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Evidence of Bladder Oversensitivity in the Absence of an Infection in Premenopausal Women with a History of Recurrent Urinary Tract Infections

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Abstract

OBJECTIVE—

- To compare the mean voided volume and bladder sensation during filling cystometry in women with a history of recurrent UTI and controls.

PATIENTS AND METHODS—

- This was a case- control study including adult women seen in the urogynecology clinic.
- Cases were 49 women with at least three documented positive urine cultures $>10^5$ colonies/ml in the previous twelve months and no active infection at the time of data collection.
- Controls were 53 women with stress urinary incontinence and no history of recurrent urinary tract infection or co-existent urge urinary incontinence.
- We compared bladder diary variables and filling cystometry data in the absence of an active infection.

RESULTS—

- There was no significant difference in the median age, parity and BMI of women with a history of recurrent UTI and controls.
- Median number of voids per day and median number of voids per liter of fluid intake was significantly greater in women with recurrent UTI than controls (12 vs. 7 voids/day and 6 vs. 4 voids/L, $P = .005$ and $.004$ respectively).

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- The median average voided volume was significantly lower in women with recurrent UTI than controls (155 vs. 195 mL, $P = .008$).
- On filling cystometry, median volumes of strong desire to void and maximum cystometric capacity were significantly lower in women with recurrent UTI than controls (all $p < .05$).

CONCLUSION—

- In the absence of an infection, premenopausal women with a history of recurrent UTI have significantly greater urinary frequency, lower average voided volume and a lower threshold of bladder sensitivity than controls.

Keywords

bladder sensation; urgency; urinary tract infections; bladder diary; cystometry

INTRODUCTION

Urinary tract infections have been implicated in the etiology of interstitial cystitis/painful bladder syndrome (IC/PBS). (1-3) Prior studies have described symptoms and laboratory tests suggestive of urinary tract infection at the onset of IC/PBS (1,2) as well as a significant history of childhood recurrent urinary tract infections.(4) However, the mechanism by which recurrent urinary tract infections contributes to the development of IC/PBS is not clear.

Prior studies suggest that oversensitivity of the presumed site of pain generation is a possible mechanism for the development of chronic pain syndromes such as IC/PBS, (5) irritable bowel syndrome, (6) fibromyalgia (7) and vulvodynia (8). In a study examining tolerance to bladder filling on filling cystometry, women with interstitial cystitis had significantly lower volumes and more pain with bladder filling than healthy controls.(5) The joint report (9) of the International Urogynecologic Association and International Continence Society has defined bladder oversensitivity as symptoms of frequency and/or nocturia, reduced average voided volume on the bladder diary and increased perceived bladder sensation during filling cystometry with no abnormal increase in detrusor pressure and in the absence of known or suspected bladder infection.

The aim of the present study is to compare the average voided volume and bladder sensation during filling cystometry in women with recurrent urinary tract infections and controls. Our hypothesis is that women with recurrent urinary tract infections have evidence of increased bladder sensation than women without a history of recurrent UTI.

MATERIALS AND METHODS

Following IRB approval by the University of Pennsylvania, a retrospective case- control study was performed. Cases were women with recurrent urinary tract infections. Recurrent urinary tract infection was defined as presence of lower urinary tract symptoms (urgency, frequency or dysuria) and three documented positive urine cultures $>10^5$ colonies/ml on a voided urine specimen in the previous twelve months. (9) Controls were women with stress

urinary incontinence, and no history of recurrent infections and absence of urge incontinence symptoms on a validated questionnaire, the Urogenital Distress Inventory-6.

The electronic medical records of consecutive women in age group 18 to 40 years attending the Urogynecology clinic of the University of Pennsylvania between December 2009 and September 2010 were reviewed. Women with a final clinical diagnosis of recurrent UTI or stress urinary incontinence, as defined above, were identified. We limited inclusion to women in the age group 18 to 40 years to avoid the confounding effect of aging and menopause on bladder sensitivity. Additional inclusion criteria were availability of bladder diary and filling cystometry data, negative office cystoscopy for cases, negative dipstick urine for cases preceding bladder diary and filling cystometry testing, and one documented negative urine culture for controls.

We excluded women with conditions known to be associated with bladder hypersensitivity. These included age greater than 40 years, known diagnosis of interstitial cystitis/painful bladder syndrome, urge urinary incontinence (as determined by a positive response to the urge incontinence question on the Urogenital Distress Inventory-6), (10) pelvic organ prolapse stage 2 or greater on clinical examination based on pelvic organ prolapse quantification system (11), neurologic disorder known to affect the lower urinary tract, previous hysterectomy or surgery for incontinence or pelvic organ prolapse, current or recent vaginal pessary use, other known urinary tract pathologies such as calculus and urethral diverticulum, history of pelvic cancer or radiation to the pelvis and diabetes mellitus.

