ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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Relationship Between Allergic Conjunctivitis and Hepatitis B, C, and Antinuclear Antibody: Case-Control Research

Alerjik Konjonktivit Hepatit B, C ve Antinükleer Antikor Arasındaki İlişki: Vaka-Kontrol Araştırması

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ABSTRACT Objective: The etiopathogenesis of allergy and autoimmune diseases involves genetic and environmental factors which might be common to both immunopathologies and infection also plays a significant role in the induction of allergy and autoimmunity. In this study, we aimed to evaluate the prevalence of hepatitis B, C, and antinuclear antibody (ANA) in patients with allergic conjunctivitis (AC). **Material and Methods:** A total of 128 patients with AC were enrolled and divided into 3 groups according to etiology: mite, pollen, and pollen/mite. Patients who complained of rhinoconjunctivitis underwent a skin-prick test. Hepatitis B surface antigen (HBsAg), anti-hepatitis C virus antibody (anti-HCV Ab), erythrocyte sedimentation rate (ESR), and ANA values of patients were evaluated. ANA screening was investigated with indirect immunofluorescence. p values <0.05 were accepted as statistically significant. **Results:** One hundred (78.1%) of the patients were women. Seventy-three (57%) patients were allergic to pollen, 33 (25.8%) to mites, and 22 (17.2%) to both pollen and mites. ANA test results were positive in 11 (8.6%) patients. HBsAg was detected in only (0.8%) 1 patient. Anti-HCV test was negative in all patients. The mean age of the patients was 37.45±10.46 years and mean ESR was 14.10±7.32 mm/h. Sex, ANA, and HBsAg distributions were statistically similar among the groups. No relationship was detected between AC and hepatitis B, C, or ANA positivity. **Conclusion:** AC was not significantly associated with hepatitis B, C, or ANA positivity. The prevalence of hepatitis B was lower among the AC patients than in the general population of Turkey, whereas the prevalence of hepatitis C was consistent at 0%. These results should be supported with larger numbers of patients with AC.

Keywords: Allergic conjunctivitis; antinuclear antibody; HBsAg; hepatitis C virus; autoimmunity

ÖZET Amaç: Alerji ve otoimmün hastalıkların etiyopatogenezi, her iki immünopatolojide ortak olabilecek genetik ve çevresel faktörleri içerir, enfeksiyonda alerji ve otoimmünitenin indüksiyonunda önemli bir rol oynar. Bu çalışmada, alerjik konjonktiviti (AK) olan hastalarda hepatit B, C ve antinükleer antikor (ANA) prevalansını değerlendirmeyi amaçladık. **Gereç ve Yöntemler:** Total olarak AK olan 128 hasta kaydedildi ve etiyolojiye göre 3 gruba ayrıldılar: Akar, polen ve polen/akar. Rinokonjonktivit şikâyeti olan hastalara skin-prick testi yapıldı. Hastaların hepatit B yüzey antijeni (HBsAg), anti-hepatit C virüs antikoru (anti-HCV Ab), eritrosit sedimantasyon hızı (ESH) ve ANA değerleri değerlendirildi. ANA taraması indirekt immünofloresan ile araştırıldı. p<0,05 değerleri istatistiksel olarak anlamlı kabul edildi. **Bulgular:** Hastaların 100'ü (%78,1) kadındı. Yetmiş üç (%57) hastada polen, 33'ünde (%25,8) akar ve 22'sinde (%17,2) hem polen hem de akar alerjisi vardı. ANA testi 11 (%8,6) hastada pozitifti. HBsAg sadece 1 (%0,8) hastada saptandı. Tüm hastalarda anti-HCV testi negatifti. Hastaların ortalama yaşı 37,45±10,46 yıl ve ortalama ESH 14,10±7,32 mm/saat idi. Gruplar arasında cinsiyet, ANA ve HBsAg dağılımları istatistiksel olarak benzerdi. AK ile hepatit B, C veya ANA pozitifliği arasında ilişki saptanmadı. **Sonuç:** AK, hepatit B, C veya ANA pozitifliği ile anlamlı olarak ilişkili değildi. AK hastalarında hepatit B prevalansı Türkiye geneline göre daha düşük iken, hepatit C prevalansı %0 ile tutarlı idi. Bu sonuçlar, daha fazla sayıda AK olan hasta ile desteklenmelidir.

