ORIGINAL ARTICLE

PERSISTENT ALLERGIC RHINITIS AND ITS POTENTIAL TO CAUSE POOR ASTHMA CONTROL

Persistan Allerjik Rinit Zayıf Astım Kontrolüne Neden Olma Potansiyeli

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ÖZET

Amaç: Birçok çalışma alerjik rinitin astım yönetimi üzerindeki kötüleştirici etkisini göstermiştir. Bu çalışmada persistan allerjik rinit ile zayıf astım kontrolü arasındaki ilişkiye değinmeyi amaçladık.

Gereç ve Yöntemler: Çok merkezli, kesitsel olan bu çalışma, 01.02.2022 ile 01.08.2022 tarihleri arasında göğüs hastalıkları polikliniğine başvuran astım ve persistan allerjik rinit hastalarının katılımıyla gerçekleştirildi. Hastaların demografik verileri, Astım Kontrol Testi (AKT) skorları ve astım kontrol durumları kaydedildi. Örneklem astım kontrol durumuna göre "kontrolsüz astım" ve "kontrollü astım" olmak üzere iki gruba ayrıldı. Allerjik rinit (AR) tanısını değerlendirmek için Allerjik Rinit Skoru (ARS) kullanıldı.

Bulgular: Bu çalışmaya yaş ortalaması 44,54 olan 195 hastayı (47 (%24,1) erkek ve 148 (%75,9) kadın) dahil ettik. Hastaların %26,7'sinde astım kontrolü sağlanırken, %73,3'ünde kontrol edilemeyen astım vardı. Astımı kontrol edilemeyen hastalarda persistan allerjik rinit oranı, kontrollü astımı olan hastalara göre anlamlı olarak yüksek bulundu (p=0,012).

Sonuç: Bu çalışma persistan allerjik rinitin astım kontrolü üzerinde kötüleştirici etkisi olduğunu göstermiştir. Astım ve eşlik eden persistan allerjik rinit hastaları, astım kontrolünün zayıf olması riskinin daha yüksek olduğu göz önünde bulundurularak tedavi edilmeli ve takip edilmelidir. Persistan rinit semptomları olan hastalar artan sağlık harcamaları ile birlikte halk sağlığında da büyük sorunlara neden olmaktadır.

Anahtar Kelimeler: *Astım; Rinit; Alerjik; Yılboyu; Dispne*

ABSTRACT

Objective: Many studies have shown the worsening impact of allergic rhinitis on the management of asthma. In this study, we aimed to address the association between persistent allergic rhinitis and poor asthma control.

Material and Methods: This multi-center cross-sectional study was performed with the participation of patients with asthma and persistent allergic rhinitis visiting the pulmonology outpatient clinics between 01.02.2022 and 01.08.2022. The demographic data, Asthma Control Test (ACT) scores, and asthma control status of the patients were recorded. The sample was divided into two groups according to asthma control status "uncontrolled asthma" and "controlled asthma". The Score for Allergic Rhinitis (SFAR) was used to evaluate the diagnosis of allergic rhinitis (AR).

Results: We included 195 patients (47 (24.1%) men and 148 (75.9%) women) with a mean age of 44.54 in this study. While 26.7% of the patients showed asthma control, 73.3% had uncontrolled asthma. The rate of persistent allergic rhinitis was found to be significantly higher in the patients with uncontrolled asthma compared to the patients with controlled asthma (p=0.012).

Conclusion: This study showed that persistent allergic rhinitis has a worsening impact on asthma control. Patients with asthma and concomitant persistent allergic rhinitis should be treated and followed up considering their higher risk of poor asthma control. Those patients with persistent symptoms of rhinitis cause major problems in public health with the increased healthcare costs.

Keywords: *Asthma; Rhinitis; Allergic; Perennial; Dyspnea*

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INTRODUCTION

Asthma is a chronic respiratory disease presenting with variable and recurrent symptoms such as cough, wheezing, and shortness of breath. Asthma has been treated according to the steps published by the Global Initiative for Asthma (GINA) (1-5). It was reported to be strongly linked to allergic rhinitis (AR) (1,2). The "one airway, one disease" theory, first put forth by Grossman in 1997, helped explain the close relationship between AR and asthma (3).

It was reported that 40-50% of AR patients had an asthma diagnosis, while concomitant AR was shown in 70-90% of asthma patients (4). The AR and Its Impact on Asthma (ARIA) guidelines recommend targeting the optimal control of asthma and AR simultaneously (5,6). Numerous studies have revealed that AR worsened asthma control, but it is seen that these studies have not focused on persistent AR (7-9). A few studies were conducted to research persistent AR and its detrimental effects on asthma control (10).

Persistent AR was characterized by symptoms of AR lasting 4 days or longer per week for 4 or more consecutive weeks per year and it was reported to be associated with lower respiratory muscle strength (10, 11). This subgroup of AR mostly has symptoms associated with allergens that are present all year (9, 10, 12, 13). We aimed in this study to consider a subgroup of AR, a critical aspect shown as a risk factor for poor asthma control.