Data of validated questionnaires (O'Leary-Sant Interstitial Cystitis Symptom and Problem Index), (12) pelvic organ prolapse stage, bladder diary, filling cystometry, and cystoscopy were extracted from the medical records.

Bladder diary

Women had collected bladder diary data using a log and a container in the 2 days immediately preceding the filling cystometry. Since a negative urine dipstick was documented on the day of filling cystometry, this ensured that cases had not maintained the bladder diary during an episode of infection. Daily values were calculated from the 2-day diary by averaging data over two days. Bladder diary data was described using standard definitions for the following variables: the number of daytime and night-time voids, mean voided volume, and maximum voided volume. (9) The number of voids per liter of fluid intake, previously reported as a stable measure of urinary frequency, (13) was also calculated.

Filling Cystometry

In this study, we only included subjects for whom filling cystometry data was available. Cystometry had been performed in women with recurrent UTI if they had complained of urinary symptoms of uncertain diagnosis e.g. persistent urinary frequency and/or nocturia in the absence of a recent (less than 6 weeks) urinary tract infection. The purpose of the filling cystometry in women with recurrent UTI was to rule out presence of detrusor overactivity.

Negative urine dipstick had been documented in all women prior to filling cystometry. Filling cystometry was performed in the sitting up right position using air-charged (T-Doc) catheter and Duet® Logic G/2 (Medtronic Inc., Minneapolis, MN). Following spontaneous voiding, postvoid residual volume was measured and the bladder was filled at 50 ml/minute using warm sterile water. Intra-abdominal pressure was measured using a rectal catheter. The first desire to void (volume of filling associated with the first need to urinate but voiding can be delayed if necessary), strong desire to void (persistent desire to pass urine without fear of leakage) and maximum tolerated volume (filling volume at which the patient feels she can no longer delay micturition), and change in detrusor pressure (from the start of bladder filling to maximum cystometric capacity) were recorded. All terminology and methods are in accordance with International Continence Society nomenclature (9) unless specified otherwise.

Data were analyzed using SAS. Data was described using mean, median or percentages. We compared urinary symptom and quality of life scores, bladder diary and filling cystometry data between cases and controls using the Wilcoxon rank-sum test for continuous data and the chi-square test for categorical data. We examined the relationship between maximum voided volume and maximum cystometric capacity using the Pearson correlation coefficient. A .05 significance level was used for all statistical tests.

We based our sample size calculation on previously reported mean voided volume of 220 ± 84 mL on the bladder diary in women with stress urinary incontinence. (14) This is similar to the mean voided volume in asymptomatic women. (15) Based on this data, we estimated that we needed 50 women in each group at an alpha of 0.05 and power of 90% to detect a difference of 25% in mean voided volume between women with recurrent urinary tract infection and controls.

RESULTS

We screened electronic records of 147 women with recurrent UTI and stress urinary incontinence in the age group 18-40 years. We identified 49 women with recurrent UTI and 53 women with stress urinary incontinence meeting the eligibility criteria of the study. Twelve women (5 with recurrent UTI and 7 with stress incontinence) were excluded due to missing bladder diary or cystometry data.

There was no significant difference in the median age, parity or BMI of the two groups (Table 1). Eight six percent of the women were Caucasian. Three women in the recurrent UTI group (6%) had undergone prior abdominal surgery (tubal ligation, appendectomy or ovarian cystectomy) as compared to 4 (7.5%) in the control group. The median interval between the last documented UTI and the voiding diary was 59 days (range 43 to 85 days) and the median interval between the last documented UTI and filling cystometry was 63 days (range 46 to 91 days).

Urogenital Distress Inventory-6 (UDI-6)

Possible range for total scores for the UDI-6 is 0-100. The median total UDI-6 score was similar for cases and controls (Table 1). Levels of bother on the single stress incontinence

item of the UDI-6 are rated on a scale of 0-4. In the case group, only 5% women reported bother of 3 or 4 on the stress item of the UDI-6 while 85% women in the control group reported the same degree of bother.

