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EVALUATION OF ATOPIC STATUS IN PATIENTS WITH PRIMARY SJOGREN'S SYNDROME

PRİMER SJÖGREN SENDROMLU HASTALARDA ATOPİK DURUMUN DEĞERLENDİRİLMESİ

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ABSTRACT

AIM: The prevalence of atopy has been investigated in different autoimmune diseases in various studies. The atopic status in primary Sjögren's syndrome (pSS) patients has not been evaluated yet. We aimed to determine the relationship between pSS and atopy.

MATERIAL AND METHOD: Fifty consecutive adult patients with pSS and fifty age and sex-matched controls were recruited in this study. pSS patients were evaluated with laboratory tests and disease activity score. All subjects underwent skin prick test with a standard panel of common aeroallergens.

RESULTS: Ten patients (10/50, 20%) in the pSS group and six participants (6/50, 12%) in the control group had positivity on skin prick tests with common inhalant allergens (p=0.267). No significant differences were found regarding the clinical characteristics between atopic and non-atopic pSS patients.

CONCLUSIONS: Atopic status and allergen sensitization were evaluated in pSS patients. To our knowledge, this is the first study investigating the inhalant allergen spectrum in pSS patients. The prevalence of atopy is similar in patients with pSS to the controls.

Key words: *Allergy, atopy, Sjögren's syndrome, skin prick test, Th1/Th2 paradigm*

ÖZET

AMAÇ: Farklı otoimmün hastalıklarda atopi prevalansı çeşitli çalışmalarla araştırılmıştır. Ancak primer Sjögren sendromlu (pSS) hastalardaki atopik durum henüz değerlendirilmemiştir. Çalışmamızda pSS ve atopi arasındaki ilişkiyi belirlemeyi amaçladık.

GEREÇ VE YÖNTEM: PSS tanısı almış elli erişkin hasta ve yaş ve cinsiyet uyumlu elli tane kontrol çalışmaya alındı. pSS hastaları laboratuvar testleri ve hastalık aktivite skoru ile değerlendirildi. Tüm katılımcılara standart aeroalerjen paneliyle cilt prik testi uygulandı.

BULGULAR: pSS grubunda 10 hastanın (10/50, %20) ve kontrol grubunda altı kişinin (6/50, %12) inhalen alerjen deri prik test sonuçları pozitif bulundu (p=0.267). Atopik ve atopik olmayan pSS hastaları arasında klinik özellikler açısından anlamlı fark bulunmadı.

SONUÇ: PSS hastalarında atopik durum ve alerjen duyarlılığı değerlendirildi. Bildiğimiz kadarıyla bu, pSS hastalarında inhalen alerjen duyarlılığını araştıran ilk çalışmadır. Atopi prevalansı pSS'li hastalar ve kontroller arasında benzer bulundu.

Anahtar Kelimeler: *Alerji, atopi, Sjögren sendromu, deri prik test, Th1/Th2 paradigması*

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INTRODUCTION

Atopy is a genetic tendency to develop allergic diseases such as allergic rhinitis, asthma, and atopic dermatitis by producing immunoglobulin E (IgE) antibodies in response to common allergens especially inhaled and food (1). Th1/Th2 paradigm supposed that inadequate Th1 cell response and the predominance of Th2 cells lead to progress allergy (2). Conversely, it is widely accepted that Th1 cells play a major role in the pathogenesis of the autoimmune disease. Atopic diseases and autoimmune diseases were accepted at opposite ends of an immunological spectrum, as a result of dysregulated immune responses, based on the Th1/Th2 paradigm. It was speculated that atopy reduces the risk of developing autoimmune diseases or autoimmune diseases that prevent developing atopic diseases (3). Although, some studies reported the low prevalence of atopy in autoimmune diseases (4,5); the Th1/Th2 paradigm has been changed by the definition of Th17 and regulatory T (Treg) cells. Th17 play a role in the pathogenesis of both atopic and autoimmune diseases (6).

