interstitial cystitis/bladder pain syndrome.[10,11] Neuroinflammation of the lower urinary tract is also known to be associated with the expression of neuropeptides, such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and osteopontin (Opn) in the urine.[5,7,12,13] Clinical and pathological evidence of neuroinflammation in women with urinary urgency could provide useful insights into underlying mechanisms and help guide treatment.

Our aim was to investigate the relationship between bladder pain and biomarkers of neuroinflammation in the urine in a well characterized group of women with urinary urgency. We hypothesize that in women with urinary urgency without incontinence, bladder pain will be associated with the presence of neuropathic pain, and elevated levels of inflammatory neuropeptides in the urine.

MATERIALS AND METHODS

Study Participants

We conducted a prospective cross-sectional study of women with urinary urgency without urinary incontinence, who presented to the Urogynecology office at the Hospital of the University of Pennsylvania and the Urology office at the Pelvic and Sexual Health Institute from March to July 2013. Institutional Review Board approval was obtained from the University of Pennsylvania prior to commencement of the study. Women were eligible to

participate if they were >18 years old, and reported at least mild urgency on the Indevus Urgency Severity Scale, a single item validated questionnaire that measures the severity of urgency on a three-point scale (mild, moderate, or severe urgency).[14] Women were excluded from the study, if they reported moderate or severe urinary incontinence as measured by the Incontinence Severity Index.[15] Other exclusion criteria were recent urinary tract infection (<6 weeks), neurogenic bladder, kidney stones and recent pregnancy (<3 months postpartum).

Clinical Measures

After obtaining informed consent, study participants provided demographic data, and completed questionnaires assessing bladder pain and urinary symptoms. Demographic information was collected based on patient report, and the diagnosis of bladder pain syndrome (BPS) was determined based on the American Urologic Association guidelines for the diagnosis of interstitial cystitis/BPS.[16] All subjects completed the following validated questionnaires: Female Genitourinary Pain Index (F-GUPI), Interstitial Cystitis Symptom and Problem Index (ICSI/ICPI), and painDETECT neuropathic pain questionnaire.

The F-GUPI is a validated questionnaire that consists of three domains, pain, urinary symptoms, and their impact on quality of life. The pain domain contains a visual analog scale (VAS) to measure bladder pain on a scale of 0 to 10. The total score of the F-GUPI ranges from 0 to 23 with higher scores indicating worse symptoms.[17,18]

The ICSI and ICPI are validated tools to measure the severity of lower urinary tract symptoms.[19] Each index contains four items: urgency, frequency, nocturia and bladder pain. ICSI and ICPI scores range from 0 to 16 and from 0 to 20, respectively, with higher scores indicating worse symptoms and worse quality of life.[19]

The PainDETECT questionnaire, a 9-item instrument, was validated to evaluate the presence of neuropathic pain.[20] This instrument assesses neurological symptoms of burning, paresthesia, pain associated with touch, electric shocks, thermal hyperalgesia, and numbness. It also characterizes the severity and frequency of pain attacks. Total PainDETECT scores range from −1 to 38. Women with a score ≥19 on the PainDETECT instrument are considered to have neuropathic pain (>90% probability).[20] The instrument takes less than 10 minutes to complete, and has been previously validated in women with BPS.[21]

Urinary Neuropeptides

Women provided a first morning urine sample within one week of completing the study questionnaires. Voided urine was received in cold mailers and ice packs, and transferred to the laboratory for analysis. The samples were centrifuged at 3,000 rpm for 10 minutes at 4°C. The supernatant was separated into 1.5 ml aliquots, and preserved in −80°C freezer.