Interstitial Cystitis Symptom and Problem Index score—The range of possible scores on the Symptom and Problem Index are 0-20 and 0-16 respectively. Though the median total Interstitial Cystitis Symptom Index score was significantly higher in women with recurrent UTI than controls, the total Interstitial Cystitis Symptom Index scores were low in both groups (Table 1). The median total Interstitial Cystitis Problem Index scores were also low for both groups and there was no significant difference between cases and controls. Pelvic floor muscle tenderness was recorded in only one woman in the case group.

Bladder diary data—Median number of total and daytime voids per day was significantly higher in women with recurrent UTI than controls (Table 2). The median number of night time voids in the recurrent UTI group was greater than controls but did not reach significant levels. Median total fluid intake per day was significantly higher in cases than controls. Median number of voids per liter of fluid intake was also significantly higher in women with recurrent UTI than controls. Average voided volume was significantly lower in women with recurrent UTI than controls though there was no significant difference in maximum voided volume between the two groups.

Filling cystometry data—On filling cystometry, the first desire to void was lower in women with recurrent UTI than controls but did not reach significant levels (Table 3). Strong desire to void and maximum cystometric capacity were significantly lower in women with recurrent UTI than controls. There was no change in detrusor pressure from the start of filling to cystometric capacity in cases or controls and detrusor overactivity was not demonstrable in any case or control. Stress urinary incontinence was demonstrated during filling cystometry in 80% control women and in 2 cases. The correlation of maximum cystometric capacity with maximum voided volume on the bladder diary was 0.65 ($p < .01$).

DISCUSSION

The most important finding of this study is that women with recurrent urinary tract infections have greater urinary frequency and increased perceived bladder sensation in the absence of an active infection compared to control women. The significantly greater total number of daily voids on the bladder diary in women with recurrent UTI cannot be explained by their larger fluid intake alone nor selection bias in obtaining bladder diaries and urodynamics only in recurrent UTI patients who complained of increased urinary frequency. On the bladder diary, women with recurrent UTI had significantly smaller average voided volume and significantly greater number of voids per liter of fluid intake than controls. These bladder diary findings are supported by filling cystometry data that showed early first desire to void and significantly earlier strong desire to void and smaller maximum cystometric capacity in women with recurrent UTI than controls. The increased bladder sensation on filling cystometry was noted in the absence of any rise in detrusor pressure and in the absence of active urinary tract infection as documented by a negative urine dipstick immediately prior to the cystometry. Therefore, based on the criteria

established by the International Urogynecological Association and the International Continence Society, (9) women with recurrent UTI have increased bladder sensation or bladder oversensitivity as compared to controls.

In an ideal case-control study exploring the hypothesis that women with recurrent UTI have bladder oversensitivity, cases should be women with recurrent UTI and controls should be healthy women with no bladder disorders. Given the difficulty of performing invasive tests such as filling cystometry in healthy women, using our electronic medical records and careful inclusion and exclusion criteria, we identified women with 'pure' stress urinary incontinence to serve as controls. Diokno et al have previously reported that the mean maximum cystometric capacity in women with stress urinary incontinence (493 ml, range 120-1245 ml) is similar to that of healthy controls (531 ml, range 300-780 ml) (16). The number of daytime voids in the control group of our study (median 6.5, range 5-9) is identical to values previously reported in asymptomatic women (6.5, range 4-8) (15). These findings suggest that the presence of stress incontinence in the control group did not have any significant effect on micturition variables and bladder function. Therefore, our selection of women with stress urinary incontinence as controls, though not ideal, likely does not affect the validity of our findings.

Since women with recurrent UTI had bladder oversensitivity, we considered the possibility that these women had co-existent interstitial cystitis/painful bladder syndrome (IC/PBS). As per the most recent recommendations, (17) the diagnosis of IC/PBS is based on clinical criteria (painful symptoms that are perceived to originate from the bladder and associated with frequency or urgency). A clinical diagnosis of IC/PBS was not made by the treating clinicians (first and second authors) for women in the case group. In a previous study, an Interstitial Cystitis Symptom Index score of 5 or greater had 95% sensitivity and 93% negative predictive value for the diagnosis of interstitial cystitis. (18) The median Interstitial Cystitis Symptom Index score for women with recurrent UTI in this study was 4 (range 0-5) and only 4% women had a score of 5. Additionally the Interstitial Cystitis Problem Index score was low for cases. These findings suggest that women in our case group likely did not have co-existent interstitial cystitis.