Primary Sjögren's Syndrome (pSS) is a chronic autoimmune disease characterized by both organ-specific and systemic manifestations that primarily affects exocrine glands; especially the salivary and lacrimal, resulting in oral and ocular dryness due to lymphocyte infiltration and inflammation (7). pSS mainly affects females, and the mean age of onset is usually between forty and fifty years old (8). The pathogenesis of pSS is not fully understood. The environmental and genetic factors and components of both innate and adaptive immune systems have been supposed to have a role in the pathogenesis of pSS (9). Some studies about the expression of cytokines in labial salivary gland tissue of patients suggested that pSS is a T helper 1 (Th1) mediated disease (10,11). The results, suggesting Th2 predominance in pSS, are limited to mouse models in a few studies (12,13). After the discovery of Th17, studies revealed that there is evidence about the role of Th17 in pSS. Although it is not known, which one is more dominant, subsets of CD4 T cells, including Th1 and Th17, participate in the pSS pathogenesis (9). To our knowledge, there is not enough data about an association between atopy and pSS in the literature. Thus, we aimed to investigate, the prevalence of atopy in patients with pSS in our center and the association between the types of sensitized allergen and pSS.

MATERIAL AND METHOD

Study Population

Fifty consecutive adult patients with pSS were recruited in this cross-sectional study between July 2016 and June 2017. Fifty age and sex matched subjects who did not have pSS or other connective tissue disease were included as a control group. Diagnosis of patients was based on the 2016 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for pSS (14). Being younger than eighteen years old, having a secondary Sjögren's syndrome and/or concomitant connective tissue disease, and pregnancy were the exclusion criteria. The study was conducted in accordance with the Helsinki Declaration and ethical permission was obtained from ethical review board of University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital (27.06.2016, No:31/09). All participants signed an informed consent prior to inclusion to the study.

Patients' demographic data and medical history, clinical features of the concomitant disease(s), and family history of allergy were recorded. All subjects were questioned about atopic diseases whichever diagnosed with by a physician. The presences of atopic diseases were evaluated based on self-reported data and medical records. Some symptoms related to the manifestation of pSS that may mimic allergic rhinitis and asthma were not accepted as evidence of atopic diseases.

Laboratory

The levels of eosinophil, rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), C reactive protein (CRP), anti-nuclear antibody (ANA), anti-SSA and anti-SSB were retrieved from medical records.

Disease Severity

The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) was used for assessment of the disease activity. ESSDAI includes twelve domains related to organ systems as follows; constitutional, articular, renal, respiratory, cutaneous, muscular, peripheral nervous system (PNS), central nervous system (CNS), haematological, glandular, lymphadenopathic, biological with a score ranging from 0-123. For each domain, features of disease activity are classified in 3-4 activity levels (no, low, moderate, or no, low, moderate, and high). Scores <5 are classified as "low disease activity"; 5 to 13 are a "moderate disease activity", and ≥14 are "high disease activity" (15). The severity of the symptoms related to the primary allergic disease was assessed with a visual analogue scale (range 0-10; 0: no symptom, 10: the most severity of symptoms).

Skin Prick Tests

All the participants who gave consent underwent skin prick test to a standard panel of common aeroallergens including "Dermatophagoides pteronyssinus, Dermatophagoides farinea, grass mix, weed mix, trees mix, Blatella germenica, cat dander, mould mix" (Alk, Denmark). Histamine (10 mg/ml) was used as positive control and saline as a negative control. None of the participants had taken any drugs such as antihistamines that could affect the skin prick test results. Skin prick tests were applied on the volar forearm and were read after twenty minutes. A wheal reaction with a mean diameter of 3 mm greater than the diameter of negative control was considered positive. Patients, sensitized to one or more allergens, were considered as atopic. SPTs were evaluated by the same tester in each patient.

