ELSEVIER

INCREASED PREVALENCE OF INTERSTITIAL CYSTITIS: PREVIOUSLY UNRECOGNIZED UROLOGIC AND GYNECOLOGIC CASES IDENTIFIED USING A NEW SYMPTOM QUESTIONNAIRE AND INTRAVESICAL POTASSIUM SENSITIVITY

C. LOWELL PARSONS, JEFFREY DELL, EDWARD J. STANFORD, MICHAEL BULLEN, BRUCE S. KAHN, TRACY WAXELL, AND JAMES A. KOZIOL

ABSTRACT

Objectives. Most individuals with interstitial cystitis (IC) have both pelvic pain and urinary urgency/frequency, and many have dyspareunia. Existing questionnaires designed to assess bladder-origin pelvic pain (IC) give little attention to pelvic pain or dyspareunia, however. On the basis of our clinical experience with more than 5000 patients with IC, we have designed a pelvic pain and urgency/frequency (PUF) symptom scale that gives balanced attention to urinary urgency/frequency, pelvic pain, and symptoms associated with sexual intercourse.

Methods. We used the intravesical potassium sensitivity test (PST) to validate the PUF scale in urologic patients suspected of having IC, gynecologic patients with pelvic pain, controls, and women attending lectures given by one of us (C.L.P.). Positive potassium sensitivity is known to be associated with a bladder epithelial dysfunction present in most individuals with IC.

Results. The PST was positive in 74% of patients with a PUF score of 10 to 14, 76% of those scoring 15 to 19, and 91% of those scoring 20 or higher. All controls' PUF scores were less than 3, and the rate of positive PST in controls was 0%. The PUF scores in women screened at lectures suggested that 1 in 4.5 women have IC.

Conclusions. High PUF scores appear to correlate directly with a higher likelihood of positive PST in both urologic patients suspected of having IC and gynecologic patients with pelvic pain. The PUF appears to be a valid tool for detecting IC in these two populations, as well as in the general population. Use of the PUF alone may prove to be an accurate method for detecting IC. The IC prevalence may be as high as 1 in 4.5 women. UROLOGY **60:** 573–578, 2002. © 2002, Elsevier Science Inc.

Interstitial cystitis (IC), a clinical syndrome of urinary urgency/frequency and/or pelvic pain, may be much more common than traditionally believed. The results of recent studies suggest there are previously unsuspected numbers of patients with IC among gynecologic patients with pelvic pain[1] and older men with lower urinary tract symptoms.[2] For the diagnosis of the disease, acceptance of the intravesical potassium sensitivity test (PST), which detects the bladder epithelial abnormality present in most individuals with IC, is growing.[3–7] In more than 1500 PSTs performed to date at a variety of sites and reported in published studies, approximately 80% of patients with IC have tested positive.[3,4,8–17] The PST appears to be a highly specific test that can enable the clinician to recognize a bladder-origin problem in symptomatic patients with IC.

Although the PST may be a valid indicator of bladder epithelial dysfunction, and a positive PST may be considered diagnostic of IC in appropriate clinical situations, we believe that the diagnosis of

This study was supported by the Urological Research and Education Foundation.

From the Division of Urology, University of California, San Diego, Medical Center, San Diego, California; Private Practice of Reconstructive Pelvic Surgery in Urogynecology, Knoxville, Tennessee; St. Mary's/Good Samaritan Medical Centers, Centralia, Illinois; Department of Obstetrics and Gynecology, East Tennessee Baptist Hospital, Knoxville, Tennessee; Division of Gynecology, Scripps Clinic and Research Foundation, La Jolla, California; Abelson-Taylor, Inc., Chicago, Illinois; Division of Biomathematics, Department of Molecular and Experimental Medicine, Scripps Research Institute, La Jolla, California

Reprint requests: C. Lowell Parsons, M.D., c/o Janell Poehling, Division of Urology (8897), University of California, San Diego, Medical Center, 200 West Arbor Drive, San Diego, CA 92103-8897

