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Somatic comorbidity in women with overactive bladder syndrome

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Abstract

Purpose—To explore the influence of co-occurring somatic illnesses on prevalent overactive bladder in women of premenopausal age.

Methods—Data for the present study was derived from a nationwide survey on complex diseases among all twins in the Swedish Twin Registry born 1959–1985. The present study was limited to female twins participating in the survey (n = 12,850). Generalized estimating equations (GEE) were used to estimate odds ratios (ORs) with 95% confidence intervals (CIs). Environmental and genetic influences were assessed in co-twin control analysis.

Results—GEE analysis showed a significant association between overactive bladder and migraine (OR 1.34, 95% CI 1.15–1.57), fibromyalgia (1.83, 1.54–2.18), chronic fatigue (1.81, 1.49–2.19) and eating disorders (1.56, 1.24–1.96). There was also a significant association with allergic disorders including asthma (1.24, 1.01–1.52) and eczema (1.22, 1.04–1.43). Among reproductive disorders, urinary tract infections (1.60, 1.40–1.84), dysmenorrhea (1.53, 1.33–1.76) and pelvic pain (1.60, 1.31–1.94) showed the strongest association with overactive bladder. Results from co-twin control analysis indicated that the significant associations observed in GEE-analysis were influenced by both environmental and genetic factors without a common pathway model.

Conclusions—Our results suggest a multifactorial and complex pathogenesis of overactive bladder where associations between various somatic illnesses and overactive bladder may be affected by both environmental and genetic factors.

Keywords

Comorbidity; Overactive bladder; Somatic disease

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INTRODUCTION

Overactive bladder is a symptom syndrome which afflicts ~12% of the community dwelling population and is defined as 'urinary urgency, with or without urgency incontinence, usually with frequency and nocturia' by the International Continence Society (ICS).[1] Our current understanding of the co-occurrence of overactive bladder and somatic illnesses is largely fragmentary. With the exception for diabetes,[2] and neurologic diseases such as multiple sclerosis, Parkinson, and dementia.[3–5] the influence of co-occurring somatic disorders in women with overactive bladder is poorly understood. Previous epidemiologic studies suggest that various somatic diseases influence the occurrence of overactive bladder but have been limited by insufficient control for environmental and genetic confounding.[6–8] Increasing knowledge on how overactive bladder relates to other somatic conditions may provide important clues to the pathophysiologic mechanisms involved in the occurrence of overactive bladder. The aim of the present study was to assess if somatic illnesses are associated with overactive bladder using data from a large nationwide Swedish Twin Register screening on common complex diseases and exposures among female twins of premenopausal age.

METHODS

Data sources

This study was approved by the Regional Research Ethics Board at Karolinska Institutet and conforms to the STROBE guidelines for reporting observational studies (www.strobe-statement.org). The Swedish Twin Register, established in the 1950´s, contains data on nearly all twins born in Sweden since 1886.[9] Methods for assigning zygosity have been validated with DNA as having 98% or higher accuracy.[9] Data for the present study was derived from a comprehensive survey on common complex diseases and common exposures among all twins in the Swedish Twin Registry born 1959–1985 (n=42 852) in 2005 (described in detail previously).[10, 11] The overall response rate to the survey, the Screening Twin Adults: Genes and Environment (STAGE) study, was 66% among women (n = 12,850). The present study was limited to female twins participating in the survey since there were insufficient numbers of males with overactive bladder to allow for valid analyses.

Data ascertainment

The entire questionnaire contained approximately 1,300 questions divided into 34 sections using a branching format, meaning that participants were asked follow-up questions only if they responded positively to key initial questions. Overactive bladder was defined according to the International Continence Society criteria as a positive response to the question: "Do you experience sudden urgency to void with little or no warning?". Ascertainment of prevalent somatic diseases was performed using structured questions based on the criterion that disease had been confirmed by a physician and included: rheumatic diseases (rheumatism, Systemic lupus erythematosus, Morbus Bechterew), diabetes mellitus, inflammatory bowel diseases (Crohn's disease and ulcerative colitis), functional somatic disorders (migraine, fibromyalgia, chronic fatigue), eating disorders (anorexia, bulimia),

allergies (hay fever and eczema), asthma, myocardial infarction, infectious diseases (urinary tract infection and sexually transmitted diseases), reproductive disorders (dysmenorrhea, pelvic pain not including bladder pain, endometriosis), and endocrine diseases (hypothyroidism and other glandular disorders). Information on relevant covariates including the use of snuff, smoking habits, body mass index, childbirths, educational level (classified as elementary school, high school and college/university) and age was derived from the survey.

