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The Genetic and Environmental Contribution to the Occurrence of Bladder Pain Syndrome: An Empirical Approach in a Nationwide Population Sample

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Abstract

Background—The aetiology of bladder pain syndrome (BPS) remains poorly understood, and a number of pathogenic mechanisms have been proposed. The importance of genetic factors for BPS is receiving growing attention, but data so far are of a preliminary nature.

Objective—To empirically assess the genetic and environmental contribution to BPS in a population-based sample of twins.

Design, setting, and participants—The study included >25 000 twins born between 1959 and 1985. Individuals with BPS were identified using latent class cluster analysis (LCCA) based on self-reported symptoms from a nationwide screening for complex diseases in the Swedish Twin

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Registry. By comparing monozygotic and dizygotic twins, we estimated twin similarity and the relative proportions of phenotypic variance resulting from genetic and environmental factors.

Measurements—Twin similarity was measured.

Results and limitations—The LCCA yielded an overall BPS prevalence of 1.1% and 2.4% for males and females, respectively. In males, the contribution of genetic effects to BPS could not be assessed because of the small number of concordant twin pairs. In women, twin similarity estimates indicated a genetic component for the aetiology of BPS, but genetic factors contributed less than one-third of the total variation in susceptibility to BPS. Nonshared environmental factors accounted for more than two-thirds of the variance, whereas early nongenetic factors shared within the family were of little or no consequence to the risk of developing BPS later in life. Use of self-reported symptoms to define the disease phenotype is a limitation of the study.

Conclusions—The influence of environmental factors in the development of BPS in women is substantial, whereas genetic influences are of only modest importance for the possibility of developing the disease.

Keywords

Bladder pain syndrome; Environment; Genetic; Interstitial cystitis

1. Introduction

Bladder pain syndrome (BPS) is a heterogeneous condition involving chronic and often severe pain perceived in the urinary bladder [1]. According to the European Society for the Study of Interstitial Cystitis, BPS is diagnosed based on the presence of chronic pelvic pain or discomfort related to the bladder and at least one other symptom, such as urinary frequency [2]. Further diagnosis of BPS subtypes, such as classic interstitial cystitis (IC) with Hunner's lesions, may be based on findings at cystoscopy with hydrodistension and characteristic histomorphologic findings in bladder biopsies [3,4].

The aetiology of BPS remains poorly understood, and a number of pathogenic mechanisms have been proposed, including bladder epithelial dysfunction [5], epigenetic reprogramming of the bladder uroepithelium [6], autoimmune conditions [7], and nitric oxide synthase imbalance [8]. The importance of genetic factors for BPS is receiving growing attention, but data so far are of a preliminary nature. Until now, the evidence to support the notion that genetic factors influence the aetiology of BPS is based on observations of high IC prevalence in first-degree relatives with the disease [9] as well as studies of similarity in IC case-ascertained monozygotic and dizygotic twins [10].

In this study of young male and female twins from the nationwide Swedish Twin Registry [11], we aim to determine the prevalence of BPS using a novel statistical approach to classify the disease phenotype. For the first time, we will also be able to assess the relative importance of genetic and environmental influences on the possibility of developing BPS in a large population of monozygotic and dizygotic twins.

2. Methods

2.1. Data sources

The Swedish Twin Registry contains data on most twins born in Sweden since 1886. In 2005, all twins born between 1959 and 1985 were approached to participate in a Web-based survey of common complex diseases and exposures [11]. Those not responding to the Web questionnaire were asked to answer the survey through a computer-assisted telephone interview. The survey used a branching format, meaning that participants were asked follow-up questions only if they responded positively to key initial questions. Answering “yes” to the discriminant question, “At any time in your life, have you experienced bladder pain, pressure, or discomfort?” directed the participant to the branch of questions on symptoms associated with BPS. The section consisted of questions on lower urinary tract symptoms adopted from a validated epidemiologic questionnaire on lower urinary tract dysfunction [12] and additional questions related to bladder pain (Table 1) [13]. After 2–5 mo, 100 twins were contacted again to establish test–retest reliability. The κ values for agreement between the Web questionnaire and telephone interviews ranged from good to excellent; thus, we concluded that both sources of information could be used in the analysis without bias [11].

2.2. Study population

The gender distribution of the 42 582 eligible twins (ie, from pairs where both twins survived their first birthday) in the target population of twins born from 1959 to 1985 was approximately equal. The total response rate was 59.6% ($n = 25\,364$). The response rate for the Web questionnaire was 43.1% (49.9% for women, 36.2% for men), and an additional 16.5% (16.0% women, 17.0% men) completed a telephone interview.

