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Before the onset of interstitial cystitis/bladder pain syndrome, the presence of multiple non-bladder syndromes is strongly associated with a history of multiple surgeries

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ABSTRACT

Objective: Certain functional somatic syndromes (FSSs) such as fibromyalgia and irritable bowel syndrome are accompanied by diffuse pain amplification. Women with interstitial cystitis/bladder pain syndrome (IC/BPS) have numerous FSSs, as well as other non-bladder syndromes (NBSs) that are linked to the FSSs. They also report multiple surgeries. Since pain is a common indication for surgery, we tested the hypothesis that NBSs were associated with surgeries.
Methods: We interviewed 312 incident IC/BPS cases and controls on NBSs and number of surgeries before the index date (for cases, IC/BPS onset date). Poisson and logistic regression analyses adjusted for age, race, educational level, and menopause.
Results: Number of surgeries increased with number of NBSs in both cases and controls whether chronic pelvic pain (CPP), the only NBS generally accepted as an indication for surgery, was present or not. Logistic regression analysis showed that among cases CPP was the only individual NBS associated with a history of multiple surgeries, and then only modestly [odds ratio (OR) 1.9, confidence intervals (CI) 1.06, 3.2]. By far the strongest association was the *number* of NBSs. The OR for multiple surgeries increased with number of NBSs: for cases with 4–5 NBSs the OR was 14.1 (1.8, 113) and with 6–9 NBSs, 33.1 (3.9, 279). Controls had fewer syndromes and fewer surgeries and this linkage was less prominent.
Conclusion: Among IC/BPS cases, the number of NBSs was strongly correlated with the number of surgeries. Understanding temporal relationships will be necessary to explore causal linkages and may modify surgical practice.
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Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) [1,2] is a chronic condition comprising pain perceived to be from the bladder, plus the urinary symptoms of urgency, frequency and nocturia. At present, the majority of diagnosed patients are adult women. Its etiology is unknown. For almost a century, clinicians have noted that IC/BPS patients seemed to have experienced large numbers of surgeries outside the urinary tract [3,4]. These observations have been confirmed in controlled studies [5–8].

More recently IC/BPS patients were reported to have syndromes that were defined by symptoms outside the bladder [9]. Confirmatory investigations showed that IC/BPS patients were more likely than controls to have each of these non-bladder syndromes (NBSs): fibromyalgia (FM), chronic fatigue syndrome (CFS), irritable bowel syndrome (IBS), temporomandibular disorder (TMD), migraine, chronic pelvic pain (CPP), vulvodynia, low back pain (LBP), sicca syndrome, allergies, asthma, depression, and anxiety [10–14]. Several of these conditions, i.e., FM, CFS, IBS, and TMD, have come to be known as functional somatic syndromes (FSSs) [15]; many of these other NBSs are epidemiologically associated with the FSSs. Characteristics common to the FSSs as well as many of the other NBSs include symptom-based diagnoses, presence of pain,

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chronicity, absent or incidental local pathology, normal laboratory tests, prominence in women, and co-morbidity [12,15,16].

Recently, studies have shown that patients with some FSSs have abnormal sensory processing including pain amplification at body sites far removed from those that define the syndrome [17–20]. Indeed, reports indicate that patients with multiple syndromes have more severe abnormalities in sensory processing than those with fewer [21–23]. Since pain is a common indication for surgery, in aggregate these findings generated the following hypotheses: 1) that more persons with certain NBSs than those without have a history of multiple surgeries; and 2) that the number of NBSs is correlated with the number of surgeries.

In a case–control study seeking risk factors for IC/BPS in women, we reported that the number of surgeries [8] and of non-bladder syndromes [12,24] in 312 IC/BPS cases were each significantly greater than in matched controls. The high prevalence of these two variables allowed us to test the hypotheses above in this relatively small sample of women. Because IC/BPS patients comprise a special segment of adult women, we also compared important findings to their controls, a sample more representative of the general population.

Method

This analysis is of data collected for a case–control study that sought risk factors for IC/BPS, Events Preceding Interstitial Cystitis; methods [8,12,25,26] and demographic results [8] are presented elsewhere. Briefly, 312 women 18 years of age or older with symptoms of IC/BPS beginning within the previous 12 months and lasting ≥4 weeks that comprised pain that they perceived to be from the bladder plus at least two of the symptoms of urgency, frequency, and nocturia were enrolled. Cases were recruited nationally through patient support groups and urologist and gynecologist associations by internet and postal mailings and by presentations at national patient and professional meetings. Respondents were excluded by self-report or medical record evidence of possibly mimicking diseases. The index date for cases was the onset date of the first IC/BPS symptom and was identified by a 5 step process: 1) estimate by the participant, 2) questions about earlier symptoms, 3) questions about similar episodes, 4) medical record review, and 5) concurrence by the case. Characteristics of these cases [26] were similar to those of reported IC/BPS case series [27]. These cases met the definitions of IC/BPS of the Fourth International Consultation on Incontinence [28], the European Society for the Study of Interstitial Cystitis [29], and the American Urological Association [2].

Three hundred and thirteen controls were recruited by national random digit residential telephone dialing on weekdays, weekends, and evenings up to 10:00 PM recipient's time. Each control was matched to a case by age, gender, and national region and then was assigned an index date at an interval equivalent to that of the matched case. As suggested by the interviewers, 78% of controls then picked as their index date a personally important day, such as an anniversary, that was within one month of the assigned date.