Submitted: February 11, 2002, accepted (with revisions): May 13, 2002

0090-4295/02/$22.00
PII S0090-4295(02)01829-0

IC for the most part can be made on the basis of the symptoms alone if all the patient's IC-related symptoms are detected and quantified. Several factors make it difficult to recognize an individual's symptoms as being caused by IC. The pain of IC originates in the bladder, but it may be perceived in one or more of a variety of locations in the pelvis, from the lower abdomen or lower back to the vaginal, labial, urethral, and inguinal areas.[3] Women with IC often have dyspareunia and/or symptom flares after sexual intercourse, as well as a symptom flare the week before the start of the menstrual cycle.[3,18–22] The nature of these symptoms may lead a woman to a gynecologist, whose pelvic pain paradigm is likely to point toward a gynecologic diagnosis and away from IC.

In 1997, O'Leary and coworkers[23] reported the validation of two tools for quantitating the symptoms of IC, the Interstitial Cystitis Symptom Index and Interstitial Cystitis Problem Index.[23] The Interstitial Cystitis Symptom Index and Interstitial Cystitis Problem Index are useful in measuring urinary frequency and bladder discomfort, but they do not address dyspareunia or pelvic pain other than bladder pain.

On the basis of our experience evaluating and treating more than 5000 patients with IC during the past two decades, we have developed a new IC symptom questionnaire, the pelvic pain and urgency/frequency (PUF) patient symptom scale (Fig. 1). The PUF scale addresses pelvic pain, including symptoms associated with sexual intercourse, as well as urinary urgency/frequency. It quantitates both the severity of the IC symptoms and the extent to which the patient is troubled by each symptom. The PUF scale is designed to be self-administered and requires approximately 5 minutes to complete.

To validate the PUF scale, we administered both the PST and the PUF scale to urologic patients with IC, gynecologic patients with pelvic pain, and normal women. To test the PUF scale as a survey instrument, we administered it to a sample of women from the general population. We then assessed the PUF scale scores as predictors of the outcome of the PST.

MATERIAL AND METHODS

Administration of PUF Scale and PST in Three Test Groups and Controls

In the first part of the study, the subjects in the three test groups and a control group completed the PUF scale (Fig. 1) and then underwent the PST.

The urology IC-clinic group consisted of consecutive urology clinic patients at the University of California, San Diego, Medical Center (UCSD) with a clinical diagnosis of IC according to the symptom complex as defined by the National Institutes of Health criteria with the exception that most patients did not undergo urodynamic studies. All were required to have urgency/frequency issues and/or pelvic pain and to void more than eight times in a 24-hour period, with symptoms continuous for at least 9 months.

The urology IC-other group consisted of urologic patients at 12 other centers in the United States who were diagnosed with IC as described above for the group at UCSD.

The gynecologic pelvic pain group consisted of patients who had presented with pelvic pain at four United States gynecologic sites.

The control group consisted of patients without IC symptoms who were seen at UCSD or at one of the gynecologic sites. The controls had no urologic symptoms, no pelvic pain, and no pain or symptoms associated with sexual intercourse and reported voiding no more than seven times in a 24-hour period.

The PST was performed as reported previously.[1]

Administration of PUF Scale in a Random Survey of Women

In the second part of the study, women from the general population were randomly surveyed using the PUF scale. The women screened were all healthcare professionals or their spouses attending IC presentations given by one of us (C.L.P.) in the United States.

Statistical Analysis

The reproducibility of the PUF scale was assessed in 32 randomly selected women presenting to the urology clinic at UCSD: each of these women completed the PUF scale initially and again from 5 to 7 days later during a repeat visit. Agreement between the two scores was assessed using a weighted kappa statistic,[24] with a jackknife estimate of standard error. Computations were performed in Stata, version 5.0.[25] The kappa statistic measure of agreement is scaled from 0.0 (chance agreement) to 1.0 (perfect agreement), with values greater than 0.6 indicative of substantial agreement.[26]

The accuracy of a diagnostic or prognostic test can be summarized by the test sensitivity or true-positive rate and test specificity or true-negative rate. In the present setting, we used the PST as the reference standard and studied the accuracy of the PUF questionnaire for predicting the PST outcome by applying both tests to the same sample of patients. Receiver operating characteristic (ROC) curves[27] were drawn to relate the sensitivity and specificity of the PUF scores as predictors of potassium testing at various cutoff values. The area under the ROC curve,[28] a measure of the prognostic ability of the PUF questionnaire for potassium testing, was determined by the trapezoidal method. The area under the ROC curve typically will vary from 0.5 (no prognostic ability) to 1.0 (perfect prognosis).