2.3. Statistical analysis

To identify potential cases of BPS, we used latent class cluster analysis (LCCA), which has been used previously to subtype complex diseases [14–16]. LCCA is considered analogous to cluster analysis and is a multivariate exploratory statistical approach that provides classes (or *clusters*) with homogenous profiles based on a given data set. The statistical program is given no prior knowledge about how symptoms might interrelate, and subjects are empirically grouped so that individuals within a class are as similar as possible to each other but as different as possible from members of other classes. This empirical approach provides mutually exclusive phenotype profiles that can identify probable disease classes (such as BPS) from other disease or nondisease classes.

To determine the optimal number of clusters, we fitted models with two to six clusters to the data, and the selection of the final LCCA model was based on both the Akaike's Information Criterion (AIC) and the Bayesian Information Criterion (BIC). When using a large number of items for cluster solutions, two or more clusters are often indistinguishable in terms of their structure. We therefore limited the number to five BPS-related items without preconditions: present bladder pain, duration of bladder pain, relief of pain after urination, nocturnal frequency, and ever having experienced bladder pain. Because the aetiology of

BPS can differ between males and females, we fitted separate models for men and women throughout the analyses.

Twin similarity was calculated as probandwise concordance rates for the latent classes in monozygotic and dizygotic twins. As a further measure of similarity, we used tetrachoric correlations. Higher probandwise concordance rates and correlations of susceptibility between monosex and like-sex dizygotic twins suggest that genetic factors influence susceptibility to disease.

Heritability of the phenotype was estimated using a structural equation model based on the assumption that the proportion of variance in the phenotype is the result of additive genetic effects (heritability); shared environmental effects; and random, nonshared environmental effects. Thus, heritability estimates the proportion of the total variance explained by genetic effects, whereas shared and nonshared environmental effects include all nongenetic influences. All responders to the items were used for the LCCA, but heritability and variance components estimates were restricted to twins with known zygosity. Furthermore, because of differences in prevalence and cluster structure for men and women, opposite-sex twins were excluded. For the latent class analyses, we used Latent GOLD v.4 software (Statistical Innovations, Belmont, MA, USA). We used the structural equation modelling software Mx v.1.7.03 to estimate the ACE model [17]. All other analyses were performed using SAS v.9.1 software (SAS Institute, Cary, NC, USA). This study was approved by the Regional Ethics Board at Karolinska Institutet and conforms to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting observational studies [18].

3. Results

In total, 23 000 twins were included in the LCCA. Mean age was 33.1 yr of age (standard deviation [SD]: 7.7) for women and 33.3 yr of age (SD: 7.7) for men. The overall prevalence of current bladder pain was 2.4% among women and 1.1% among men. Table 1 shows the item-specific responses to symptoms associated with BPS.

The final four-class LCCA model identified on the basis of the minimum AIC and BIC (data available on request) identified four phenotypes in the population (Table 2). Of the 12 840 women, 8853 (68.9%) reported no symptoms associated with BPS and were empirically grouped, forming class 1. This class was labelled “Healthy.” The second-largest class contained 2352 women (18.3%) and was symptomatically dominated by nocturnal micturitions without symptoms of bladder pain (ie, nocturia). Respondents in the third class (10.2%) all acknowledged a history of bladder pain, but very few (3.4%) reported present symptoms. The majority in this class reported no improvement in bladder pain after voiding (60%); of those who experienced present bladder pain, >90% had a duration <3wk. This grouping of symptoms could indicate lower urinary tract infections or other genital infection and was therefore labelled “Infectious disease.” The fourth and smallest class (2.4%), termed “BPS,” was characterised by the presence of bladder pain, long duration of bladder pain, frequent nocturnal urinations, and relief of pain after urination; all members of this group had experienced bladder pain in the past.

In the 10 160 men, the first class (86%) of the four-class solution was entirely made up of subjects not experiencing any symptoms associated with BPS. The second class was again dominated by nocturnal micturitions (7.4%) but no other BPS-related symptoms and was termed “Nocturia.” In the third class (5.6%), all subjects had experienced bladder pain in the past, but only 2.1% acknowledged present pain. The duration of bladder pain was short, and the majority reported unchanged or worsening symptoms after voiding. Similar to women, men in the fourth class (1.1%) had current bladder pain of relatively long duration that improved after voiding; more than two nocturnal micturitions were common. Therefore, class 4 also was labelled “BPS” in men.