Anahtar Kelimeler: Alerjik konjonktivit; antinükleer antikor; HBsAg; hepatit C virüs; otoimmünite

Allergic and autoimmune diseases might involve common genetic and environmental factors. Infection has a significant impact on the induction of allergic and autoimmune diseases, either as an initiative or as a defensive factor. Although the mechanisms cause different pathologies in the individual, recent evidence suggests a possible common pathogenetic connection.[1]

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Allergy is described as an excessive immune reaction to an external allergen, and autoimmune diseases to an internal antigen, or autoantigen. Allergic and autoimmune diseases might mimic each other. Furthermore, both allergy and autoimmunity can exist in the same patient.[1]

Autoimmune and allergic diseases are both characterized by immune dysregulation. Autoimmune disorders are mainly mediated by T helper (Th)1 cells, whereas allergic disorders are mediated mainly by Th2 cellular immune response.[2,3]

Allergic conjunctivitis (AC) is immunoglobulin E (IgE)-mediated hypersensitivity of the conjunctiva and has also been attributed to Th2 response. The Th1 response is inhibited by the Th2-associated cytokines interleukin 4 (IL-4) and IL-13; on the contrary, interferon (IFN)-γ, that is related with Th, decreases the Th2 response, as stated in the conventional Th1/Th2 paragon.[4]

The detection and measurement of autoantibodies against nuclear proteins [antinuclear antibodies (ANA)] and cytoplasmic proteins (anticytoplasmic antibodies) has a critically significant impact on the diagnosis of systemic autoimmune rheumatic diseases.[5]

The immunopathogenesis of viral infections is mediated by Th1 cells. Type I interferons (IFNα and IFNβ proteins) and type III IFNs (IFNλ proteins) are the primary constituents of the antiviral natural immune system.[6] The most prevalent chronic viral infection in the world is hepatitis B virus (HBV). Nearly 30% of the world's population shows expression of present or previous HBV seroconversion.[7] The 2003-2010 National Health and Nutrition Examination Survey study declared a seroprevalence of antibody to hepatitis C virus (anti-HCV) among the population of 6 years of age or older of 1.3%, and that chronic HCV infection could be seen in 1.0% of individuals in the US.[7] The prevalence of HCV in individuals with inflammatory rheumatic conditions seems to be parallel with the general population.[8] Besides, it looks like that HCV prevalence is higher in systemic lupus erythematosus, according to the studies published before.[9] Centers for Disease Control and Prevention (CDC) declared the prevalence of HBV as 5-7% and HCV as 0-1.096% in Turkey.[7]

Previous researches assessing the connection between AC and autoimmune diseases or systemic diseases have yielded different results. We considered that Th1-mediated autoimmune and viral diseases are less frequent in patients with Th2-mediated AC than the frequency normally seen in community. We planned our study by selecting the easiest and cheapest methods to support our hypothesis. Therefore we showed IgE-mediated reactions by performing skin prick test (SPT) in patients with AC and evaluated hepatitis B surface antigen (HBsAg), anti-HCV, erythrocyte sedimentation rate (ESR), and ANA parameters for viral and autoimmune evaluation.

To our knowledge, there have been no researches investigating the relationship between AC and HBsAg, anti-HCV antibody, or ANA, which is a simple and cost-effective parameter evaluating autoimmunity. Therefore, we conducted this study to determine whether there is any significant association between these parameters and AC.

