Prodrome and Non-prodrome Phenotypes of Bladder Pain Syndrome/Interstitial Cystitis

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OBJECTIVE To test the hypothesis that risk factors for bladder pain syndrome/interstitial cystitis (BPS/IC) in women differ between those with and without the BPS/IC prodrome.

MATERIALS AND METHODS Incident cases of BPS/IC and healthy controls were recruited nationally. More than half the BPS/IC cases reported subsyndromal urinary symptoms for decades before onset of BPS/IC and were identified as having the prodrome. Risk factors for BPS/IC were examined separately for cases with and without the prodrome using a set of matched controls.

RESULTS Two risk factors distinguished 178 prodrome from 134 non-prodrome cases. One was "UTIs" in the year before BPS/IC onset, possibly a manifestation of the prodrome itself. The other was the presence of the maximal number of nonbladder syndromes (NBSs): prodrome cases were 12 times more likely than non-prodrome cases to have ≥4 NBSs. Additional risk factors for prodrome and/or non-prodrome cases were the direct association of exogenous female hormones, as well as 3 inverse associations: type 2 diabetes mellitus, multiple pregnancies, and current daily smoking.

CONCLUSION Prodrome cases developed urinary symptoms in their early 20s (ie, the prodrome) and were at very high risk of numerous NBSs. Non-prodrome cases developed urinary symptoms in their early 40s (ie, full-blown BPS/IC) and were no more likely than controls to have the maximal number of NBSs. These findings are consistent with recent suggestions of two BPS/IC phenotypes: one with systemic and psychosocial manifestations and the other more specific to the bladder. Additionally, several risk factors identified here might be hints of related or causal nervous system pathophysiologies. UROLOGY ■■: ■■–■■, 2018. © 2018 Elsevier Inc.

Bladder pain syndrome/interstitial cystitis (BPS/IC) comprises chronic bladder pain plus urgency, frequency, and/or nocturia. As diagnosed at present, most patients are women. Despite decades of investigation, its pathogenesis remains unknown; recent etiologic research has expanded to a continuum including the bladder and the central nervous system (CNS).[1]

Seeking clues to the cause of BPS/IC, we performed a case-control study to identify its risk factors. In incident patients, we carefully assessed its onset date by probing questions and medical record review. Unexpectedly, the subsequent baseline interview revealed that more than half the cases reported what appeared to be subsyndromal urinary symptoms *before* BPS/IC began. The median onset of these symptoms was 22 years before BPS/IC.[2] These symptoms did not appear to be full-blown BPS/IC: chronic urinary symptoms were not mentioned in medical records; in 42% of these cases, the only prior symptom was urinary frequency, which does not meet any diagnosis of BPS/IC; and the flurry of medical activities that immediately followed the reported BPS/IC onset date[3] suggested something different had occurred on that date. Hence, we termed these prior subsyndromal symptoms as a BPS/IC prodrome.[2]

We earlier postulated that the prodrome represented a separate phenotype of BPS/IC and sought distinctions between cases with and without the prodrome. Although we found no differences in pain sites, urinary symptoms, or hydrodistention findings, we did note differences in a few variables from *before* BPS/IC onset.[2] This generated the hypothesis that other prior variables (ie, risk factors) might differ between those with and without the prodrome, and herein we have tested that hypothesis.

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MATERIALS AND METHODS

Detailed methods have been published.[2,4-6] Through national urology, gynecology, and patient groups, from 2004 through 2008, we recruited women who self-reported ≤12 months of physician-diagnosed BPS/IC. Inclusion criteria were perceived chronic bladder pain plus 2 of urgency, frequency, and nocturia. A 6-step process identified BPS/IC *symptom* onset. 1) At the telephone screening interview, each was asked to estimate the date of the first symptom that she now recognized as BPS/IC. Follow-up questions probed for (2) these specific symptoms for ≥4 weeks and ≤5 years before that date, and (3) more broadly for bladder discomfort, pain, or pressure; frequency; or urgency that began before and persisted most days through that date. All outpatient and inpatient medical records from ≤12 months before that date were reviewed for (4) chronic urinary symptoms and (5) diseases that might cause such. (6) Medical record dates of chronic urinary symptoms that differed from the estimated date were discussed with the case until consensus. This date of symptom onset (not BPS/IC diagnosis) was the Index Date. Through this sequence, 623 of 1177 women screened were excluded for Index Dates >12 months before the screening interview. Of the remaining, 312 met all other criteria[3] and were enrolled as incident BPS/IC cases. Controls were recruited by residential random digit dialing, and frequency-matched on sex, age, and national region. Each control was assigned an Index Date at an interval before the screening interview equivalent to that of a case.