Urinary NGF and BDNF concentrations were determined using the Emax ImmunoAssay System (Promega, Madison, WI, USA), a precise and highly sensitive ELISA kit, which had a minimum sensitivity of 7.8 pg/ml. Urinary Osteopontin (Opn) levels were determined using Human Osteopontin EIA kit (Enzo Life Sciences, Farmingdale, NY) which had a

minimum sensitivity of 0.110 ng/ml. Urinary VEGF levels were measured using Human VEGF EIA kit (Thermo Scientific, Waltham, MA) with a minimum sensitivity of 5pg/ml. All assays were performed according to the manufacturer's instructions. The amounts of urinary biomarkers in each urine sample were calculated based on a standard curve. All samples were run in duplicate, and the values were averaged. Similar to prior studies, total urinary NGF, BDNF, VEGF and Opn levels were normalized to urinary creatinine (mg/dl) concentration (NGF/Cr, BDNF/Cr, VEGF/Cr and Opn/Cr levels) for each individual.[22]

Statistical Analysis

Based on patient reported visual analog scale of bladder pain, women with urinary urgency were divided into two groups: bladder pain (score>3) group and no bladder pain group (score≤3). We compared demographic data, clinical questionnaire scores, and urinary neuropeptide levels between the two groups using parametric and non-parametric t-tests, as appropriate. Categorical variables of the two groups were compared using Pearson Chi-square and Fisher exact tests, as appropriate. We assessed the relationship of clinical variables including age, body mass index (BMI), symptom scores with urinary neuropeptide levels using simple linear regression. Then, a multivariable linear regression analysis was built to examine the association between urinary symptom severity and urinary neuropeptides, adjusting for potential confounders. A variable was retained in the model if it was associated with the primary outcome with $p<0.2$ in the univariable analysis. In order to assess for a medium effect size for a multiple regression model with four predictors at an alpha of 0.05, and a statistical power of 0.8, a sample size of 84 women was calculated. Statistical analyses were conducted using STATA 12.1 (Stata Corp., College Station, TX).

RESULTS

Of the total of 103 women enrolled into this study, 101 completed the clinical questionnaires. Eighteen did not return a urine specimen, and one subject did not return her urine specimen on ice. Thus, 84 women (83%) provided complete questionnaire and urinary biomarker data.

Of the 101 women with completed questionnaire data, 62 women (61.4%) were assigned to the bladder pain group (bladder pain on VAS score >3) and 39 (38.6%) were assigned to the no bladder pain group (VAS ≤ 3). There were no significant differences in age, race, BMI, menopausal status or surgical history between the pain and no pain groups (Table 1). Women in the bladder pain group had higher parity, were more likely to be diagnosed with BPS, and more likely to have received treatment with tricyclic antidepressants and bladder installations, as compared to the no pain group (Table 1).

Urinary Symptoms

There was no significant difference in the severity of urgency as measured by the Indevus Urgency scale as well as the ICSI between the bladder pain and no pain groups (Table 2). The total F-GUPI score including urinary symptom and quality of life domains were significantly higher (worse) in women with bladder pain (Table 2). Total ICSI and ICPI scores were also higher (worse) in women in the bladder pain group.

Neuropathic pain score, as measured by the painDETECT, was significantly higher (worse) for the bladder pain group than for the no pain group. Overall, 25.8% women in the bladder pain group met the criteria for the diagnosis of neuropathic pain (painDETECT score ≥ 19).

Urinary Biomarkers

In the cohort of 84 women with urgency who provided urine specimens, mean levels for all four neuropeptides were higher in the bladder pain group, however these differences did not reach significant levels (Table 2). NGF/Cr levels were significantly higher in women with urinary urgency and neuropathic pain as compared to women with urgency but no neuropathic pain (Table 3).

The relationship between important clinical variables and urinary neuropeptides is presented in Table 4. Bladder pain was significantly associated with elevated levels of VEGF and Opn on univariable analysis (Table 4). On multivariable analysis, after controlling for age, BMI, and urinary urgency, bladder pain remained significantly associated with elevated VEGF and Opn levels (β 0.04 pg/mg Cr, 95% CI 0.001-0.07, p=0.04 and β 0.34 ng/mg Cr, 95% CI 0.05-0.64, p=0.02, respectively). Neuropathic pain score was significantly associated with higher NGF levels, and this relationship remained significant after controlling for age, BMI, and urinary urgency (β 0.37 pg/mg Cr, 95% CI 0.04-0.69, p=0.03).

Urinary urgency was associated with higher NGF and BDNF levels, however, these relationships did not remain significant after controlling for age and BMI.