Indicators of twin similarity—that is, concordance rates and tetrachoric correlations—are presented in Table 3. Information was available for 3160 same-sex twin female pairs and 2099 male pairs with known zygosity. Higher concordance rates among monozygotic compared to dizygotic female twins (0.06 vs 0.02) suggest that genetic effects contribute to the aetiology of BPS (class 4). The correlation in susceptibility to BPS was also higher among monozygotic compared to dizygotic twins (0.33 vs 0.06). In males, there was only one concordant pair among monozygotic twins and none among dizygotic twins. Concordance rates and tetrachoric correlations could therefore not be meaningfully calculated for male dizygotic twins.

We subsequently proceeded with the age-adjusted quantitative genetic analyses, summarised in Table 4. Among women, genetic factors accounted for approximately one-third of the total variation in susceptibility to disease class 4, whereas nonshared environmental factors contributed the other two-thirds of the variation. A similar pattern of contribution in susceptibility to disease was observed for classes 2 and 3 in women, where shared environment was of little or no consequence. Among males, there were insufficient numbers of twin pairs in class 4 to perform the analysis. For class 2 in men, genetic factors contributed 38% and nonshared environment 62%; but for class 3, essentially none of the susceptibility to developing disease was attributed to genetic factors, whereas 29% and 62% were attributed to shared and nonshared environment, respectively.

4. Discussion

In this large population-based study among young twins, we found support for the notion that genetic factors contribute to the occurrence of BPS in women, because twin resemblance was greater in monozygotic than dizygotic twins. However, the largest proportion of the variation in risk for BPS in women could be explained by individual, specific environmental factors. In males, twin analysis of BPS as defined in class 4 was not possible because of the small number of cases.

The overall BPS prevalence of 2.4% in women and 1.1% in men generated by the LCCA of the present study corresponds well to previous community-based estimates of disease [19–21]. As expected, the largest class for both males and females reported no symptoms; and as expected, women carried a disproportional disease burden. Those relatively few men and women characterised as BPS in the present study appear to form an empirically distinct group of subjects with features in common (ie, a BPS phenotype).

The indicators of twin similarity suggested a genetic component to the aetiology of BPS in women, and genetic effects accounted for about 30% of the total variation in liability to disease. There were, however, few concordant twin pairs available for the analyses, and the results must therefore be interpreted with some caution. The heritability results for BPS were somewhat lower than heritability estimates for other female lower urinary tract disorders, such as stress urinary incontinence, where a heritability of 41% has been reported [22]. This could be the result of the heterogeneity of BPS as a diagnostic term, where heritability for specific afflictions that the term *BPS* encompasses, such as classic Hunner's type IC, remains undecided. In this context, it is worth noting that this specific entity typically afflicts a somewhat older population and therefore may be underrepresented in our sample [3].

Nonshared environment contributed the greatest proportion of variance to the liability for BPS in women, whereas shared environmental factors had minimal influence on disease occurrence in both males and females. Thus, early nongenetic (environmental) factors shared within the family, such as childhood micturition training, common eating and drinking behaviours, attitudes towards smoking and alcohol consumption, and physical activity, are of little consequence to the risk of developing BPS in adulthood. Childhood micturition patterns and toilet training have been shown to influence occurrence of overactive bladder symptoms in adult life [23]. Nonshared environmental influences may include a diversity of life style factors as well as reproductive factors and comorbidities occurring later in life. Importantly, our results suggest that environmental effects have a strong influence on the origins of BPS and that the risk for disease occurrence may be amenable to intervention. It is now essential to explore farther which specific environmental factors are involved in the progression towards a chronic state of bladder pain.

The complexity of BPS is reflected by the multitude of aetiologic factors implicated in the pathogenesis of disease, the absence of universally accepted disease definitions, and lack of appropriate tools to discriminate those stricken by actual disease from those with transient manifestations of bladder pain. New phenotyping strategies in genetic research are therefore called for, and empirical grouping of subjects based on symptoms such as latent class or cluster analysis may be a useful and valid approach to identifying subjects with a disease. Although LCCA is a commonly used empirical technique for the study of other diseases, it represents a novel way of approaching the multifaceted aetiology of BPS. Using LCCA to define disease-specific phenotypes may therefore provide further insights into the underlying and overlapping causal pathways leading to BPS.

Class 2 was dominated by nocturnal micturitions without bladder pain in both sexes, and heritability estimates suggested a genetic component to the aetiology of nocturia as well. The subsequent quantitative analysis estimated that genetic factors accounted for 34% of variation in liability for disease in females and 38% in males. The higher genetic contribution to nocturia, when defined as two or more micturitions per night, suggests that even though there is an overlap of symptoms between nocturia and BPS, the conditions are aetiologically different from one another. Further genetic epidemiologic studies may provide important clues to the pathogenesis of nocturia, for which little is known.