The underlying cause of bladder oversensitivity in women with recurrent UTI is not clear, though a neurogenic mechanism seems likely. Visceral pain is transmitted centrally for processing via the spinothalamic tract via "silent," unmyelinated C-fibers. (19) C-fibers are abundant in the bladder (20) and may undergo electrophysiologic changes that result in the perpetuation of an acute insult into chronic symptoms. (19) During an acute episode of urinary tract infection, inflammation of bladder mucosa and underlying nerves result in symptoms of urgency and frequency. (20) It is conceivable that in some women with recurrent UTI, repeated inflammation of the bladder and its mucosa gradually result in hypersensitivity of the nerves of the bladder. Therefore an initial pattern of episodes of urinary tract infection and associated symptoms that responds promptly to antibiotics is gradually transformed into a more chronic pattern of persistent symptoms even in the absence of bacteriuria.

Using three different diagnostic methods (urinary nitrites, urine culture and urinary symptoms), Warren et al have shown that a proportion of patients with IC/PBS have an episode of UTI at the onset of disease (1). Our case-control study suggests that women with recurrent UTI have bladder oversensitivity. Ness et al have reported that women with interstitial cystitis have bladder oversensitivity and decreased threshold of pain stimulation. (5) Prospective studies will be required to determine if bladder oversensitivity can lead to the development of interstitial cystitis in women with recurrent UTI.

Limitations of our study are that though we used validated questionnaires, women may have reported symptoms only from episodes of infection. Misclassification bias should also be considered. Women in the control group did not undergo cystoscopy to rule out hypersensitivity bladder disorders. However, the mean voided volume in women with stress urinary incontinence (195 ml) in our study was similar to reported values (190 mL (20) and 200 mL (15)) in healthy controls. The absence of detrusor hyperactivity on filling cystometry in both groups makes the presence of overactive bladder unlikely in these women. Finally, misclassification of hypersensitivity disorders in the control group would bias results towards the null hypothesis and therefore was likely not present.

Our finding that women with recurrent UTI have bladder oversensitivity and urinary frequency even in the absence of an acute infection has useful clinical implications. Given the lack of effective therapies for bladder oversensitivity, it is important that women with recurrent UTI undergo prompt evaluation and treatment of episodes of infection to prevent the development of bladder oversensitivity. Our findings are limited to young women in the age group of 18-40 years. Larger prospective studies involving broad range of age groups will be required to determine if women with recurrent UTI are at risk for developing interstitial cystitis.

CONCLUSIONS

Even in the absence of infection, premenopausal women with recurrent urinary tract infections have bladder oversensitivity as compared to control women.

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Ethics: The study was approved by the University of Pennsylvania Institutional Review Board, Office of Human Research.

REFERENCES

1. Warren JW, Brown V, Jacobs S, et al. Urinary tract infection and inflammation at onset of interstitial cystitis/painful bladder syndrome. *Urology*. 2008; 71:1085–1090. [PubMed: 18538691]
2. Warren JW, Diggs C, Brown V, et al. Dysuria at onset of interstitial cystitis/painful bladder syndrome in women. *Urology*. 2006; 68:477–481. [PubMed: 16979747]
3. Burkhard FC, Blick N, Hochreiter WW, et al. Urinary urgency and frequency, and chronic urethral and/or pelvic pain in females. Can doxycycline help? *J Urol*. 2004; 172:232–235. [PubMed: 15201781]