Logistic regression analysis was also used to model the relationship between the PUF score and the PST outcome, with additional information potentially provided by group membership. Goodness of fit of the regression models was assessed by means of deviance and Hosmer-Lemeshow statistics.[29]

RESULTS

In our assessment of the reproducibility of the PUF scale by testing and retesting in 32 randomly selected women, the agreement between the two values was strong: the weighted kappa statistic was 0.890 (standard error 0.051).

PUF Scores and Potassium Testing in Three Test Groups and Controls

Overall, 382 individuals were screened with both the questionnaire and the PST: 48 controls, 109

PELVIC PAIN and URGENCY/FREQUENCY
PATIENT SYMPTOM SCALE

Please circle the answer that best describes how you feel for each question.

		0	1	2	3	4	SYMPTOM SCORE	BOTHER SCORE
1	How many times do you go to the bathroom during the day?	3-6	7-10	11-14	15-19	20+		
2	a. How many times do you go to the bathroom at night?	0	1	2	3	4+		
	b. If you get up at night to go to the bathroom does it bother you?	Never	Mildly	Moderate	Severe			
3	Are you currently sexually active YES _____ NO_____							
4	a. **IF YOU ARE SEXUALLY ACTIVE,** do you now or have you ever had pain or symptoms during or after sexual intercourse?	Never	Occasionally	Usually	Always			
	b. If you have pain, does it make you avoid sexual intercourse?	Never	Occasionally	Usually	Always			
5	Do you have pain associated with your bladder or in your pelvis (vagina, lower abdomen, urethra, perineum, testes, or scrotum)?	Never	Occasionally	Usually	Always			
6	Do you have urgency after going to the bathroom?	Never	Occasionally	Usually	Always			
7	a. If you have pain, is it usually		Mild	Moderate	Severe			
	b. Does your pain bother you?	Never	Occasionally	Usually	Always			
8	a. If you have urgency, is it usually		Mild	Moderate	Severe			
	b. Does your urgency bother you?	Never	Occasionally	Usually	Always			

SYMPTOM SCORE = (1, 2a, 4a, 5, 6, 7a, 8a)	
BOTHER SCORE = (2b, 4b, 7b, 8b)	
TOTAL SCORE (Symptom Score + Bother Score) =	

FIGURE 1. *PUF patient symptom scale. © 2000 C. Lowell Parsons, M.D. Used with permission*

patients from the urologic clinic at the UCSD, 104 patients from other urologic groups in the United States, and 121 patients from gynecologic groups in the United States

Table I presents the PUF scores and PST results. In the combined cohort of 382 individuals, increasing PUF scores were associated with an increasing likelihood of a positive PST. Within the range of PUF scores between 5 and 24, gynecologic patients were somewhat less likely to have a positive PST than were their urologic patient counterparts. All 48 controls had PUF scores of 2 or less and negative PSTs. Using data from all 382 patients, we generated an ROC curve relating sensitivity and specificity of the PUF questionnaire for determining the PST outcome. The area under the ROC curve was 0.82 (standard error 0.025)

We examined the relationship between the PUF questionnaire and PST outcome further using logistic regression analysis; some results are summarized in Table II. As expected, the PUF score is a strong predictor of PST outcome: a simple model incorporating one independent variable, the PUF score, fits reasonably well (deviance $d_p = 338.06$, degrees of freedom [df] = 380, $P = 0.94$). We could achieve a significantly improved fit, how-

TABLE I. *Rates of positive PST in urology patients with IC, gynecologic patients with pelvic pain, and controls