All participants were interviewed on pre-index date medical history and exposures [12]. Twenty-three non-bladder syndromes or diseases were queried. For eight, diagnostic algorithms based on consensus definitions constructed by experts were used. These were CPP [30], FM [31], CFS [32], IBS [33], sicca [34], migraine [35], panic disorder [36], and vulvodynia [37]. For each, a variant of "At any time in your life before your index date, have you had (a pertinent symptom or symptom complex)" was the screening query. A positive response led to a branch of questions for the criteria defining the syndrome. Of the other syndromes or diseases, 14 were by self-report of physician diagnosis and one (allergy) by self-report only.

Eleven syndromes were significantly more prevalent in cases than controls: all eight of those diagnosed by consensus definitions (CPP, FM, CFS, IBS, sicca, migraine, panic disorder, and vulvodynia) plus allergy, asthma and depression (the latter two by self-report of treatment with prescription medication). Definitions, prevalences, associations with each other, and odds ratios for IC/PBS of these NBSs have been reported [12].

At the baseline interview each participant also was asked: "At any time before your index date of _____, did you have any type of surgery that required anesthesia, i.e., general anesthesia, an epidural or spinal, or a regional block, not including local anesthesia or IV sedation?" If she answered yes, she was asked the number of surgeries at any time in her life prior to the index date [8].

We examined relationships between the 11 NBSs associated with IC/BPS and the number of lifetime surgeries prior to the index date in both cases and controls. Bivariable analyses of means were by t tests. Comparisons of means by number of NBSs were by non-parametric test of trend across ordered groups, an extension of the Wilcoxon rank-sum test, and by Poisson regression analysis, adjusting for age, race, education and menopause status. Logistic regression analysis [38] used the same adjustment variables and incorporated additional independent variables with p values of ≤0.10; the dependent variable was history of multiple surgeries, defined as ≥4 lifetime surgeries (selected because only 20% of controls reported this number). This study was approved by the University of Maryland Institutional Review Board and all participants gave signed informed consent.

Results

Table 1 shows that prior to the onset of IC/BPS, the mean number of reported surgeries increased with the number of non-bladder syndromes. Controls had fewer NBSs and fewer surgeries but findings in general were similar.

Because chronic pelvic pain is a common indication for surgery, Table 2 displays IC/BPS cases by whether they had CPP or not before the index date. In both those with and without CPP, the mean number of surgeries significantly increased with the number of NBSs (of the controls, removal from analysis of the few with CPP did not substantively change the results in Table 1).

We adjusted for possible confounding by age, race, educational level, and the presence of natural menopause in two types of analysis. The first was Poisson regression which confirmed the association of the number of non-bladder syndromes with the number of surgeries (Fig. 1).

The second was a series of logistic regression analyses using the dependent variable, "history of multiple surgeries", i.e., ≥4 lifetime surgeries. Bivariable analyses showed that in IC/BPS cases the mean number of lifetime surgeries before the onset date was higher in those who had each of these seven NBSs than in those who did not: CPP (p value by t test, .0001), FM (.0008), CFS (.008), migraine (.014), depression (.036), vulvodynia (.047) and panic disorder (.055). These seven NBSs were incorporated into the logistic regression analyses. In both cases and controls, only chronic pelvic pain remained associated with a history of multiple surgeries, with modest odds ratios (OR) (1.9 and 2.8, respectively) and lower ends of the confidence intervals (CI) only slightly above 1.0 (Tables 3 and 4).

In the next set of analyses, the number of non-bladder syndromes was substituted for the individual syndromes. To obtain sufficient numbers of participants per category and to test for a stepwise increase, we clustered women into those with zero, 1–3, 4–5 and 6–9 NBSs. In some cases, the ORs for a history of multiple surgeries increased with the number of NBSs: for those with 4–5 NBS the OR for multiple surgeries was 14.1 (CI 1.8, 113) and with 6–9 NBSs, it was 33.1 (3.9, 279) (Table 3). Each of these ORs was much higher than that for any individual NBS, including CPP. Substituting the number of classic functional somatic syndromes, i.e., FM, CFS, and IBS, for the number of NBSs in Table 3 yielded the following: for cases with one FSS, the OR for multiple surgeries was 1.1 (.6, 2.1), with two FSSs 3.6 (1.7, 8.0), and with three FSSs 3.1 (1.2, 7.9).

Table 1
IC/BPS cases and controls: mean number of lifetime surgeries by number of non-bladder syndromes per person.

Number of non-bladder syndromes	Number of IC/BPS cases	Number surgeries, mean (95% CI)	Number of non-bladder syndromes	Number of controls	Number surgeries, mean (95% CI)
Zero	22	1.9 (1.0, 2.7)	Zero	55	1.7 (1.2, 2.2)
1	48	3.1 (2.0, 4.1)	1	116	1.7 (1.4, 1.9)
2	70	2.3 (1.9, 2.8)	2	68	2.4 (1.8, 2.9)
3	61	3.0 (2.2, 3.7)	3	30	2.8 (2.1, 3.5)[a]
4	41	3.5 (2.6, 4.3)[a]	4 or more	44	2.8 (2.0, 3.5)[a]
5	32	3.5 (2.7, 4.4)[a]	–	–	–
6 or more	38	4.8 (3.8, 5.7)[a]	–	–	–
Test of trend	–	<0.001	Test of trend	–	<0.001

[a] Vs. zero, ≤0.05 by t test.

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