Statistics

In order to evaluate the association between overactive bladder and somatic diseases, logistic regression was used based on generalized estimating equations (GEE), which take into account the correlated (twin) structure of the data. The GEE analysis was adjusted for age and childbirth and odds ratios (ORs) were estimated with 95% confidence intervals (CIs). Women who responded positively on the question about current bladder pain were excluded from all analyses in order not to include cases of Bladder pain syndrome/ Interstitial cystitis (BPS/IC) (n=155).

Monozygotic twins share an identical genotype whereas dizygotic twins on average share 50 percent of their segregating genes. The co-twin control analysis is used to control for genetic background and unmeasured early environment shared by twins when studying the relationship between a putative exposure and a disease in disease discordant twin pairs. If estimates from co-twin control analysis, compared to GEE estimates, are attenuated, then the associations are confounded by familial factors. If the attenuation is present for both mono- and dizygotic twins, the associations are confounded by shared environmental factors. A reduction of the associations only among monozygotic twins suggests that the associations are confounded by genetic factors. A p-value <0.05 was considered significant for all analyses. All statistical analyses were performed using SAS software (version 9.2, SAS Institute, Cary, NC).

RESULTS

Table 1 present the characteristics of participants in the survey in relation to prevalent overactive bladder. Background characteristics including mean age, educational level, body mass index, pregnancy, snuff use and smoking were similar between the groups.

The prevalence of somatic diseases in women with and without overactive bladder is shown in Table 2. Women with overactive bladder reported a higher prevalence of all somatic disorders registered in the study. A higher prevalence of functional somatic disorders including migraine, fibromyalgia, chronic fatigue and eating disorders was particularly notable among women with overactive bladder. Among reproductive disorders, the prevalence of pelvic pain and dysmenorrhea was considerably greater among women with overactive bladder compared to those without.

Results from the GEE and subsequent co-twin control analysis are presented in Table 3. The GEE analysis confirmed the association between incident overactive bladder and migraine (OR 1.34, 95% CI 1.15–1.57), fibromyalgia (OR 1.83, 95% CI 1.54–2.18), chronic fatigue

(OR 1.81, 95% CI 1.49–2.19) and eating disorders (OR 1.56, 95% CI 1.24–1.96). There was also a significant association with allergic disorders including asthma (OR 1.24, 95% CI 1.01–1.52) and eczema (OR 1.22, 95% CI 1.04–1.43). Among reproductive co-occurring diseases, urinary tract infections, dysmenorrhea and pelvic pain showed the strongest association with overactive bladder.

In the co-twin analysis we analyzed only same sex pairs with information about zygosity and who were discordant for the outcome, i.e. one twin had overactive bladder while the healthy co-twin was used as a matched control (Table 3). When looking separately at functional somatic syndromes the significant association between overactive bladder and migraine was lost in both mono- and dizygotic twins. However, the point estimates were of similar magnitude as the GEE-effect indicating a loss of statistical strength due to smaller sample sizes in the co-twin control analysis. For eating disorders the point estimate in monozygotic twins diminished and lost significance, indicating that genetic factors may confound the association. For chronic fatigue on the other hand, the effect on overactive bladder remained at a significant level in both mono- and dizygotic twins suggesting that the conditions share pathoetiologic mechanisms not explained by shared genetic or environmental factors. For asthma and eczema the drop in the point estimates for both mono- and dizygotic twins suggest that the association found in the GEE-analysis was confounded by shared environmental effects.

For urinary tract infections and dysmenorrhea the co-twin control analysis suggested that the associations with overactive bladder were not confounded by common genetic factors since the association remained in monozygotic twins, who are genetically identical but discordant for overactive bladder. The opposite pattern was observed for pelvic pain where the association was lost among mono- but not dizygotic twins which indicates that the association between pelvic pain and overactive bladder may be confounded by shared genetic pathways.

DISCUSSION

This large population based study among female twins substantiates the notion that co-occurring somatic disease influences the occurrence of overactive bladder and possibly shares common etiologic pathways. The association with overactive bladder was particularly noticeable for functional somatic syndromes but also for gynecologic conditions of which pelvic pain showed the strongest relation to overactive bladder. Our findings suggest a multifactorial and highly complex pathogenesis of overactive bladder where associations between somatic illnesses and overactive bladder may be affected by both environmental and genetic confounding.

Surveys among community-dwelling women suggest that overactive bladder is a common condition, which increases with age.[12] Despite recent years efforts to shed light on the etiology of overactive bladder, only modest progress has been made. Indications of non-bladder illnesses being more prevalent among women with overactive bladder suggest that the condition may share pathophysiologic mechanisms with other somatic diseases. Further study of these relationships may therefore provide important clues to the elusive etiology of

overactive bladder. However, previous studies have been limited by lack of control for environmental and genetic factors which may confound the associations. For this purpose, studies on female twins with known zygosity are ideal.