Previous symptoms of bladder pain dominated LCCA class 3, where the majority of both men and women reported unchanged pain after voiding. Of the few respondents acknowledging current bladder pain, the duration of discomfort was short. Based on the characteristics of the class and a higher prevalence among women, we labelled class 3 as a likely combination of urinary tract infections and sexually transmitted diseases [24]. This label also corresponds well with the dominance of environmental factors.

This study on BPS among young twins has several strengths, including a uniquely large, nationwide study population unbiased by volunteer-based ascertainment. The population-based study design minimises ascertainment bias and allows for gender-specific analysis. We believe that screening questions on lower urinary tract function were reliable in both sexes, although not validated for use in both males and females, because the distribution of BPS corresponds well with previous population-based estimates [19–21]. A weakness lies within the use of self-reported symptoms to define the disease phenotype, as *BPS* is a rather heterogeneous diagnostic term that may encompass different conditions associated with chronic bladder pain. Although most would agree that symptoms of BPS and of the betterdefined classic Hunner's type IC are the same and that it is reasonable to assume that a minority of cases with BPS in our study would be attributed to classic IC, we have not been able to make a subdivision in the absence of diagnostic confirmation by cystoscopy and histologic findings [2]. Nonetheless, we recognise that the overlap with other types of bladder pain and the age range of our subjects may have caused an underestimation of the heritability for classic IC.

5. Conclusions

The influence of environmental factors in the causation of BPS among women is substantial, whereas genetic influences are only of modest importance for liability to the disease. Our data suggest that the liability to develop this often severely debilitating disorder may be amenable to intervention by targeting environmental risk factors. The findings in the present study highlight the need for further epidemiologic studies that may help to direct the search for more effective treatments and prevention strategies.

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Table 1

Prevalence of symptoms and mean age

		Women		Men	
		<i>n</i> = 12 840		<i>n</i> = 10 160	
		<i>n</i>	%	<i>n</i>	%
At any time in your life, have you experienced bladder pain, pressure, or discomfort?	No	11 205	87.3	9843	93.3
	Yes	1635	12.7	677	6.7
Do you experience current bladder pain?	No	12 528	97.6	10 052	98.9
	Yes	312	2.4	108	1.1
For how long have you experienced bladder pain?	No pain	11 205	87.3	9843	93.3
	<3 wk	1293	10.1	510	5.0
	4 wk to 5 mo	112	0.9	62	0.6
	6 mo	230	1.8	105	1.0
How does voiding affect the bladder pain?	Worsens	136	1.1	29	0.3
	Unchanged	11 959	93.1	9832	96.8
	Improves	745	5.8	299	2.9
How many times per night do you need to void?	0–1	9825	76.5	9237	90.9
	2–3	2632	20.5	827	8.1
	>3	383	3.0	96	0.9

Table 2

Latent class analysis of five questions related to bladder pain syndrome*

		All	Class 1: Healthy	Class 2: Nocturia	Class 3: Infection**	Class 4: BPS
Women	<i>n</i>	12 840	8853	2352	1312	323
Bladder pain	No	87.3	100.0	100.0	0.0	0.0
	Yes	12.7	0.0	0.0	100.0	100.0
Duration of bladder pain	No pain	87.3	100.0	100.0	0.0	0.0
	<3 wk	10.1	0.0	0.0	91.0	30.7
	4 wk to 5 mo	0.9	0.0	0.0	5.9	10.8
	6 mo	1.8	0.0	0.0	3.1	58.5
Effect of voiding on bladder pain	Worsens	1.1	0.0	0.0	6.3	16.7
	Unchanged	93.1	100.0	100.0	53.7	15.2
	Improves	5.8	0.0	0.0	40.0	68.1
Nocturnal urinary frequency	0–1	76.5	100.0	0.0	62.4	47.7
	2–3	20.5	0.0	88.4	33.1	37.2
	>3	3.0	0.0	11.6	4.6	15.2
Current bladder pain	No	97.6	100.0	100.0	96.6	17.3
	Yes	2.4	0.0	0.0	3.4	82.7
Age	Mean (SD)	33.1 (7.7)	33.0 (7.7)	33.5 (7.2)	33.2 (7.9)	33.4 (7.8)
Men	<i>n</i>	10 160	8733	750	570	107
Bladder pain	No	93.3	100.0	100.0	0.0	0.0
	Yes	6.7	0.0	0.0	100.0	100.0
Duration of bladder pain	No pain	93.3	100.0	100.0	0.0	0.0
	<3 wk	5.0	0.0	0.0	84.6	26.2
	4 wk to 5 mo	0.6	0.0	0.0	8.6	12.2
	6 mo	1.0	0.0	0.0	6.8	61.7
Effect of voiding on bladder pain	Worsens	0.3	0.0	0.0	3.5	8.4
	Unchanged	96.8	100.0	100.0	57.9	17.8
	Improves	2.9	0.0	0.0	38.6	73.8
Nocturnal urinary frequency	0–1	90.9	100.0	0.0	78.1	55.1
	2–3	8.1	0.0	91.1	19.6	29.9
	>3	0.9	0.0	8.9	2.3	15.0
Current bladder pain	No	98.9	100.0	100.0	97.9	10.3
	Yes	1.1	0.0	0.0	2.1	89.7
Age	Mean (SD)	33.3 (7.7)	33.1 (7.7)	34.9 (7.5)	33.6 (7.7)	33.5 (7.4)

