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ORIGINAL ARTICLE

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Prevalence of autoimmune disorders among bladder pain syndrome patients' relatives

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ABSTRACT

Purpose: Possible genetic background and autoimmune etiology of Bladder Pain Syndrome (BPS, formerly Interstitial Cystitis, IC) has been suggested. We studied whether familial clustering of BPS, other autoimmune diseases or fibromyalgia exist among BPS patients' genetically close relatives; possibly reflecting some common predisposing genetic background of these diseases.

Materials and methods: Altogether 420 first- or second-degree relatives of 94 BPS patients fulfilling the NIDDK criteria were asked to fill in a survey on the self-reported diagnosis of urinary tract diseases, fibromyalgia and 23 autoimmune diseases, together with filling the O'Leary–Sant symptom score. The ones with high symptom scores were interviewed and, if necessary, referred to a further clinical consultation. The prevalence of other diseases was compared to previously published prevalence percentages.

Results: 334 (80%) of 420 family members returned the questionnaire. Only one of the relatives fulfilled the NIDDK criteria, and one sibling pair among the original BPS patients was found. Asthma, ulcerative colitis, fibromyalgia, iritis and rheumatoid arthritis were more common in the study population than in the reference populations. The reported prevalence of atopic dermatitis and rhinoconjunctivitis causing allergies were lower. In addition, the results show that the O'Leary–Sant symptom score is not reliable in screening for new BPS cases.

Conclusions: Our study suggests that in BPS patients' families, fibromyalgia and autoimmune diseases including asthma, and especially the non-allergic form of asthma, may be over-represented.

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Introduction

According to the present International Society for the Study of Interstitial Cystitis (ESSIC) definition, Bladder Pain Syndrome (BPS) is diagnosed on the basis of persistent or recurrent chronic pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like the persistent urge to void or urinary frequency. Confusable diseases as the cause of the symptoms must be excluded [1]. Estimations on the prevalence of BPS have varied a lot due to non-uniform definitions used in past, for example, from 18.1 to 450 per 100,000 women in Finland, and a clear female predominance is repeatedly seen across different cohorts [2–4]. The etiology of BPS is unknown. Various etiologies for BPS have been suggested, and it seems likely that the syndrome includes a combination of several different multifactorial diseases with heterogeneous causing factors.

It has been suggested that BPS might be of autoimmune origin, based on the strong female preponderance and the clinical co-existence of BPS and other known autoimmune diseases in patients and families [4]. Autoimmune diseases have typically at least partial genetic background [5]. If a condition has a strong genetic component, it often can be seen to cluster in families. BPS has also been linked to non-urological pain syndromes like fibromyalgia [6].

In this cross-sectional cohort study, we evaluated whether the first- or second-degree relatives of BPS patients have more BPS, autoimmune diseases or fibromyalgia than the general population; possibly reflecting some common predisposing genetic background of these diseases.

Materials and methods

Patients with BPS, fulfilling the NIDDK criteria with bladder pain [7], were collected from seven different Finnish

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Supplemental data for this article can be accessed here.

Urological Departments during years 2005–2013. Their first-degree relatives (parents, siblings, children) and second-degree relatives in the line of direct descent (grandparents and grandchildren) were asked to join the study. The study-protocol was approved by the Helsinki University Hospital Ethics Committee of Surgery (protocol number: Dnro HUS 341/E6/04) and all participants gave written informed consent with guarantees of confidentiality.

Altogether 115 BPS patients from various parts of Finland were personally asked by their urologists to join the study, of which 103 (90%) returned the completed questionnaires. They were asked to fill in a questionnaire about their diagnoses of autoimmune diseases (Table 1) and about their first- and second-degree relatives' contact information. Four probands deceased before they filled in a questionnaire on autoimmune diseases.

The presence of Hunner's lesions was checked from the cystoscopy documents of each patient. 29 of the patients were Hunner's lesion positive, 72 negative; in two cases this data was missing.

Among the 103 responders, 94 (82%) had living relatives who agreed to join the study. These 94 patients had altogether 508 listed first- and second-degree relatives, of whom 420 (83%) were willing to join the study according to their proband. The questionnaires, together with a prepaid return envelope, were sent to these 420 family members. If a person did not respond, the material was sent twice again, and before the last mailing, a member of the study group contacted the person by phone.