The notion that somatic diseases may share pathophysiologic mechanisms with bladder disorders has been substantiated both in experimental and epidemiologic research.[13] Previously, Bladder pain syndrome (BPS)/ Interstitial cystitis (IC) has been associated with several functional somatic syndromes, allergies, irritable bowel syndrome and infectious disease.[14, 15, 16] The present study show that functional somatic syndromes are related not only to BPS/IC, which is characterized by chronic pain during bladder filling, but also to overactive bladder. Some of the typical symptoms for the two diseases are shared, such as nocturia and frequency, and our data suggest that the two conditions may also have pathophysiologic features in common as reflected by the shared affinity for functional somatic syndromes such as chronic fatigue, eating disorders, migraine and fibromyalgia.

The co-occurrence of functional somatic syndromes in women with overactive bladder does, however, not seem to have a common explanatory etiologic model since the variance component patterns varied for the syndromes. Previous studies have shown a significant contribution of genetic factors to liability to anorexia nervosa,[17] and the co-twin control analysis of the present study suggested that shared genetic factors may influence the association between eating disorders (i.e. anorexia and bulimia) and overactive bladder, i.e. that the conditions may have genetic pathoetiologic pathways in common. In contrast, non-shared environmental factors in later life had the greatest influence on the association between chronic fatigue and overactive bladder. Thus, the specific influences on overactive bladder by functional somatic syndromes needs to be explored individually and not under the assumption that these syndromes can be clustered together.

The co-twin control analysis suggested that for asthma and eczema the association with overactive bladder was dominated by environmental effects rather than common genetic traits. This corresponds well to studies on asthma heritability which indicate that genetic influences on asthma are substantial but that genetic contribution to disease liability decreases with increasing age.[18] Although further studies are needed to uncover which environmental exposures constitutes the link between asthma and overactive bladder it is noteworthy that β3-agonists, initially intended for the treatment of asthma, are prescribed for the treatment of overactive bladder.[19, 20]

The risk for overall urinary incontinence has been found to be higher among women who experienced microbiologically confirmed urinary tract infections compared with those who did not.[21] We found no indication of shared genetic factors contributing to this association but rather that non-shared environmental factors between twins discordant for overactive bladder had the greatest influence on the association. This suggest that factors such as smoking, drinking habit, voiding patterns, and life style may contribute both to the occurrence of overactive bladder and urinary tract infections later in life. Contrary to the environmental influence on the association between overactive bladder and urinary tract infections, the association with pelvic pain diminished among mono- but not dizygotic twins to indicate a relationship confounded by shared genetic factors. Pelvic pain is a rather

heterogeneous diagnostic term which may entail occult endometriosis, bladder pain syndrome (interstitial cystitis), adhesions after surgery, and psycho-somatic pain. These conditions are likely to have very different etiologic mechanism and similar to the reasoning of an underlying association between functional somatic syndromes and overactive bladder we believe caution is advised when interpreting these results and that these conditions should not be amalgamated in future studies.

Despite the large scale of this nationwide twin study we did not have sufficient statistical strength to study environmental and genetic effects on associations for some of the low-prevalent somatic illnesses in this young population of mostly premenopausal age. The imprecise estimates are exemplified by the broad confidence intervals in the co-twin control analysis for mono- and dizygotic twins with diabetes. We also recognize that diagnosis ascertainment based on participant reports to some extent is a source of potential misclassification and recall bias. The wide-ranging scope of the survey did, however, not allow for a more detailed data collection on each specific disease due to limitations. We therefore believe that our findings need to be substantiated in case-ascertained studies using established diagnosis criteria.

In conclusion, our results support the notion of an intricate pathogenesis of overactive bladder which is influenced by co-occurring diseases. In order to advance our understanding of the complex etiology, and potential treatments, of this highly prevalent and debilitating symptom syndrome, research efforts that take into consideration the impact of co-occurring diseases are required.

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Table 1

Characteristics of study participants.

	Overactive bladder			
	No		Yes	
Age (years), mean (sd)	33.4	(7.6)	34.1	(7.8)
Birthyear				
1959–1964	2707/11637	(23.3)	271/1033	(26.2)
1965–1969	2288/11637	(19.7)	210/1033	(20.3)
1970–1974	2190/11637	(18.8)	184/1033	(17.8)
1975–1979	2064/11637	(17.7)	181/1033	(17.5)
1980–1985	2388/11637	(20.5)	187/1033	(18.1)
Educational level				
Elementary school	512/11511	(4.4)	50/1020	(4.9)
High school	5631/11511	(48.9)	482/1020	(47.3)
College/university	5368/11511	(46.6)	488/1020	(47.8)
Obesity (BMI>30)	589/11341	(5.2)	83/1022	(8.5)
Pregnancy	7029/10970	(64.0)	618/925	(66.8)
Snuff users	311/8979	(3.5)	22/762	(2.9)
Smokers	655/8980	(7.3)	46/761	(6.0)

Figures are number of subjects (%) unless specified.