Statistical Analysis

The statistical analysis was performed using the SPSS program version 11.5 (SPSS Inc., Chicago, IL, USA). The variables were investigated using visual (histograms,

probability plots) and analytical methods (Shapiro-Wilk's test) to determine whether or not normally distributed. Data were presented as mean± standard errors mean (SEM); median and minimum-maximum (min-max) or percentage frequencies as appropriate. Intergroup comparisons were made using the t test/ Mann-Whiney U test for continuous variables and chi-square test or the Fisher's exact test for categorical variables. A p-value of less than 0,05 was considered as statistically significant.

RESULTS

Almost the whole of the patients (98%) was female, and the mean age was 50.84±1.71 years. The median disease duration was 5 (1-25) years. The demographic and clinical parameters are presented in **Table 1.** Drugs, which have been receiving by the patients in the study group, were as follows; hydroxychloroquine (thirty-five patients, 70%), hydroxychloroquine, and corticosteroid (eleven patients, 22%), hydroxychloroquine, and methotrexate (two patients, 4%), and hydroxychloroquine, corticosteroid, and azathioprine (two patients, 4%). The positivity rate of ANA was 46 (92%); granular pattern was observed in 39 patients (78%), homogen in 5 patients (10%), centromeric in one patient (2%), and nucleolar in one patient (2%). ANA were positive in twenty-seven patients (54%) at a serum dilution of 1/100-1/320, in 15 patients (30%) at serum dilution of 1/320-1/1000, and, in 4 patients (8%) at serum dilution of 1/1000-1/3200. Forty of patients (80%) had anti-SSA antibodies and 23 (46%) had anti-SSB antibodies. Twenty patients (40%) were rheumatoid factor (RF) positive.

Five patients (10%) had allergic rhinitis (AR), three patients (6%) had asthma, five patients (10%) had drug allergy (NSAID, penisilin, methotrexate), and one patient (2%) had food allergy (hazelnut, spice). Two of three patients with asthma were atopic. Both two patients sensitized with house dust mite. In control group, one subject had asthma and one subject had food allergy. Ten patients (10/50, 20%) in the pSS group and six participants (6/50, 12%) had positivity with common inhalant allergens in the control group (p=0.275) **(Table 1).**

Table 1. Demographic and clinical characteristics of pSS patients and control group

	pSS	CG	P value
n	50	50	
Age (mean±SEM), years	50.80±1.70	51.70±1.70	0.727
Gender (female/male)	49/1	48/2	1.0
Presence of allergic diseases,n(%)			
Allergic rhinitis	12 (24)	6 (12)	0.118
Asthma	6 (12)	1 (2)	0.112
Urticaria	6 (12)	1 (2)	0.112
Drug allergy	5 (10)	1 (2)	0.204
Atopic dermatitis	3 (6)	-	0.242
Food allergy	1 (2)	2 (4)	1.000
Skin prick test positivity, n(%)	10 (20)	5 (10)	0.161
House dust mites	7 (14)	2 (4)	0.081
Pollens	5 (10)	2 (4)	0.436
Blatella germenica	2 (4)	2 (4)	1.000
Moulds	1 (2)	-	1.000
Cat dander	-	-	-

SEM: standard error of mean, CG: control group

Table 2. Comparison of clinical characteristics of pSS patients according to the atopic status

pSS	Non-atopic	Atopic	P value
n	40	10	
Age at diagnosis, years	45.10±1.90	43.70±3.10	0.743
Duration of pSS, months; median (min-max)	5 (1-25)	8 (3-17)	0.209
Presence of extraglandular symptoms, n(%)	13 (32.50)	1 (10)	0.156
ANA positivity, n(%)	36 (90%)	10 (100%)	0.397
RF positivity, n(%)	13 (65%)	7 (35%)	0.067
CRP (mg/l), median (min-max)	3.5 (1.00-29.10)	5.95 (1.00-16.60)	0.166
ESR (mm/h), median (min-max)	17.50 (2-71)	32 (10-53)	0.047*
Eos counts (/μL), median (min-max)	100 (0-1000)	100 (0-1000)	0.166
ESSDAI,median (min-max) (mean±SEM)	2 (2-12) 3.30±0.40	2 (2-5) 2.30±0.30	0.177