DISCUSSION

In a well characterized group of women with urinary urgency without incontinence, we demonstrate that patient reported bladder pain is significantly associated with the presence of a clinical biomarker of neuroinflammation (*i.e.* neuropathic pain) and inflammatory neuropeptides in the urine. Specifically, women with urinary urgency and bladder pain reported higher neuropathic pain scores than women without bladder pain. Additionally, bladder pain was independently associated with higher levels of urinary VEGF and Opn, while neuropathic pain was associated with higher levels of NGF. Severity of urinary urgency was associated with higher NGF and BDNF levels in the urine, but this relationship did not persist after controlling for the effect of age and BMI. Taken together, these findings provide evidence for the presence of neuroinflammatory processes in women with urinary urgency, particularly in those who report bladder pain.

Women with urinary urgency without incontinence present a diagnostic and therapeutic challenge for clinicians. Our study provides several clinically useful ways to phenotype these women and guide future treatment. First, our study demonstrates that patient reported bladder pain on a VAS is a clinically useful method of triaging women with urinary urgency because it is associated with worse urinary symptom and neuropathic pain scores, and elevated levels of two inflammatory neuropeptides, VEGF and Opn. Next, our study demonstrates that determining the type of pain in women with urinary urgency could provide additional clinical insights into the condition. In our study, 25% women with urgency and bladder pain reported neuropathic pain. The painDETECT questionnaire is not a diagnostic

tool for evaluation of neuropathic pain, but a score of ≥ 19 makes the presence of neuropathic pain highly likely. In a previous study, we demonstrated that neuropathic pain is associated with worse urinary and bowel symptoms, and worsened quality of life.[11] Since the painDETECT takes less than 5 minutes to complete, the instrument could be used to identify patients who may benefit from treatments that specifically target neuropathic pain such as amitriptyline, gabapentin and/or neuromodulation.

We also demonstrated that pain in women with urinary urgency is associated with the presence of several neuropeptides in the urine including NGF, VEGF, and Opn. These findings provide insights into underlying mechanisms in women with urinary urgency. NGF is a well-known marker of neuroinflammation, and prior studies have reported association of NGF with both bladder pain and urinary urgency.[12] Our finding that NGF is specifically associated with clinical neuropathic pain even after controlling for urgency, provides strong evidence for the role of ongoing neuroinflammation in women with urinary urgency. VEGF is a stimulator of angiogenesis, while Opn is a known marker of tissue inflammation.[13,23] VEGF and Opn expression have previously been demonstrated in bladder biopsies of animal and human studies.[24,25] Recent studies supported an increasing role of VEGF signaling in neurogenesis of urinary chronic pelvic pain syndrome (UCPPS).[26,27] Our study shows that urinary VEGF in also a potentially useful biomarker in women with urinary urgency. Our finding that bladder pain is associated with the expression of Opn in the urine of woman with urinary urgency is novel, and has not been previously reported. The presence of VEGF and Opn in the urine of women with bladder pain suggests that in addition to neuroinflammation, neovascularization, increased nerve sprouting, and covert tissue inflammation could be additional pathologic mechanisms in women with urinary urgency. VEGF and Opn are also potential urinary biomarkers that could be validated in future studies for phenotyping or measuring response to treatment for women with urinary urgency.

We did not find a robust relationship between urinary urgency and urinary neuropeptides. While some studies have reported that NGF levels are associated with both pain and urgency, others have failed to find such a relationship.[12,28,29] Differences in findings across studies may be related to the inclusion of subjects with incontinence and failure to control for potential confounding factors. We recruited a well characterized group of women with urgency and excluded women with incontinence using validated questionnaires. In this deeply phenotyped group of women with urgency and no incontinence, urgency was associated with elevated levels of NGF and BDNF on univariable analysis but these relationships did not persist after controlling for confounding factors. Our failure to find a relationship between urgency and urinary biomarkers may be related to a relatively small sample size. Alternatively, similar to other conditions such as fibromyalgia and herpetic neuralgia, neuroinflammation in the lower urinary tract may be more likely to manifest as pain rather than urgency. Larger studies will be required to determine if urgency is independently associated with inflammatory biomarkers after controlling for pain.