The relatives were asked to fill in the O'Leary–Sant symptom score and a questionnaire about their diagnosed urinary tract diseases. BPS was regarded as potential if the person had $\geq$7 points in the O'Leary–Sant symptom score together with a positive bladder pain score. These relatives were interviewed on the telephone by an experienced urologist to define the urological condition. Still BPS suspicious cases were asked to fill in voiding diaries and re-interviewed, and/or referred to further examination at their local urological clinics, for confirming the diagnosis. If a person reported her/himself to have a diagnosis of BPS, it was confirmed by reviewing her/his medical files.

To test the clustering of other autoimmune diseases in the BPS patients' families, all participants were asked to report if they had certain autoimmune diseases or fibromyalgia (Table 1). The rhinoconjunctivitis causing allergies (pollen, animals) were analyzed separately, based on the attendee's notifications of his/her specific allergens. The prevalence of each disease in BPS families was compared with the known general prevalence of the disease in question; preferably in a Finnish population (Table 1). The concept of allergies in the literature varies from study to study, therefore no reliable reference for allergies, in general, was found, but the comparison was made within rhinoconjunctivitis causing allergies. The prevalences were counted both for the whole group (Table 1) and separately for families determined as Hunner positive or Hunner negative depending on proband's data (Supplemental material). SPSS (Statistical Package for Social Sciences) version 25.0 was used in the data analysis.

Results

Eventually, 334 (80%) of 420 family members returned the questionnaire, of which 95 (28%) were from Hunner's lesion positive patients' families, 230 (69%) from Hunner negative. Nine of the replies were from relatives of the two probands with unknown Hunner lesion status. The demographics of the study cohort are shown in Table 2. Two of the probands were siblings. Four (0.95%) of the relatives (all women, all first-degree relatives) indicated themselves having a diagnosis of BPS. After checking their medical records, only one of these diagnoses was confirmed. Other conditions were confirmed as recurrent UTIs ($n = 1$), urinary incontinence ($n = 1$) and pollakisuria with normal finding in cystoscopy ($n = 1$). Moreover, none of these relatives scored $\geq$7 points in the O'Leary–Sant symptom score at the time of filling the questionnaires.

Altogether 10% (35) of the 334 family members got $\geq$7 points and positive bladder pain entry in the O'Leary–Sant symptom score (median = 10, mean = 10.8, min. = 7, max. = 17) (Table 2). Of these, 91% (32 individuals) were first-degree and 8.6% (three people) second-degree relatives. However, according to the phone interview by an experienced urologist of the BPS study group, only 7 (20%) of these 35 relatives were suspected of having BPS (6 females, 1 male). Based on the voiding diary and further interview, four out of these seven did not have BPS. Finally, only three of the 334 relatives (0.9%, all female, all first-degree relatives) were referred to their local urological clinic for further clinical examination. Based on the clinical evaluation, none had BPS. The final diagnoses are listed in Table 3.

At least one autoimmune disease was reported by 57% (191 people) of the relatives and 62% (61 people) of the patients, of which the most common ones were sequential: allergies, asthma and atopic dermatitis (Table 1). Compared to the general population, asthma, fibromyalgia, ulcerative colitis, iritis and rheumatoid arthritis were more common in the study population than in the reference populations (Table 1). The prevalence of atopic dermatitis was lower, 12% compared to 28% in the comparative cohort [10]. The prevalence of self-reported allergies was 41% and rhinoconjunctivitis causing allergies 20%, which is also lower than expected (27–33% for rhinoconjunctivitis causing allergies in the general Finnish population [8]).

When comparing the Hunner's lesion positive patients' families with the ones of Hunner negative (Supplemental material), it was detected that all of the five Sjögren's syndrome cases were in the Hunner negative patients' families (one Sjögren's case was missing Hunner data). The prevalence of fibromyalgia and atopic dermatitis was a bit higher in the Hunner negative patients' families (5.0 vs 2.4% and 13 vs 8.9%, respectively). Some other differences were also seen when comparing these groups, but these results may be stochastic because of the small size of the cohorts.

Allergic asthma is determined as asthma with allergic rhinoconjunctivitis. The percentage of non-allergic asthma was surprisingly high in all groups (Table 4).

Table 1. The prevalence of the studied autoimmune diseases and fibromyalgia.