Group (n)	Mean PUF Score§	PST Positive (n)	PST-Positive Patients in Each PUF Score Range†‡					
			0–4‖	5–9	10–14	15–19	20–24	25+
Urology IC (213)			1/8 (12 5)	8/12 (67)	30/39 (77)	52/66 (79)	43/46 (93)	38/42 (90)
UCSD (109)	19 69 (6 67)	90 (82 6)						
Other (104)	18 36 (6 07)	82 (78 8)						
Gynecologic pelvic pain (121)	17 54 (5 62)	91 (75 2)	0	3/8 (37 5)	15/22 (68)	35/48 (73)	25/29 (86)	13/14 (93)
Controls (48)			0	0	0	0	0	0
Total (382)			1/56 (1 8)	11/20 (55)	45/61 (74)	87/114 (76)	68/75 (91)	51/56 (91)

Key: PST = potassium sensitivity test; IC = interstitial cystitis; PUF = pelvic pain and urgency/frequency; UCSD = University of California San Diego Medical Center
Numbers in parentheses are percentages, unless otherwise noted
* *All the patients and controls were women; median age 40 years in urology patients with IC and 36 years in gynecologic patients with pelvic pain*
† *The total maximal symptom score obtainable on the PUF scale is 35*
‡ *Data presented as the number of PST-positive patients/total number in group with the percentage in parentheses*
§ *Numbers in parentheses are the standard deviation*
‖ *The only PST-positive urology patient had a PUF score of 4.*

TABLE II. *Analysis of deviance table for logistic regression models

Model	Deviance	Degrees of Freedom
PUF score	d_p = 338 06	380
PUF + group 2	d_{pg2} = 311 41	379
PUF + group 4	d_{pg4} = 308 43	377

Key: PUF = pelvic pain and urgency/frequency.
* *Dependent variable in these models was PST outcome (−/+) The PUF score model incorporates a single covariate, PUF score, along with an intercept term; deviance is denoted d_p. The PUF + group 2 model incorporates PUF score and indicator variables for group membership dichotomized as either normal or non-normal; deviance is denoted d_{pg2}. The PUF + group 4 model incorporates PUF score and indicator variables for group membership, categorized as urology IC-clinic, urology IC-other gynecologic pelvic pain and controls; deviance for this model is denoted d_{pg4}.*

ever, by incorporating group membership (PUF + group 4 in Table II, the four groups were the urology IC-clinic, urology IC-other, gynecologic pelvic pain, and controls) into the model as categorical variables. The improvement in fit can be assessed by the difference in deviances ($d_p - d_{pg4} = 29.63$, df = 3, $P < .00001$) This model could be simplified further by dichotomizing the group membership into controls versus noncontrols (PUF + group 2 in Table II), with little loss in the goodness of fit (difference in deviances was $d_{pg2} - d_{pg4} = 2.98$, df = 2, $P = 0.22$). This reduced model, with the parameters of PUF score and group membership (normal versus not normal), provided an adequate representation of the data (the Hosmer-Lemeshow statistic C for this model = 6 74, df = 8, $P = 0.56$).

PUF Scores in a Random Survey of Women

PUF scores from a sample of 317 women attending IC lectures given by one of us (C.L.P.) were as follows. One hundred sixty-seven women (52 7%) had PUF scores between 0 and 4; 83 (26.2%) had PUF scores between 5 and 9; 43 (13 6%) had PUF scores between 10 and 14; 19 (6.0%) had PUF scores between 15 and 19; and 5 (1 6%) had PUF scores greater than 20. The distribution of PUF scores among this cohort of women is quite unlike that among the controls or the gynecologic and urologic patients recruited for the earlier phase of this study and appears to be a mixture of the controls' results (ie, PUF scores less than 5) and the patients' results