MATERIAL AND METHODS

This single-center clinical research was directed in collaboration between the Ophthalmology and the Allergy and Immunology outpatient clinic of İzmir Tepecik Training and Research Hospital. The research was performed in adherence with the tenets of the Declaration of Helsinki and the Health Sciences University İzmir Tepecik Training and Research Hospital approved the protocol (no: 2019/5-5; date: 28/03/2019). Prior to the study, all the patients gave a written informed consent.

Before including in the study, the patients' medical histories were checked and they underwent physical examination. Patients who complained of rhinoconjunctivitis symptoms such as nasal drainage, nasal obstruction, sneezing, and itchy, red, and watery eyes underwent a SPT, as explained below. The inclusion criteria for the study were positive SPT for pollen and/or house mite and no history of immunomodulatory treatments such as immunotherapy or corticosteroid therapy. Patients who did not have symptoms of AC, had negative pollen/mite SPT results, or who were receiving immunotherapy were excluded from the study.

Between 1 April 2019 and 30 September 2019, patients who presented to the immunology and allergy outpatient clinic with complaints of AC symptoms and positive SPT were referred for ophthalmologic examination to confirm AC.

In total, 128 patients with AC confirmed with SPT and ophthalmologic examination participated in the study. The patients were separated into 3 groups: pollen, mite, and pollen+mite allergy. HBsAg, anti-HCV, ESR, and ANA values of these patients were recorded. ANA screening was investigated with IIF using Hep 2010 cells as the substrate (Euroimmun Lübeck, Germany) and ANA screening dilution was 1/160.

SKIN PRICK TEST

Allergic sensitization was demonstrated by using the SPT. SPTs were performed according to the European Academy of Allergy and Clinical Immunology guidelines and contain 20 for the most common inhalant allergens in Turkey. A large panel of aeroallergens (house dust mites, weed-weed-cereal pollens, molds, animal epithets and latex) were used in SPTs. Allergens (ALK-Abello, Spain) were applied with the help of Stallerpoint (Stallergenes, Antony Cedex, France). Erythema and induration were evaluated 20 minutes after the application. In the presence of erythema, an induration of 3 mm or more was accepted as a positive result. Standardized histamine (1.7 mg/mL) was used as a positive control and a standard negative prick solution (sodium chloride, 9 mg/mL; phenol, 4 mg/mL; and glycerol, 563 mg/mL) (Allergopharma Ltd, Reinbek, Germany) was used as negative control.

STATISTICS ANALYSIS

All data were evaluated using IBM SPSS Statistics version 25.0 Standard Concurrent User (IBM Corp., Armonk, New York, USA) statistics package software. Descriptive statistics were given as number (n), percentage (%), mean±standard deviation ($\bar{x}$±SD), median (M), 25th percentile (Q_1), and 75th percentile (Q_3) values. Normal distribution for numerical data was evaluated by Shapiro-Wilk normality test and Q-Q graphics. Homogeneity of variances was evaluated by Levene test. Age was normally distributed and compared between groups using one-way analysis of variance (ANOVA). For the normally distributed but not homogeneously structured ESR variable, comparisons between groups were evaluated using Brown-Forsythe test. The Games-Howell multicomparison test was used as a post hoc test for ESR. Numerical variables were compared according to sex and ANA positivity using independent samples t-test. Relations between age and ESR were evaluated by Pearson correlation analysis. Comparisons between categorical variables were evaluated by Fischer's exact test developed for r×c and 2×2 sized tables. $p<0.05$ value was accepted as statistically significant.

RESULTS

A hundred (78.1%) of the patients were women and 28 (21.9%) were men. Seventy-three (57%) patients were allergic to pollen, 33 (25.8%) to mites, and 22 (17.2%) to both pollen and mites (Table 1). The mean age of the patients was 37.45±10.46 years and the mean ESR was 14.10±7.32 mm/h (Table 2). The pollen allergy group included 56 (76.7%) women and 17 (23.3%) men, the mite allergy group included 26 (78.8%) women and 7 (21.2%) men, and the pollen+mite allergy group included 18 (81.8%) women and 4 (18.2%) men ($p=0.917$) (Table 3).