BMI denotes body mass index.

Table 2

Prevalence of co-occurrent disease in relation to prevalent overactive bladder.

	Overactive bladder			
	No		Yes	
	n/ N	(%)	n/ N	(%)
Bechterew's disease	48/9998	(0.5)	8/879	(0.9)
Systemic lupus erymatosus	16/10000	(0.2)	2/882	(0.2)
Struma	235/9996	(2.3)	29/882	(3.3)
Gland disorder, excl. struma	163/10002	(1.6)	13/880	(1.5)
Migraine	2787/9958	(28.0)	296/878	(33.7)
Crohn's disease	43/9998	(0.4)	2/879	(0.2)
Ulcerative colitis	77/9987	(0.8)	9/877	(1.0)
Eating disorder	831/9999	(8.3)	107/878	(12.2)
Chronic fatigue	1009/10743	(9.4)	162/983	(16.5)
Rheumatism	66/10667	(0.6)	10/967	(1.0)
Fibromyalgia	1382/10430	(13.3)	205/941	(21.8)
Asthma	919/8718	(10.5)	48/393	(12.2)
Eczema	2550/10534	(24.2)	257/944	(27.2)
Hay fever	1832/10506	(17.4)	178/941	(18.9)
Diabetes	100/10018	(1.0)	14/880	(1.6)
Heart attack	3/4364	(0.1)	1/396	(0.3)
Urinary tract infection	4946/11520	(42.9)	560/1023	(54.7)
Dysmenorrhea	3521/10756	(32.7)	386/906	(42.6)
Pelvic pain	1026/10676	(9.6)	131/897	(14.6)
Endometriosis	390/10887	(3.6)	42/921	(4.6)
Sexually transmitted disease	2050/9690	(21.2)	219/909	(24.1)

Table 3

Results from logistic regression and co-twin control analysis.

	GEE		Co-twin control			
			Monozygotic		Dizygotic	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Bechterew's disease	1.67	(0.77–3.66)		†	2.00	(0.18–22.06)
Systemic lupus erymatosus	1.42	(0.30–6.65)		†		†
Struma	1.37	(0.90–2.08)	0.82	(0.18–3.69)	0.62	(0.15–2.60)
Gland disorder, excl. struma	0.99	(0.55–1.78)		†	4.00	(0.45–35.79)
Migraine	1.34	(1.15–1.57)	1.21	(0.62–2.36)	1.30	(0.70–2.42)
Crohn's disease	0.60	(0.14–2.55)		†		†
Ulcerative colitis	1.44	(0.70–2.95)	0.33	(0.03–3.21)	1.00	(0.06–15.99)
Eating disorder	1.56	(1.24–1.96)	0.90	(0.29–2.83)	1.71	(0.57–5.20)
Chronic fatigue	1.81	(1.49–2.19)	2.55	(1.24–5.21)	2.54	(1.11–5.78)
Rheumatism	1.35	(0.62–2.95)	0.25	(0.02–2.48)	1.00	(0.14–7.10)
Fibromyalgia	1.83	(1.54–2.18)	1.85	(1.02–3.36)	1.59	(0.77–3.27)
Asthma	1.24	(1.01–1.52)	1.03	(0.47–2.28)	0.60	(0.26–1.38)
Eczema	1.22	(1.04–1.43)	1.01	(0.63–1.62)	0.94	(0.55–1.63)
Hay fever	1.15	(0.97–1.37)	1.16	(0.55–2.44)	1.13	(0.59–2.17)
Diabetes	1.55	(0.85–2.84)	4.71	(0.51–43.32)	0.47	(0.09–2.60)
Heart attack	3.52	(0.36–34.02)		†		†
Urinary tract infection	1.60	(1.40–1.84)	1.77	(1.16–2.70)	0.86	(0.50–1.47)
Dysmenorrhea	1.53	(1.33–1.76)	2.48	(1.45–4.23)	1.18	(0.71–1.95)
Pelvic pain	1.60	(1.31–1.94)	1.00	(0.50–2.00)	1.88	(0.91–3.91)
Endometriosis	1.26	(0.90–1.75)	0.50	(0.09–2.73)	1.97	(0.74–5.27)
Sexually transmitted disease	1.14	(0.96–1.35)	1.63	(0.87–3.03)	1.07	(0.52–2.32)

All analyses adjusted for age and pregnancy.

† Insufficient number of observations for analysis.

596 pairs (361 MZ + 235 DZ) were discordant on OAB.