4. Peters KM, Killinger KA, Ibrahim IA. Childhood symptoms and events in women with interstitial cystitis/painful bladder syndrome. *Urology*. 2009; 73:258–262. [PubMed: 19036420]
5. Ness TJ, Powell-Boone T, Cannon R, et al. Psychophysical evidence of hypersensitivity in subjects with interstitial cystitis. *J Urol*. 2005; 173:1983–1987. [PubMed: 15879797]
6. Verne GN, Robinson ME, Price DD. Hypersensitivity to visceral and cutaneous pain in the irritable bowel syndrome. *Pain*. 2001; 93:7–14. [PubMed: 11406333]
7. Gracely RH, Grant MA, Giesecke T. Evoked pain measures in fibromyalgia. *Best Pract Res Clin Rheumatol*. 2003; 17:593–609. [PubMed: 12849714]
8. Bohm-Starke N, Hilliges M, Brodda-Jansen G, et al. Psychophysical evidence of nociceptor sensitization in vulvar vestibulitis syndrome. *Pain*. 2001; 94:177–183. [PubMed: 11690731]
9. Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Neurourol Urodyn*. 2010; 29:4–20. [PubMed: 19941278]
10. Shumaker SA, Wyman JF, Uebersax JS, et al. Health-related quality of life measures for women with urinary incontinence: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. Continence Program in Women (CPW) Research Group. *Qual Life Res*. 1994; 3:291–306. [PubMed: 7841963]
11. Abrams P, Andersson KE, Birder L, et al. Fourth International Consultation on Incontinence Recommendations of the International Scientific Committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse, and fecal incontinence. *Neurourol Urodyn*. 2010; 29:213–240. [PubMed: 20025020]
12. O'Leary MP, Sant GR, Fowler FJ Jr, et al. The interstitial cystitis symptom index and problem index. *Urology*. 1997; 49:58–63. [PubMed: 9146003]
13. Fitzgerald MP, Brubaker L. Variability of 24-hour voiding diary variables among asymptomatic women. *J Urol*. 2003; 169:207–209. [PubMed: 12478137]
14. Fink D, Perucchini D, Schaer GN, et al. The role of the frequency-volume chart in the differential diagnosis of female urinary incontinence. *Acta Obstet Gynecol Scand*. 1999; 78:254–257. [PubMed: 10078589]
15. Fitzgerald MP, Stablein U, Brubaker L. Urinary habits among asymptomatic women. *Am J Obstet Gynecol*. 2002; 187:1384–1388. [PubMed: 12439535]
16. Diokno AC, Wells TJ, Brink CA. Comparison of self-reported voided volume with cystometric bladder capacity. *J Urol*. 1987; 137:698–700. [PubMed: 3560325]
17. Hanno P, Lin A, Nordling J, et al. Bladder Pain Syndrome Committee of the International Consultation on Incontinence. *Neurourol Urodyn*. 2010; 29:191–198. [PubMed: 20025029]
18. Clemons JL, Arya LA, Myers DL. Diagnosing interstitial cystitis in women with chronic pelvic pain. *Obstet Gynecol*. 2002; 100:337–341. [PubMed: 12151160]
19. Butrick CW. Interstitial cystitis and chronic pelvic pain: new insights in neuropathology, diagnosis, and treatment. *Clin Obstet Gynecol*. 2003; 46:811–23. [PubMed: 14595223]
20. Cervero F. Sensory innervation of the viscera: peripheral basis of visceral pain. *Physiol Rev*. 1994; 74:95–138. [PubMed: 8295936]

TABLE 1

Demographic data of women with recurrent urinary tract infections and controls

	Recurrent UTI N = 49 Median (range)	Controls N = 53 Median (range)	P value *
Age (years)	28 (18-37)	29 (18-40)	0.8
Parity	1 (0-2)	1 (0-3)	0.7
BMI (kg/m ²)	25 (23-29)	25.6 (23-30)	0.6
Total Interstitial Cystitis Symptom Index score ¹	4 (1-5)	0.5 (0-3)	0.013
Total Interstitial Cystitis Problem Index score ²	2 (1-4)	1 (0-1)	0.3
Total Urogenital Distress Inventory-6 score ³	20 (12-30)	16 (10- 25)	0.4

* Wilcoxon rank-sum test

¹
range 0-20²
range 0-16³
range 0-100

TABLE 2

Bladder diary values for women with recurrent urinary tract infections and controls

	Recurrent UTI N = 49 Median (range)	Controls N= 53 Median (range)	P value*
Number of voids in 24 hours, <i>n</i>	12 (9-18)	7 (5-10)	.005
Number of daytime voids, <i>n</i>	11 (9-14)	6.5 (5-9)	.002
Total night-time voids, <i>n</i>	1 (0- 3)	0.5 (0-1)	.07
24-hr fluid intake (mL)	2165 (1535-3355)	1840 (950- 3280)	.08
24-hr urine volume (mL)	1860 (1120-2739)	1350 (865-2570)	.08
Voids per liter of fluid intake, <i>n</i>	6 (4-6)	3.8 (3.1-4.8)	.004
Maximum voided volume (mL)	385 (300-465)	490 (350- 570)	.3
Average voided volume (mL)	155 (150-220)	195 (170-275)	.008

* Wilcoxon rank-sum test

TABLE 3

Bladder sensation during filling cystometry and postvoid residual volume in women with recurrent UTI and controls

	Recurrent UTI N = 41 Median (range)	Controls N = 41 (Median (range))	P value*
First desire to void (mL)	125 (50-250)	175 (60-264)	0.06
Strong desire to void (mL)	193 (75-350)	289 (255-359)	0.03
Maximum cystometric capacity (mL)	275 (175-359)	392 (166-625)	0.004
Postvoid residual volume (mL)	12 (0-19)	15 (0-22)	0.8

* Wilcoxon rank-sum test