ANA: Antinuclear antibody, RF: Rheumatoid factor, CRP: C reactive protein, ESR: Erythrocyte Sedimentation Rate,
Eos: eosinophil, ESSDAI: The EULAR Sjögren's Syndrome Disease Activity Index, SEM: standard error of mean, *statistically significant

Seven patients (14%) were sensitized to house dust mite, five patients (10%) were sensitized to pollens, two patients (4%) were sensitized to Blatella germenica and one patient was sensitized to moulds in the pSS group. Two subjects (4%) were sensitized to house dust mite, two subjects (4%) were sensitized to pollens, and two subjects (4%) were sensitized to Blatella germenica in the control group. Six patients (12%) with pSS were monosensitized and four patients (8%) were polysensitized. In control group, five subjects (10%) were monosensitized. There was no subject polysensitized to allergens. The presence of atopy was similar between patients with a duration of pSS<10 years (n=5/35, 14.30%) and ≥10 years (n=5/15, 33.30%) (p=0.143).

Clinical characteristics of pSS patients according to atopic status were shown in **table 2.** Age at diagnosis, duration of pSS, presence of extraglandular symptoms, ANA positivity, CRP and RF levels, eosinophil counts, and ESSDAI scores were similar between atopic and non-atopic patients with pSS. ESR levels were significantly higher in atopic patients than non-atopic patients (p= 0.047).

DISCUSSION

In the present study, we investigated the atopic status and allergen sensitization of pSS patients. Atopy rates were similar in patients with pSS and controls. AR was the most common allergic disease in pSS patients, followed by asthma. The most common aeroallergen sensitization was house dust mite but not significant. No significance was found regarding the clinical characteristics between atopic and non-atopic pSS patients. To our knowledge, this is the first study investigating the inhalant allergen spectrum in pSS patients.

There has been growing interest in the relationship between autoimmune diseases and atopy. The relevant studies reported varied results about the prevalence of atopy in autoimmune diseases. Unlike the Th1/Th2 paradigm, some studies have reported that atopy and autoimmune diseases may co-exist (16). Genetic and environmental factors, as well as the design of study groups (children or adults), may have influenced the differences in the prevalence rate of atopy in autoimmune diseases. Another factor would be that some of those studies were based on the questionnaires (4-6,16). Epidemiologic studies were designed mostly on patients with SLE and RA (4,16). Possible association atopy and pSS is still unknown.

In a nationwide population-based cohort study, the risk of autoimmune diseases, including SS in atopic patients, has been studied. The authors reported a 2.5-fold increased risk of SS among atopic subjects. The coexistence of the atopic triad (AR, asthma, and AD) exacerbated the risk of autoimmune disease (17). Another population-based cohort study revealed that a 1.4-fold increased risk of developing asthma in pSS patients. In that study, the percentages of comorbidities of AR and AD in patients with pSS were 21.10% and 2.40%, respectively. These were significantly higher than the frequencies in patients without SS (8.30% and 1.40%, respectively). These prevalence rates of atopic diseases were determined from databases according to diagnostic codes based on the International Classification of Diseases (ICD) (18). Some studies reported that asthma is one of the comorbid diseases in SS patients (19,20). One of these studies reported that 11.80% of SS patients were comorbid with asthma (19). Kang et al. reported a higher prevalence of asthma in SS patients according to controls (20). In these studies, whether asthma was allergic or not, has not been addressed. In our study, the rates of asthma and AR in patients with pSS were 6%, and 10%, respectively. Our rates were lower than the rates of atopic diseases reported in the previous studies (18,19). This result may arise from the number of study population or differences in the study methods. AD was not reported by any participants. The percentage of asthma was low, but two of the three patients were atopic. These results suggest us the Th1 pathway is dominant in pSS, but Th2 or different immunologic mechanisms contribute the pathogenesis.