We can compute the expected number of individuals in this cohort of 317 women who would have positive PSTs as a function of the observed PUF scores and the prior probability of being normal versus not normal, using the reduced logistic regression model described above. In this regard, we assigned a prior probability of "normal" to be 0.995 for PUF scores less than 5 and a range of prior probabilities for normal between 0.1 and 0.5 for PUF scores of 5 or greater. This range of prior probabilities may well be somewhat optimistic, given that none of our 48 controls had PUF scores greater than 2. With these prior probabilities, the number of individuals in this cohort expected to have positive PSTs was 69 (22% of the cohort), with a range from 47 to 84

COMMENT

In collaboration with urologists and several gynecologists, we developed the PUF scale (Fig. 1), a symptom questionnaire that focuses not only on the urgency/frequency issues of IC but also on the pelvic pain issues and, in particular, the pain and symptoms associated with sexual intercourse. Patients with IC may have pain only or urgency only, but most have elements of both. Because the num-

bers of patients with IC in both the urologic and the gynecologic patient populations appear to be significant, a questionnaire that is useful in both specialties must address IC symptoms that appear to be "gynecologic" (pelvic pain, dyspareunia), as well as those that a patient might categorize as "urologic" (urinary urgency/frequency). In our clinical experience, we have found that pain tends to be the symptom most troubling to patients with IC; if they note urinary urgency at all, they consider it less significant than the pain and may not report it. The nature of the pain, as we have stated, may lead the patient to see a gynecologist; if urgency is continuous and very prevalent, the patient is more likely to see a urologist.

Our results suggest that the PUF scale is remarkably effective at predicting the outcome of the PST. Of the individuals who scored 15 or greater on the PUF, more than 84% had a positive PST. No individual who scored less than 4 on the PUF had a positive PST. The PUF scores and PST results were essentially the same whether administered to a patient with pelvic pain by a gynecologist or to a patient with IC by a urologist.

Extrapolating our IC prevalence findings in urologic patients with IC and in gynecologic patients with pelvic pain to the general population, we hypothesized that the prevalence of clinically active IC among women in the general population should be approximately 1 in 5. To test this possibility, we used the PUF scale to screen 317 women who attended lectures given by one of us (C.L.P.). Because more than 90% of the women completed the PUF scale, a reasonably accurate assessment of symptom prevalence in the population could be made free of such problems as percent response biases. The PUF scores from this sample indicated that nearly 22% of the group would test positive on the PST. If this finding is extrapolated to the general population, it appears that approximately 1 in 4.5 of the 130 million women in the United States may have clinically active IC.

The data from the current study are consistent with our earlier finding that 85% of a population of gynecologic patients with pelvic pain had a positive PST.[1] The number of women receiving gynecologic care for pelvic pain is estimated at 15 to 20 million; it would appear that most of them may have IC. The results of the current study provide dramatic additional support for the concept of IC as a disease that affects at least 28 million women, the overwhelming majority of whom are incorrectly diagnosed or undiagnosed.

CONCLUSIONS

We developed a pelvic pain urgency/frequency symptom questionnaire, the PUF scale, and validated it using a diagnostic test, the PST, in both urologic and gynecologic patients. A PUF score of 15 or more is associated with an 84% chance of having a positive PST, a strong indication that IC may be present. PUF scores in a random sample of women suggest that nearly 22% of women in the general population may have IC.

REFERENCES

1. Parsons CL, Bullen M, Kahn BS, *et al*: The gynecological presentation of interstitial cystitis as detected by intravesical potassium sensitivity. Obstet Gynecol **98**: 127–132, 2001.

2. Bernie JE, Hagey S, Albo ME, *et al*: The intravesical potassium sensitivity test and urodynamics—implications in a large cohort of patients with lower urinary tract symptoms. J Urol **166**: 158–161, 2001.

3. Parsons CL, Zupkas P, and Parsons JK: Intravesical potassium sensitivity in patients with interstitial cystitis and urethral syndrome. Urology **57**: 428–433, 2001.

4. Parsons CL, Greenberger M, Gabal L, *et al*: The role of urinary potassium in the pathogenesis and diagnosis of interstitial cystitis. J Urol **159**: 1862–1867, 1998.

5. Parsons CL, Lilly JD, and Stein PC: Epithelial dysfunction in nonbacterial cystitis (interstitial cystitis). J Urol **145**: 732–735, 1991.