BPS = bladder pain syndrome; SD = standard deviation.

* Figures are proportions of individuals per cluster.

** “Infection” includes indicators of lower urinary tract and genital infections.

Table 3

Heritability* estimates for assignment to latent classes in like-sex twin pairs by zygosity and gender

Birth cohort	Monozygotic female twins (<i>n</i> = 1867)	Dizygotic female twins (<i>n</i> = 1293)	Monozygotic male twins (<i>n</i> = 1229)	Dizygotic male twins (<i>n</i> = 870)
Class assignment				
Class 2: Nocturia	Both afflicted (<i>n</i>): 119	Both afflicted (<i>n</i>): 61	Both afflicted (<i>n</i>): 19	Both afflicted (<i>n</i>): 7
	One afflicted (<i>n</i>): 446	One afflicted (<i>n</i>): 343	One afflicted (<i>n</i>): 133	One afflicted (<i>n</i>): 109
	Concordance: 0.21%	Concordance: 0.15%	Concordance: 0.13%	Concordance: 0.06%
	Correlation: 0.37	Correlation: 0.20	Correlation: 0.40	Correlation: 0.15
Class 3: Infection	Both afflicted (<i>n</i>): 38	Both afflicted (<i>n</i>): 13	Both afflicted (<i>n</i>): 11	Both afflicted (<i>n</i>): 6
	One afflicted (<i>n</i>): 310	One afflicted (<i>n</i>): 209	One afflicted (<i>n</i>): 109	One afflicted (<i>n</i>): 76
	Concordance: 0.11%	Concordance: 0.06%	Concordance: 0.09%	Concordance: 0.07%
	Correlation: 0.25	Correlation: 0.07	Correlation: 0.35	Correlation: 0.30
Class 4: BPS**	Both afflicted (<i>n</i>): 6	Both afflicted (<i>n</i>): 1	Both afflicted (<i>n</i>): 1	Both afflicted (<i>n</i>): 0
	One afflicted (<i>n</i>): 94	One afflicted (<i>n</i>): 60	One afflicted (<i>n</i>): 21	One afflicted (<i>n</i>): 14
	Concordance: 0.06%	Concordance: 0.02%	Concordance: -	Concordance: -
	Correlation: 0.33	Correlation: 0.06	Correlation: -	Correlation: -

BPS = bladder pain syndrome; LUTS = lower urinary tract symptoms.

* Heritability estimates for latent class 1 not presented because this class represents individuals without LUTS.

** Concordance and correlations estimates for class 4 in males are not presented because of an insufficient number of cases.

Table 4

Variance components estimates for genetic and environmental effects with adjustment for age

	Females, 95% CI (range)			Males, 95% CI (range)		
	Genetic	Shared environment	Nonshared environment	Genetic	Shared environment	Nonshared environment
Class assignment *						
Class 2: Nocturia	0.34 (0.06–0.44)	0.03 (0.00–0.26)	0.64 (0.56–0.72)	0.38 (0.00–0.52)	0.00 (0.00–0.34)	0.62 (0.48–0.77)
Class 3: Infection	0.23 (0.00–0.34)	0.00 (0.00–0.24)	0.77 (0.66–0.88)	0.04 (0.00–0.50)	0.29 (0.00–0.46)	0.67 (0.50–0.82)
Class 4: BPS	0.30 (0.00–0.49)	0.00 (0.00–0.39)	0.70 (0.51–0.90)	-	-	-

CI = confidence interval; BPS = bladder pain syndrome; LUTS = lower urinary tract symptoms.

* Heritability estimates for latent class 1 are not presented because this class represents individuals without LUTS.