Strengths of our study include identification of a well-characterized cohort of women with urinary urgency and without incontinence. We purposefully did not classify women as overactive bladder or BPS, as we wanted to investigate the relationship between severity of lower urinary tract symptoms and urinary biomarker levels. We measured clinical

biomarkers of neuroinflammation using validated questionnaires and several established urinary neuropeptides that measure a variety of inflammatory processes. Finally, we controlled for the confounding effect of a number of variables that are known to cause variance in biomarker levels including age, obesity (BMI) and urgency. Our study is limited by its relatively small sample size, and the absence of a healthy control group. These limitations may have prevented us from finding a relationship between urinary urgency and biomarker levels.

In conclusion, our study provides clinical evidence of ongoing neuroinflammation and its important contributing role to bladder pain in women with urinary urgency. Our study also demonstrates clinically useful ways of measuring neuroinflammation in women with urinary urgency, and identifies several key urinary biomarkers (*i.e.* VEGF, Opn, and NGF) that could guide phenotyping and response to treatment.

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Table 1.

Demographic data of 101 women with urinary urgency

	No Bladder Pain (VAS ≤3) N=39	Bladder Pain (VAS>3) N=62	P-value
Age (years)	48.9 +/−16.9	44.6 +/−15.1	0.18[a]
Race (N, %)			
Caucasian	32 (82.1)	55 (88.7)	0.64[b]
African American	4 (10.3)	5 (8.1)	
Other	2 (5.1)	2 (3.2)	
BMI (kg/m2)	25.6 +/−6.9	24.4 +/−4.9	0.32[a]
Parity (median, range)	2 (0-9)	0 (0-5)	**0.01**[c]
Postmenopausal (N, %)	20 (51.3)	26 (41.9)	0.68[b]
Current Treatment(s) (N, %)			
Anticholinergics	2 (5.1)	2 (3.2)	0.63[d]
Analgesics	8 (20.5)	26 (41.9)	0.05[b]
Pentosan Polysulfate	7 (17.9)	10 (16.1)	0.79[b]
TCAs	1 (2.6)	13 (21.0)	**0.02**[d]
Antihistamines	6 (15.4)	19 (30.6)	0.08[b]
Gabapentin	3 (7.7)	6 (9.7)	0.54[d]
Bladder Instillations	0 (0.0)	7 (11.3)	**0.03**[d]
Botox Injections	0 (0.0)	1 (1.6)	0.99[d]
Sacral Neuromodulation	0 (0.0)	0 (0.0)	
Past Surgical History (N, %)			
Hysterectomy	7 (17.9)	11 (17.7)	0.99[d]
Incontinence Procedure	2 (5.1)	2 (3.2)	0.63[d]
Oophorectomy	5 (12.8)	6 (9.7)	0.74[d]
Past Medical History (N, %)			
Bladder Pain Syndrome	5 (12.8)	30 (48.4)	**<0.001**[d]
Vulvodynia	0 (0.0)	6 (9.7)	0.08[d]
Pelvic Floor Dysfunction	1 (2.6)	7 (11.3)	0.25[d]
Irritable Bowel Syndrome	9 (23.1)	18 (29.0)	0.65[b]
Fibromyalgia	5 (12.8)	7 (11.3)	0.76[d]
Chronic Fatigue Syndrome	3 (7.7)	5 (8.1)	0.99[d]
Migraine	6 (15.4)	14 (22.6)	0.47[b]

	No Bladder Pain (VAS ≤3) N=39	**Bladder Pain (VAS>3) N=62**	**P-value**
Anxiety	10 (25.6)	20 (32.3)	0.54[b]
Depression	4 (10.3)	16 (25.8)	0.08[d]
Diabetes	3 (7.7)	3 (4.8)	0.67[d]

[a] Independent t-test

[b] Chi2 test

[c] Equality of medians

[d] Fisher exact test

VAS= visual analog scale

Table 2.