6. Buffington CA, and Woodworth BE: Excretion of fluorescein in the urine of women with interstitial cystitis. J Urol **158**: 786–789, 1997.

7. Lilly JD, and Parsons CL: Bladder surface glycosaminoglycans as a human epithelial permeability barrier. Surg Gynecol Obstet **171**: 493–496, 1990.

8. Parsons CL, Stein PC, Bidair M, *et al*: Abnormal sensitivity to intravesical potassium in interstitial cystitis and radiation cystitis. Neurol Urodyn **13**: 515–520, 1994.

9. Parsons CL: Potassium sensitivity test. Tech Urol **2**: 171–173, 1996.

10. Teichman JMH, Nielsen-Omeis BJ, and McIver BD: Modified urodynamics for interstitial cystitis. Tech Urol **3**: 65–68, 1997.

11. Teichman JM, and Nielsen-Omeis BJ: Potassium leak test predicts outcome in interstitial cystitis. J Urol **161**: 1791–1796, 1999.

12. Chambers GK, Fenster HN, Cripps S, *et al*: An assessment of the use of intravesical potassium in the diagnosis of interstitial cystitis. J Urol **162**: 699–701, 1999.

13. Payne CK, and Browning S: Graded potassium chloride testing in interstitial cystitis. J Urol **155**: 438A, 1996.

14. Chen Ty-H, Begin LR, and Corcos J: Assessment of potassium chloride test in comparison with symptomatology, cystoscopic findings and bladder biopsy in the diagnosis of interstitial cystitis. J Urol **165**(5 suppl): 67–68, 2001.

15. Daha L, Riedl CR, Knoll M, *et al*: Comparative (saline vs. 0.2 M potassium chloride) assessment of maximum bladder capacity: a well-tolerated alternative to the 0.4 M potassium sensitivity test (PST). J Urol **165**(5 suppl): 68, 2001.

16. Nickel JC, Barkin J, Forrest J, *et al*: Randomized, double-blind, dose-ranging study of pentosan polysulfate sodium (PPS) for interstitial cystitis (IC). J Urol **165**(5 suppl): 67, 2001.

17. Parsons CL, Forrest J, Nickel JC, *et al*: Effect of pentosan polysulfate therapy on intravesical potassium sensitivity. Urology **59**: 329–333, 2002.

18. Hand JR: Interstitial cystitis: a report of 223 cases. J Urol **61**: 291–310, 1949.

19. Parsons CL: Interstitial cystitis: clinical manifestations and diagnostic criteria in over 200 cases. Neurourol Urodyn 9: 241–250, 1990.

20. Koziol JA, Clark DC, Gittes RF, *et al.* The natural history of interstitial cystitis: a survey of 374 patients. J Urol **149**: 465–469, 1993.

21. Parsons CL, Kamarei M, and Monga M: Interstitial cystitis, in Goldman MB, and Hatch MC (Eds): *Women and Health*. San Diego, Academic Press, 2000, pp. 1110–1119

22. Koziol JA: Epidemiology of interstitial cystitis Urol Clin North Am **21**: 7–71, 1994

23 O'Leary MP, Sant GR, Fowler FJ, Jr, *et al.* The interstitial cystitis symptom index and problem index Urology 49: 58–63, 1997

24 Cohen J: Weighted kappa: nominal scale agreement with provision for scaled disagreement or partial credit Psych Bull 70: 213–220, 1968.

25 StataCorp: *Stata Statistical Software, release 5 0*. College Station, Texas, Stata Corporation, 1997

26 Landis JR, and Koch GG: The measurement of observer agreement for categorical data. Biometrics 33: 159–174, 1977.

27. Metz CE: Basic principles of ROC analysis. Semin Nuclear Med 8: 283–298, 1978.

28 Hanley JA, and McNeil BJ: The meaning and use of the area under the receiver operating characteristic (ROC) curve Radiology **143**: 29–36, 1982

29. Hosmer DW, and Lemeshow S: *Applied Logistic Regression* New York, John Wiley, 1989