TABLE 1: Frequency table of categorical variables of all patients.

Variable	n	%
Gender		
Woman	100	78.1
Man	28	21.9
PT		
Mite	33	25.8
Pollen	73	57.0
Mite+Pollen	22	17.2
ANA		
Negative	117	91.4
Positive	11	8.6
HbsAg (CO)		
Negative	127	99.2
Positive	1	0.8
Anti-HCV Ab (SCO)		
Negative	128	100
Positive	0	0.0

PT: Prick test; ANA: Antinuclear antibody; HBsAg: Hepatitis B surface antigen; HCV Ab: Hepatitis C virus antibody.

TABLE 2: Frequency table of numeric variables of all patients.

	Mean	SD	Minimum	Maximum	25.percentile	Median	75. percentile
Age (years)	37.45	10.46	19.00	64.00	29.00	37.50	45.75
Sedimentation (mm/h)	14.10	7.32	2.00	56.00	9.00	13.00	18.00

SD: Standard deviation.

TABLE 3: Distributions of sex and positivity for ANA, HBsAg, and anti-HCV Ab in patients with pollen, mite, and pollen/mite allergy.

	SPT						Test statistics	
	Mite		Pollen		Mite+Pollen			
Variables	n	(%)	n	(%)	n	(%)	χ^2	p value
Gender								
Woman	26	78.8	56	76.7	18	81.8	0.269	0.917
Man	7	21.2	17	23.3	4	18.2		
ANA								
Negative	31	93.9	65	89.0	21	95.5	1.248	0.520
Positive	2	6.1	8	11.0	1	4.5		
HbsAg (CO)								
Negative	33	100	72	98.6	22	100	0.759	1.000
Positive	0	0.0	1	1.4	0	0.0		
Anti-HCV Ab (SCO)								
Negative	33	100	73	100	22	100	-	-
Positive	0	0.0	0	0.0	0	0.0		

SPT: Skin-prick test; ANA: Antinuclear antibody; HBsAg: Hepatitis B surface antigen; HCV Ab: Hepatitis C virus antibody.

ANA test was negative in 117 (91.4%) patients and positive in 11 (8.6%). Of the 11 ANA-positive patients, 2 were in the mite allergy group (6.1%), 8 were in the pollen allergy group (11%), and 1 was in the pollen+mite allergy group (4.5%) ($p=0.520$). HBsAg was detected in only 1 (0.8%) patient, while the other 127 (99.2%) were HBsAg-negative. The only 1 HBsAg-positive patient was in the pollen allergy group (1.4%). All of the patients tested negative for anti-HCV (Table 3).

There were no significant differences between the pollen, mite, and pollen+mite allergy groups in terms of sex, ANA, or HBsAg distributions (Table 3). Anti-HCV could not be evaluated because all patients tested negative.

The age difference between the groups was not remarkable. ESR was satistically higher in the mite+pollen allergy group compared to the mite allergy group but similar to that of the pollen allergy group (Table 4).

Age and ESR were statistically similar between patients with and without ANA (Table 5). There was a positive correlation between age and ESR (p=0.017).

Women had significantly higher ESR compared to men (Table 6).

TABLE 4: Comparison of SPT groups according to age and erythrocyte sedimentation rate.

	SPT						Test statistics	
	Mite		Pollen		Mite+Pollen			
	X	SD	X	SD	X	SD	F	p value
Age (years)	35.96	9.01	37.83	11.10	38.41	10.45	0.469	0.627
Sedimentation (mm/h)	11.70[a]	4.28	14.30[ab]	8.07	17.05[b]	7.38	3.741	0.026

[a,b]Superior symbols show the difference between groups. The groups with same letters are statistically similar; SPT: Skin-prick test; SD: Standard deviation.