Reported prevalence % (number)	BPS patients (99)	1st degree relatives (292)	2nd degree relatives (42)	All relatives (334)	The whole families (433)	Comparative population (Country)
Allergies	45% (45)	35.3% (103)	55% (23)	37.7% (126)	39.5% (171)	Not available
Rhinoconjunctivitis causing allergies	23% (23)	17% (51)	33% (14)	19% (65)	20% (88)	27–33% (Finland) [8]
Asthma	12% (12)	15% (43)	12% (5)	14% (48)	14% (60)	9.4% (Finland) [9]
Atopic dermatitis	16% (16)	8.9% (26)	21% (9)	10% (35)	12% (51)	28.1% (Finland) [10]
Fibromyalgia	11% (11)	2.4% (7)	2.4% (1)	2.4% (8)	4.4% (19)	0.75% (Finland) [11] 2.5% (Europe) [12]
Psoriasis	6.0% (6)	3.8% (11)	0.0% (0)	3.3% (11)	3.9% (17)	5.3% (Sweden) [13]
Thyroiditis	4.0% (4)	4.5% (13)	0.0% (0)	3.9% (13)	3.9% (17)	3.0% (Scotland) [14]
Ulcerative colitis	1.0% (1)	4.5% (13)	4.8% (2)	4.5% (15)	3.7% (16)	0.177% (Finland) [15]
Rheumatoid arthritis	6.1% (6)	2.4% (7)	0.0% (0)	2.1% (7)	3.0% (13)	0.44% (Nordic countries) [16]
Lichen ruben (planus)	2.0% (2)	3.1% (9)	2.4% (1)	3.0% (10)	2.8% (12)	1.9% (Sweden) [17]
Celiac disease	3.0% (3)	1.4% (4)	0.0% (0)	1.2% (4)	1.6% (7)	2.0% (Finland) [18]
Iritis	1.0% (1)	1.7% (5)	0.0% (0)	1.5% (5)	1.4% (6)	0.0687% (Finland) [19]
Sjögren's syndrome	3.0% (3)	1.0% (3)	0.0% (0)	0.90% (3)	1.4% (6)	0.22–3.39% (Scandinavia) [20]
Alopecia areata	1.0% (1)	1.7% (5)	0.0% (0)	1.5% (5)	1.4% (6)	2% (Wolrdwide) [21]
Vitiligo	0% (0)	1.7% (5)	0.0% (0)	1.5% (5)	1.2% (5)	0.5–2.0% (Worldwide) [22]
Polymyalgia rheumatica	2.0% (2)	0.68% (2)	0.0% (0)	0.60% (2)	0.92% (4)	0.70–0.91% (USA and UK) [23]
Primary biliary cirrhosis	0% (0)	0.34% (1)	0.0% (0)	0.30% (1)	0.23% (1)	0.018% (Finland) [24]
Crohn's disease	0.0% (0)	0.34% (1)	0.0% (0)	0.30% (1)	0.23% (1)	0.038% (Finland) [15]

All participants were asked to fill in a list of autoimmune diseases and fibromyalgia by picking 'yes' or 'no' written in the questionnaire after each one of the diseases listed, signifying whether he/she has the diagnose in question or not. If the person indicated him/herself allergic, he/she was asked to specify the allergen. Four of the original 103 probands deceased before they filled in questionnaire on autoimmune diseases.
This table includes those of the diseases asked, that at least one person had. In addition, the existence of following were asked: lupus erythematosus (SLE, DLE, SCLE, NLE), autoimmune pemphigus (pemphigoid, epidermolysis bullosa), mixed connective tissue disease, dermatomyositis, scleroderma, vasculitis (temporal arteritis, Takayasu's arteritis, polyarteritis nodosa, Kawasaki disease, purpura, Henoch–Schönlein purpura, leukocytoclastic vasculitis, lymphocytic vasculitis, cryoglobulinemic vasculitis) and autoimmune hepatitis.

Table 2. The demographic data of the study sample.

	BPS patients (103)	1st degree relatives (292)	2nd degree relatives (42)	All relatives (334)	Relatives with BPS indicative points in the O'Leary–Sant symptom score (35)
Median age at the time of BPS diagnosis (mean)	50 years (49.0)				
Median age at the time of filling in the questionnaires (mean)	63 years (60.5)	53 years (52.4)	25 years (30.6)	51 years (49.7)	63 years (58)
The age range; min.–max.	22–88 years	18–84 years	18–90 years	18–90 years	19–90 years
Percentage (number) of women	85% (88)	60% (174)	50% (21)	58% (195)	71% (25)

BPS indicative points in the O'Leary–Sant symptom score were classified as $\geq$7 points and positive bladder pain entry.