MATERIAL AND METHODS

We included patients with asthma and persistent AR presenting to pulmonology outpatient clinics between 01.02.2022 and 01.08.2022. This multicenter cohort study was performed at Ahi Evran University Research and Training Hospital, Rize State Hospital, and Kocaeli Seka State Hospital. The inclusion criteria were being diagnosed with asthma, being treated actively, and signing the informed consent form. This study was approved by the local ethics committee (date: 25.01.2022, approval number: 2022-02/06). The Declaration of Helsinki, published by the World Medical Association, set the ethical guidelines for conducting this multi-center cross-sectional study. Patients who did not agree to sign the informed consent form were excluded. The sample consisted of two groups of patients, namely controlled asthma patients and uncontrolled asthma patients.

In the current literature, there were few studies about the aspects that were aimed to be evaluated in this study. We needed a total of 154 patients to obtain statistically significant results using the z-test with alpha error probability=0.05 (two-sided) and 1-beta error probability=0.80. After the analyses, the sample size presented >95% power.

Treatment status based on the GINA steps was determined according to the frequency of typical symptoms of asthma in the last 4 weeks (14). GINA Step 1 includes patients with symptoms seen less frequently than twice a month. GINA Step 2 includes patients with symptoms seen more frequently than twice a month but less frequently than daily. GINA Step 3 includes patients with symptoms most days of the week, and additional decreased pulmonary functions indicate GINA Step 4. Severely uncontrolled asthma indicates GINA Step 5.

Because the medical treatment of the disease does not differ between GINA Steps 1 and 2, the two steps were combined into one group. GINA Steps 4 and 5 present a subgroup of asthma that is difficult to treat and control, and most of the patients visiting the pulmonology outpatient clinics were GINA Step 3 patients. As a result, GINA Step 4 and 5 patients were evaluated as one group. Consequently, the patients were divided into three groups based on the GINA steps.

Asthma Control Test (ACT) is a useful tool to assess asthma control after 4 weeks of treatment (15). Schatz et al. proved the accuracy and validity of ACT (16). An ACT score of 25 was classified as complete control, while scores of 24 or lower were classified as uncontrolled asthma. Asthma control was evaluated by asking five questions about the most frequent asthma symptoms experienced by patients on a scale of 1 to 5. The symptoms of asthma are evaluated by being kept from getting done at work or school, having shortness of breath, waking up at night or earlier than usual because of asthma symptoms, using rescue inhalers or nebulizer medication, and rating asthma control by the patient.

The Score for Allergic Rhinitis (SFAR) is a validated assessment tool for the diagnosis of AR questioning the most frequent symptoms and diagnostic tests. Annesi

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-Maesano et al. Validated SFAR and determined a cut-off value of ≥7 (17). The Score for Allergic Rhinitis (SFAR) was used to evaluate the diagnosis of AR due to the lack of availability of a prick test. The diagnosis of persistent AR was decided based on symptoms of AR lasting 4 or more days per week for 4 or more consecutive weeks per year.

Statistical Analysis

The statistical analyses were performed using the Statistical Package for the Social Sciences version 23.0 software for Windows (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp., USA). Descriptive statistics are presented as mean and percentage values in tables. The normality of the distributions of the continuous variables was examined by the Shapiro-Wilk test, and it was found that these data did not have a normal distribution. The Spearman rank correlation test was used to examine correlations between numeric variables. Relationships between categorical variables were analyzed using the Pearson chi-squared test. The Mann-Whitney U test was used to compare the laboratory parameters of the two groups. A p-value of <0.05 was considered significant.

RESULTS

We included 195 patients in this study. While 46.2% (n:90) of the patients visited Ahi Evran University Research and Training Hospital, 28.2% (n:55) visited Rize State Hospital, and 25.6% (n:50) visited Kocaeli Seka State Hospital. According to their SFAR scores, 132 patients had AR, while the persistent subgroup was diagnosed in 16 patients.

The demographic and comorbidity-related data of the patients are presented in Table 1. The sample included 75.8% (n:148) female and 24.2% (n:47) male patients. The patients were mostly nonsmokers (60.5%, n:118). Hypertension (HT) was the most frequent comorbidity in the patients (24.6%, n:48), and it was followed by diabetes mellitus (DM) (12.3%, n:24) and ischemic heart disease (IHD) (11.8%, n:23). There was complete asthma control in 26.7% (n:52) of all patients, while 73.3% (n:143) had uncontrolled asthma.

The diagnosis of AR was found in 67.7% (n:132) of the patients, including persistent AR in 8.2% (n:16) (Table 3). There was no case of persistent AR in the controlled asthma group. Persistent AR was found to be at a significantly higher rate in the uncontrolled asthma group (p=0.012).

Table 1. The comparison of the demographic and comorbidity-related data of the two groups.