An important aspect of our study was evaluating the presence of atopy in pSS with the skin prick tests. The inhibitory effect on skin prick tests of drugs that have been using in the study group was evaluated before the prick tests performed. Among these drugs; hydroxychloroquine, methotrexate, and azathioprine do not suppress skin tests. Long term systemic steroid treatment has a possible effect on prick tests even none of clinical significance (21). The diameter of skin wheal of histamine had been checked before skin prick tests in case of usage of long-term systemic steroid. The steroid doses, used for pSS in our study, did not interfere with the tests. According to skin prick results, we did not find significant differences between pSS and control group. Common aeroallergen sensitization was evaluated in pSS patients for the first time in our study. The prevalence of common aeroallergen sensitization varies in different geographical regions and countries. According to the previous studies from Türkiye, pollen sensitization was the most common sensitization detected in skin prick tests and the frequency varied between 43 to 74% among sensitized cases. The frequency of dust mite sensitization was near 30% (22). In our study, house dust mite sensitization was the most common sensitization in patients with pSS. Similarly, Guo et al. reported a predominance of dust mite sensitization (n:12/35, 34%) by serum specific IgE in children with SLE (16). If this was not a coincidence; it may be related to the propensity to induce different T cell responses by allergens or similar pathways in the pathogenesis of mite sensitizations and autoimmune diseases. The intrinsic features of different allergens may be critical to Th2 initiation as well as driving Th2 responses in autoimmune diseases (23). It is interesting that polysensitized cases were detected in the pSS group but not in controls. Polysensitization is an immunological phenomenon that was hypothesized with a functional defect in T regulatory cells which may cause to developing polysensitization to allergen (24). These results suggest that immunological mechanisms in

pSS may lead to allergen(s) sensitivity. In further studies, it can be questioned that chronic exposure of allergens is a predisposing factor for pSS or vice versa.

Finally, we evaluated whether the presence of atopy influences the disease severity of pSS. It was reported that pre-existing atopic disease in some autoimmune diseases leads to a less severe disease course (3). To the best of our knowledge, there is not any study that directly investigates the relationship between atopy and disease activity of pSS. Only one study reported by Pertovaara et al. suggested that Th2 genotypes may be associated with a milder form of pSS. They hypothesized that whether pSS is a Th1 mediated autoimmune disease or Th2 mediated. They investigated the polymorphism of the genes encoding for interleukin (IL)-4, IL-13, and interferon γ, which cytokines involved in the regulation of Th1/Th2. They found that the percentage of pSS patients, who presented with extraglandular manifestations carrying interleukin (IL)-4 allele, was fewer than those not carrying this allele (11). In our study, we could not find any significant difference regarding disease activity between atopic and non-atopic patients in pSS. The frequency of extraglandular manifestations in non-atopic patients was higher than atopic patients, but it would not be plausible that to comment about this situation because of the small number of patients. We find significant ESR level in atopic patients, but we did not find this significance in ESSDAI, which is more valuable for clinical assessment of pSS. For this reason, it cannot be exactly interpreted that ESR level in atopic patients is significant or not.

Study Limitations

However, there are some limitations in our study. First, it was a hospital-based study, so patients were unrepresentative for the Turkish population or general population. The rates of atopy prevalence between the groups were distinct, but not significant; this situation can be explained with high rate of type 2 error. Number of our study population was small, but it would be a pioneer to other clinical trials. Second, we did not analyze the related cytokines about atopy in our study. Understanding the immunopathological roles of immune cells and cytokines will clarify the association between atopy and pSS.

CONCLUSIONS

In conclusion, the prevalence of atopy is similar in patients with pSS to the controls. It is compatible with the hypothesis that pSS is mainly Th1 mediated autoimmune disease. But there is not an opposing relationship between atopy and pSS.

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