DISCUSSION

AC is frequently observed and manifests in four clinical forms; seasonal or AC, vernal keratoconjunctivitis, atopic keratoconjunctivitis and giant papillary conjunctivitis. AC is observed in hot and dry regions and seasonal AC, which follows a seasonal profile accounts for about 50% of cases of ocular allergy. AC can be both unilateral or bilateral, however involvement is frequently bilateral. Patients with AC have a large range of symptoms and clinical signs. Among the common findings; bilateral red, itchy eyes, edema of eyelid or conjunctiva resulting in chemosis, watery or thick secretion and in severe cases papillary hypertrophy of the tarsal conjunctiva can be considered.[10]

The IgE antibody production against environmental allergens is the main step of the allergic disease. Thus, the urgent type of allergic inflammation is a Th2 cell- and IgE-dependent process principally. In accordance with the primary T cell reaction, IgE-mediated allergy can be considered as standard Th2 disease, while in most other hypersensitivity and autoimmune diseases are predominated with Th1 cells, cytotoxic cells, complement and the production of inflammatory cytokines such as IFN-g, IL-12 and IL-17.[11] Previous studies examining the connection between allergic and autoimmune diseases have been based on the hypothesis that the similar exaggerated reaction which progresses against exogenous antigens in patients with allergy could progress against endogenous antigens as well.

Organ-specific autoimmune diseases disturb not only the target organ but also induce Th2-mediated immune reaction and effect the whole immune system. Besides, the Th1-mediated immune reaction is unsatisfactory in these patients.[11]

Regarding the inverse relationship between Th1 and Th2 immune reactions, it looks like that patients with Th2-mediated disease may have a lower risk of Th1-mediated diseases. In some researches, the hypothesis of lower incidence of atopic diseases in patients with autoimmune diseases was confirmed.[12] On the other hand, other studies have found an inverse dependency.[13,14] However, studies from England and Turkey did not identify any connection between allergic and autoimmune diseases, similar to our study.[15,16]

There have been studies evaluated the connection between allergic rhinitis (AR) and AC, and autoimmune or systemic diseases previously. According to the study by Degirmenci et al., the prevalence of Hashimoto thyroiditis which is Th1-mediated, was higher in patients with AR, which is Th2-dominant, than in the controls.[17] A

TABLE 5: Comparison of age and erythrocyte sedimentation rate in patients with and without ANA.

	ANA					
	Negative		Positive		Test statistics	
	$\bar{X}$	SD	$\bar{X}$	SD	t value	p value
Age (years)	37.64	10.60	35.45	8.97	0.661	0.510
Sedimentation (mm/h)	14.02	7.48	15.00	5.53	0.424	0.972

ANA: Antinuclear antibody; SD: Standard deviation.

TABLE 6: Comparison of erythrocyte sedimentation rates by sex.

	Gender					
	Female		Male		Test statistics	
	$\bar{X}$	SD	$\bar{X}$	SD	t value	p value
Sedimentation (mm/h)	15.47	7.52	9.21	3.53	6.217	<0.001

SD: Standard deviation.

study by Chen et al. showed that patients with type 1 diabetes mellitus (T1DM) were at an higher risk of developing AC, and that risk increased with diabetes progression.[18] Couto et al. observed that Vogt-Koyanagi-Harada disease and AC might coexist in the same patient.[19] They emphasized the importance of considering allergic diseases as the reason of ocular symptoms in patients with autoimmune disorders.

Consistent with the literature, in our study most of the AC patients were women (78.1%) and most (57%) had pollen allergy. Our results were compatible with previous studies in terms of gender and etiology.[17] We evaluated the relationship between ESR and age and gender. In our study ESR revealed significantly higher values in women than that of men.