Table 3. The final diagnosis of the 35 relatives who scored BPS indicative, that is, $\geq$7 points and positive at the bladder pain entry, in the O'Leary–Sant symptom score.

Number of people	Diagnosis
15	Nonspesified pollacisuria/dysuria
5	Prostatism
4	Evident reasons for pollacisuria (e.g. polydipsia, furosemide medication)
4	Recurrent urinary tract infections
3	Overactive bladder
2	Urinary incontinence
1	Deceased before contacted
1	Could not be contacted

Discussion

If a disease has a firm genetic background, it can often be seen to cluster in families. In the present study, the number of confirmed BPS in the close relatives of our BPS patients was low, 0.6%. Only one sibling pair among BPS patients was found, and one out of the other 334 relatives (0.3%) had BPS. This was less than relatives' self-reported prevalence of the disease (0.95%) and is less than in the general population. However, this is in line with earlier findings of Warren et al., who noticed that among BPS patients who were

Table 4. Proportion of non-allergic asthmatics in the cohort.

Population (number of the whole population)	Non-allergic asthmatics of all asthmatics (percentage)
Hunner positive BPS patients (28)	2/3 (67%)
Hunner positives' relatives (95)	5/15 (33%)
Hunner positive families (123)	7/18 (39%)
Hunner negative BPS patients (69)	3/8 (38%)
Hunner negatives' relatives (230)	16/31 (52%)
Hunner negative families (299)	19/39 (49%)
Whole cohort (433)	28/60 (47%)

The allergens reported by the attendants were classified as rhinoconjunctivitis causing (pollen, animals) and other allergens (e.g. nickel, different chemicals, medicines, foodstuff). People having asthma but no rhinoconjunctivitis causing allergies, were defined as non-allergic asthmatics. The common percentage of non-allergic asthma among all asthma patients varies between 10–33% in different populations [25].
One of the patients with missing data on Hunner's lesion status and two of her relatives had asthma (patient: allergic asthma, both relatives: non-allergic asthma); these cases are counted in the whole cohort's values. (families = patients + relatives).

members on the Interstitial Cystitis Association in the US, only 0.7% of the patients' first-degree relatives had BPS, while 3.9% of them noted that they would have the disease. Nevertheless, Warren et al. showed in the same study that there was a greater concordance of BPS among monozygotic (five of eight) than dizygotic (none of 26) twin pairs, suggesting a strong genetic predisposition to BPS [26]. In our cohort, the median age of the relatives at the time of the study was quite close to the median age of the patients at the time of their BPS diagnosis; 51 vs. 50 years, respectively. As time passes, it is possible that a few BPS cases will still arise from our study population.

Thus, our results do not directly support the idea of BPS being an inherited disease. It is noteworthy that these results do not rule out the genetic background of BPS, but it is possible that there are multifactorial genetic components with reduced penetrance and a certain quite high threshold of liability behind BPS. The genetic predisposition of BPS has previously been suggested [27]. As mentioned above, Warren et al. showed that monozygotic twins have a markedly higher risk of BPS than dizygotic twins [26]. Warren and coworkers also showed that first-degree adult female relatives of BPS patients had a 17-fold prevalence of BPS, compared to the general American female population of the same age [28]. As a curiosity, the BPS family of an affected mother and three affected grown-up children out of four has also been described [29].

To our knowledge, there are no previous publications about the relationship between atopic dermatitis and BPS. The prevalence of atopic dermatitis among the study group was lower than in general, irrespective of the presence or absence of Hunner's lesion in the proband.

The prevalence of rhinoconjunctivitis causing allergies compared to the general population was lower in all of our BPS patient groups and whole families' groups, regardless of the Hunner's lesion status. Interestingly, the prevalence of rhinoconjunctivitis causing allergies were constantly lower in the first-degree relatives' groups than in the corresponding second-degree relatives' (Table 1 and Supplemental material). However, this phenomenon needs larger study groups to be confirmed in the future.