At the subsequent baseline interview of cases and controls, female telephone interviewers queried demographics; occupations; exposures to toxins, cigarettes, animals, and well water; surgeries[5] and radiation and chemotherapy; antibiotics, nonsteroidal anti-inflammatory medications, and drugs with known bladder side effects; urethral catheterization and diseases; bed wetting, incontinence, and delays in urination; activities including sports, bathing practices, bicycle and horse riding, and international travel; sexual and parity history[6]; hyperthyroidism; and urinary stones. The use of female hormones other than for birth control was asked. Time periods for most variables were lifetime, 12 months, and 1 month before the Index Date. "Ever smoker" was defined as ≥100 cigarettes/lifetime; "current daily smoker" as smoking everyday (vs some days or not at all) during the 12 months before the Index Date. Also queried were clinician-diagnosed urinary tract infection and "episodes of a day or more of burning or pain as you urinated" ≤12 months before the Index Date; this category was termed "UTIs" in the past year. On a lifetime basis before the Index Date, 24 nonbladder syndromes (NBSs) were queried, generally by symptoms based on expert consensus definitions. On bivariate analyses, 11 were associated with BPS/IC: fibromyalgia (FM), chronic fatigue syndrome (CFS), irritable bowel syndrome (IBS), chronic pelvic pain (CPP), migraine, vulvodynia, depression, panic disorder, sicca syndrome, allergies, and asthma.[4] Type 2 diabetes was diagnosed with "yes" to "diabetes or borderline diabetes or high blood sugar levels" and to treatment with oral medications. Additionally, the baseline interview assessed pre-Index Date urinary symptoms. On multivariate analyses, cases exceeded controls in three: frequency, bladder pain, and pelvic pain with urinary features.[2] From several perspectives, these symptoms did not appear to be fully developed BPS/IC.[2] The presence of ≥1 of these symptoms defined the prodrome.

Pearson's chi-square was used for categorical variables and Student *t* test for continuous variables. Because of the large number of items, $P \leq .001$ was used to include a variable in logistic regression analyses. Tables include the number of individuals with each variable so the reader can understand the proportion of individuals possibly affected; the balance of each group represents the number without the variable. Backward stepwise selection procedure was applied based on the Wald test (specifically on *P* values calculated via *z* statistic because Wald statistic is asymptotically distributed as a standard normal distribution), and 95% Wald confidence intervals (CIs) were calculated for the estimation of the odds ratio (OR) for each risk factor kept in the model. This study was approved by the University of Maryland School of Medicine Institutional Review Board.

RESULTS

Three hundred twelve cases (mean age 42.3 years) were compared to 313 controls (42.9 years). Logistic regression analyses revealed 8 variable categories that distinguished cases from controls: 5 were associated with increased odds and 3 with decreased odds of BPS/IC (Table 1). The NBSs were the most prominent. Each of the 11 NBSs associated on bivariate assessments was studied individually in separate logistic regression analyses (data not shown). Five remained linked to BPS/IC after controlling for other confounders: CPP (OR 3.4; 95% CI 2.0, 5.6), panic disorder (OR 2.0; 95% CI 1.3, 3.2), IBS (OR 2.0; 95% CI 1.2, 3.4), FM (OR 1.9; 95% CI 1.1, 3.3), and depression (OR 1.8; 95% CI 1.2, 2.7). Increasing numbers of these 5 NBSs per person led to a step-up in risk; the presence of 4 or all 5 of these NBSs resulted in the highest OR for BPS/IC (Table 1). Substituting the number per person of all of the original 11 NBSs did not materially change the findings in Table 1.

Table 1 shows that the other factors associated with increased odds of BPS/IC were the prodrome, "UTIs" in the past year, lifetime (but not past year or month) use of exogenous female hormones, and several demographic features. The 3 inverse associations were type 2 diabetes mellitus (T2DM), multiple pregnancies (substituting live births did not materially change the findings), and current daily smoking ("ever smoker" did not differ between cases and controls).

We separately compared prodrome cases and non-prodrome cases to controls. Since controls were frequency-, not individually, matched, we compared each subgroup of cases to all 313 controls. Prodrome and non-prodrome cases did not differ in mean or median ages. Most of the risk factors were confirmed for the prodrome cases (Table 2). Moreover, in addition to the 5 previously mentioned NBSs, 3 more of the 11 original NBSs were significantly more common: CFS (OR 4.4; 95% CI 2.3, 8.4; $P = .000005$), migraine (OR 1.7; 95% CI 1.04, 2.9; $P = .04$), and sicca (OR 5.6; 95% CI 1.5, 20.8; $P = .01$). The maximal number of NBSs (ie, 4 or 5 per person) had a very high OR for BPS/IC (OR 51.4; 95% CI 13.4, 197.8; $P = .00000001$). The risk of BPS/IC with the number of "UTIs" in the year before the Index Date also was markedly enhanced. Two inverse risk factors fell short of statistical significance: multiple pregnancies and T2DM.