Our study is the first study evaluated the relationship between ANA and AC. In our study, 117 (91.4%) of the patients had negative ANA test, which is a marker of autoimmunity with high specificity at 1:160 serum dilution.[5] This result is also compatible with the Th1/Th2 paradigm. As the ANA positivity at this serum dilution is regarded as a highly sensitive marker of autoimmunity, it is consistent with the Th1/Th2 paradigm that we observed no relationship between ANA and AC. However, the results of recent studies searching the relationship between AC and autoimmune diseases are contentious, as shown in the studies of Degirmenci et al., Chen et al., and Couto.[17-19] These contradictory results might be due to the differences in the study design, patients' features, environmental factors, and geographical location, in addition with the influence of the orher cells of immune system such as Th17, Tregs, and B lymphocytes in both disorders.

The clinical consequence of HBV infection is reliant on the complicated interaction between HBV replication and host immune response.[20] People with acute HBV infection have strong T-cell responses where as, patients with chronic HBV infection have weak T-cell responses to a few epitopes.[20,21]

There is increasing proof that viral infection might be included in the development of autoimmune diseases such as autoimmune thyroid disease and T1DM. HCV infection is often related with extrahepatic autoimmune manifestations.[22,23] This relationship arouses the curiosity if HCV infection causes autoimmunity along immune-related mechanisms, or via target organ effects. According to Hammerstad et al., HCV infection might cause thyroid dysfunction by various mechanisms.[24] These evidences strengthen a common mechanism for viral induction of autoimmunity along with direct infection of target tissues.

To the best of our knowledge, this study is the first evaluating the relationship between AC and HBsAg or anti-HCV seroprevalence. In this sample of AC patients, the prevalence of hepatitis B was 0.8% and that of hepatitis C was 0%. Compared to prevalence rates reported by the CDC (5-7% for hepatitis B, 0-1.096% for hepatitis C in Turkey), our hepatitis B rate was lower, while the hepatitis C rate was consistent. We detected no relationship between AC and HBsAg or anti-HCV antibody. Viral infections are Th1-mediated and AC is Th2-mediated, therefore, our results may be explained by this different immunologic pathway as well as the Th1/Th2 paradigm.

Autoimmunity and allergy are the diseases whose origins involve polygenic heredity, including numerous common gene loci and alleles, as well as many similar environmental factors. Clinically, it is mandatory to consider the pervasive nature of the symptoms where one may imitate the other, or both immunopathologies may exist at the same time in the patient. Hence, autoimmunity and allergy can be regarded the "yin and yang" of immunopathology, they are their own reciprocal contradictions, but each comprimises the seed of the other and may transform into the other.

CONCLUSION

In conclusion, our study is the first study evaluating the relationships between AC and ANA, HBsAg, and anti-HCV antibody. According to our results, most of the AC patients were women and the etiology of AC was mostly pollen allergy, which is consistent with the literature. We detected no significant association between AC and HBsAg, anti-HCV, or

ANA positivity. Our results were compatible with Th1/Th2 paradigm. Compared to CDC data, the prevalence of hepatitis B in the AC patients was lower than in the general population (0.8% vs. 5-7%), whereas the prevalence of hepatitis C was consistent at 0%. Our results should be supported with larger numbers of patients with AC.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Esin Kırıkkaya, Papatya Bayrak Değirmenci;* ***Design:*** *Esin Kırıkkaya, Papatya Bayrak Değirmenci;* ***Control/Supervision:*** *Esin Kırıkkaya, Papatya Bayrak Değirmenci;* ***Data Collection and/or Processing:*** *Esin Kırıkkaya, Papatya Bayrak Değirmenci;* ***Analysis and/or Interpretation:*** *Esin Kırıkkaya;* ***Literature Review:*** *Esin Kırıkkaya, Papatya Bayrak Değirmenci;* ***Writing the Article:*** *Esin Kırıkkaya;* ***Critical Review:*** *Esin Kırıkkaya.*

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