There are a few earlier reports of the possible association of BPS and asthma in BPS patients [30]. However, to our knowledge, the association between BPS and different asthma types has not been reported earlier. It is a peculiar finding in this study, that in the BPS families the prevalence of asthma was higher while the prevalence of atopic dermatitis and rhinoconjunctivitis causing allergies were lower than in the general population since asthma, allergies and atopic dermatitis are often linked together. This fits in with our finding that the percentage of non-allergic asthma of the asthma patients in our whole cohort (47%), in the group of relatives (48%), as well as in BPS patients (42%), was higher than in general; the common percentage of non-allergic asthma among all asthma patients varies between 10–33% [25]. The prevalence of non-allergic asthma among asthmatics seems to be even higher in Hunner's lesion negative BPS patients' families compared to Hunner positives' families (49 vs 39%, respectively) (Table 4). Our study suggests that in BPS patients' families, asthma, and especially the non-allergic form of asthma, may be over-represented. It is even possible, that there would be some shared predisposing alleles or immunologic mechanisms behind BPS and non-allergic asthma. More detailed studies on the connection between BPS and different asthma types are needed.

Our results suggest that the O'Leary–Sant symptom score is not specific in screening for new BPS cases, since none of the high ($\geq$7 points) scoring relatives finally had BPS. On the other hand, none of the relatives with previous BPS diagnosis scored $\geq$7 points, suggesting low sensitivity as well. This suggests, that the O'Leary–Sant symptom score is more suitable for following the change in the grade of the symptoms within a certain BPS patient, than for screening for new BPS cases.

A strength of this study is the thorough diagnostics of BPS. Only patients fulfilling the NIDDK criteria for BPS with bladder pain were approved as probands. All BPS diagnoses reported by the relatives were checked comprehensively from the original patient documents. Three out of four cases did not meet the NIDDK criteria of BPS, however, it is possible that they might fulfill the later ESSIC criteria, which were not used at the time our study began. It is noteworthy, that the NIDDK criteria were not originally designed to be used to diagnose BPS. In addition, and more precisely compared to many other surveys, in our study all of the relatives scoring high points in the O'Leary–Sant symptom score were personally interviewed by an experienced urologist. If the urologist concluded that BPS diagnosis seemed possible, the person was further clinically examined by an experienced urologist on a urological department. Thus, the final BPS diagnoses in this study are very reliable.

Several limitations of this study need to be considered. The detailed statistical analysis of this study is not reasonable because of the small sample size. The results involving the association on BPS, other autoimmune diseases and fibromyalgia would have gained more generalizability, if there would have been a better specific control population instead of previously published cohorts. Our original aim was to use a previous large Finnish BPS survey data [31] as our

comparison population, which unluckily was not available anymore. For practical reasons, we utilized the results from several previous epidemiological studies as comparison; in every case as close matches to a Finnish population as possible. Many of the autoimmune diseases listed in our study are rare in the population and consequently, very few were found in our cohort. Therefore, nothing can be concluded on these rare conditions due to the small sample size.

No medical files were reviewed to confirm the diagnosis of autoimmune diseases as it was based solely on a self-reported questionnaire. However, all responders who reported having an autoimmune disease diagnosis were asked to specify in which medical institute they had been treated for it. This improved the probability of reporting a correct diagnosis.

In this study, we used the NIDDK criteria in recruiting the probands, because the ESSIC classification was not published yet at the time we started. The association with the certain autoimmune disease might be more evident in certain ESSIC proposed subtypes of BPS. Further studies on the correlation between different BPS subtypes and other autoimmune diseases are warranted with the potential for a better understanding of possibly shared etiologies and treatment strategies.

We show in this clinically well-characterized cohort, that Finnish BPS patients' genetically close relatives do not have a higher prevalence of BPS than people in general. The risk for several autoimmune diseases (asthma, ulcerative colitis, iritis and rheumatoid arthritis) and fibromyalgia was higher among the BPS patients and their first- and second-degree relatives, raising the possibility that these diseases may be linked to BPS with some common predisposing genetic or immunological factors. Interestingly, the prevalence of atopic dermatitis and rhinoconjunctivitis causing allergies were lower within our study group than in general, and the proportion of non-allergic asthma within the asthmatics was markedly higher than expected. This is the first time that BPS is linked specifically to the non-allergic form of asthma, and highlights the need for further studies between different subtypes of BPS and of asthma.

Geolocation information

The patients and their relatives were collected from various parts of Finland.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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