Baseline urinary symptoms and urinary neuropeptide levels of 101 women with urinary urgency

	No Bladder Pain (VAS ≤3) N=39	**Bladder Pain (VAS>3) N=62**	**P-value**
Clinical Symptoms			
Indevus Urgency Severity Scale			
Mild	18 (46.2)	22 (34.4)	0.23[a]
Moderate	19 (48.7)	27 (42.2)	
Severe	2 (5.1)	15 (23.4)	
Female Genitourinary Pain Index (F-GUPI) Total score	12.3 +/−6.1	28.1 +/−6.9	**<0.001**[b]
Urinary Subscale	3.5 +/−2.4	5.0 +/−3.1	**0.01**[b]
Quality of Life Subscale	4.8 +/−2.2	8.1 +/−3.0	**<0.001**[b]
Interstitial Cystitis Symptom Index (ICSI) Total Score	6.7 +/−3.4	9.8 +/−4.9	**<0.001**[b]
Urgency (ICSI, Question 1)	1.2 +/−1.2	1.8 +/−1.5	0.05[b]
Frequency (ICSI, Question 2)	2.5 +/−1.5	3.1 +/−1.5	**0.03**[b]
Nocturia (ICSI, Question 3)	2.5 +/−1.9	3.0 +/−1.9	0.15[b]
Pain/burning in bladder (ICSI, Question 4)	0.51 +/−0.8	2.0 +/−1.9	**<0.001**[b]
Interstitial Cystitis Problem Index (ICPI) Total Score	4.9 +/−3.2	8.7 +/− 4.2	**<0.001**[b]
PainDETECT Total score	5.1 +/−4.8	13.3 +/−8.6	**<0.001**[b]
Neuropathic Pain (PainDETECT score ≥19)	0 (0.0)	16 (25.8)	**0.001**[a]
Urinary Neuropeptides			
NGF (pg/mg Cr)	0.21 +/−0.40	0.30 +/−0.65	0.53 [b]
BDNF (pg/mg Cr)	2.84 +/−3.63	3.15 +/−3.82	0.71 [b]
VEGF (pg/mg Cr)	0.26 +/−0.36	0.39 +/−0.51	0.22 [b]
Osteopontin (ng/mg Cr)	2.24 +/−2.22	3.75 +/−3.72	0.07 [b]

[a] Chi2 test

[b] Independent t-test

VAS= visual analog scale

Table 3.

Relationship between neuropathic pain and urinary neuropeptide levels in 84 women with urinary urgency

Urinary Neuropeptide	No Neuropathic Pain (painDETECT ≤13) N = 56	Neuropathic Pain (painDETECT ≥19) N = 16	P-value
NGF (pg/mg Cr)	0.20 +/−0.40	0.62 +/−1.03	**0.01**[a]
BDNF (pg/mg Cr)	2.95 +/−3.60	3.53 +/−4.60	0.61[a]
VEGF (pg/mg Cr)	0.31 +/−0.40	0.41 +/−0.59	0.42[a]
Osteopontin (ng/mg Cr)	2.89 +/−3.17	4.43 +/−5.78	0.16[a]

[a]Independent t-test

Table 4.

Relationship of selected clinical variables with urinary neuropeptide levels in 84 women with urinary urgency: Univariable analysis.

	NGF/Cr		BDNF/Cr		VEGF/Cr		Osteopontin/Cr	
	Coefficient 95% CI	**p-value**	**Coefficient 95% CI**	**p-value**	**Coefficient 95% CI**	**p-value**	**Coefficient 95% CI**	**p-value**
Age	0.00 (−0.01-0.01)	0.89	**0.08 (0.03-0.12)**	**<0.01**	0.00 (−0.01-0.01)	0.21	0.02 (−0.03-0.07)	0.45
BMI	−0.01 (−0.03-0.01)	0.37	0.10 (−0.03-0.24)	0.14	−0.01 (−0.03-0.00)	0.15	−0.06 (−0.20-0.08)	0.42
Urgency[a]	**0.30 (0.06-0.55)**	**0.02**	**1.63 (0.002-3.26)**	**0.04**	0.09 (−0.12-0.29)	0.39	0.62 (−1.02, 2.27)	0.45
Bladder Pain[b]	0.04 (−0.01-0.08)	0.09	0.08 (−0.21-0.37)	0.57	**0.03 (0.002-0.07)**	**0.04**	**0.32 (0.04-0.59)**	**0.03**
Neuropathic pain[c]	**0.42 (0.10-0.74)**	**0.01**	0.58 (−1.68-2.85)	0.61	0.10 (−0.15-0.35)	0.42	1.54 (−0.62-3.70)	0.16

[a] Indevus urgency scale

[b] Interstitial Cystitis Symptom Index (ICSI, Question 4)

[c] painDETECT Total Score