		Total (n=195)	Controlled Asthma (n=52)	Uncontrolled Asthma (n=143)	p-value*
Age, years, mean		44.54	46.88	43.69	0.163
BMI, kg/m^2, mean		29.28	28.83	29.45	0.967
Sex, n (%)	Female	148 (75.9)	36 (69.2)	112 (78.3)	0.189
	Male	47 (24.1)	16 (30.8)	31 (21.7)	
Smoking status, n (%)	Smoker	52 (26.7)	10 (19.2)	42 (29.4)	0.348
	Nonsmoker	118 (60.5)	34 (65.4)	84 (58.7)	
	Ex-smoker	25 (12.8)	8 (15.4)	17 (11.9)	
Diabetes mellitus, n (%)		24 (12.3)	8 (15.4)	16 (11.2)	0.430
Hypertension, n (%)		48 (24.62)	14 (26.9)	34 (23.8)	0.652
Ischemic heart disease, n (%)		23 (11.8)	7 (13.5)	16 (11.2)	0.663
Congestive heart failure, n (%)		1 (0.5)	0 (0)	1(0.7)	0.545
Hypothyroidism, n (%)		2 (1.0)	1 (1.9)	1 (0.7)	0.453
GINA step, n (%)	1-2	18 (9.2)	8 (15.4)	10 (7)	0.070
	3	164 (84.1)	43 (82.7)	121 (84.6)	
	4-5	13 (6.7)	1 (1.9)	12 (8.4)	

*: Pearson Chi-Squared test, BMI: Body mass index, GINA: Global Initiative for Asthma, kg/m^2: kilogram/square meter

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Table 2. Persistent allergic rhinitis and asthma control

	Total (n=195)	Controlled Asthma (n=52)	Uncontrolled Asthma (n=143)	p-value*
Persistent allergic rhinitis, n (%)	16 (8.21)	0 (0)	16 (11.2)	0.012

*: Pearson Chi-Square test

The laboratory results are shown in Table 4. There was no significant difference between the two groups. Eosinophilia, elevated levels of eosinophil counts, and eosinophil to lymphocyte ratios (ELR) were not risk factors for uncontrolled asthma status.

DISCUSSION

This multi-center cross-sectional study showed that persistent allergic rhinitis (AR) has a worsening impact on asthma control. Our findings were consistent with the results of previous studies. Furthermore, the sample included patients similar to those included in previous studies.

This sample was eligible to research the impact of persistent AR on asthma control. As known, asthma patients are mostly women, similar to the sample of this study. A multi-center clinical study included patients who were mostly GINA Step 3 patients. The patient groups based on GINA steps were designed considering the patient populations of the centers where the aforementioned study was conducted. Diabetes mellitus and ischemic heart disease were frequently reported extrapulmonary comorbidities in severe asthma cases (18). In this study, diabetes mellitus extrapulmonary comorbidities in severe asthma cases (18). In this study, diabetes mellitus and ischemic heart disease were listed among the top 3 comorbidities accompanying asthma, and this result was similar to those reported in previous studies.

We aimed in this study to investigate the effects of persistent AR, which is seen in a vulnerable subgroup of AR patients. When no prick test is available, it is still possible to diagnose AR, because SFAR questions most of the symptoms seen in AR, family history of allergies, and previous medical treatments for allergy. The sensitivity of SFAR was found 74%, while its specificity was 83% in the validation study. Its positive predictive value was found 84%, while its negative predictive value was 74% in the validation study. The measure was shown to have good internal consistency (Cronbach's alpha coefficient=0.79) (17). The diagnosis of AR was evaluated in this study using SFAR, which was validated by Annesi-Maesano et al (17). This validated assessment tool ensured our ability to diagnose AR despite the limitations associated with the lack of a skin prick test. AR has a worsening effect on the economic systems of countries due to labor loss, absenteeism, and poor performance, with a global reduction in productivity. Therefore, optimal treatment has a critical role in terms of public health and healthcare costs (11). It is crucial to identify a vulnerable subgroup of this disease to prevent the potential harm of impaired asthma control with concomitant persistent AR.

In this study, persistent allergic rhinitis was found as a risk factor for poor asthma control. In the current literature, most of the conducted studies focused on the worsening impact of allergic rhinitis on asthma. Albataineh et al conducted a cross-sectional study of 93 patients with asthma (8). They divided their sample into two groups according to asthma control as "uncontrolled" and "controlled". The uncontrolled asthma group included partly and poorly controlled asthma patients, similar to the design of this study. Asthma was found to be under control in 42.5% of their patients. They determined that atopy to two or more allergens was among the main risk factors for uncontrolled asthma.

As shown in many studies, the treatment of asthma with concomitant AR is quite important. In a prospective multi-center study by Yasuo et al. 157 patients with asthma were divided into two groups of patients, those with rhinitis and those without rhinitis (2). They compared the pulmonary function parameters, ACT scores, GINA step categories, and Visual Analog Scale scores of the two groups. The GINA steps of the patients in the group with rhinitis were higher. In the group of patients with rhinitis, step 2 asthma rates were lower, and step 4 asthma rates were higher. The distributions of GINA steps did not lead to a statistically significant difference between the groups. Even if the

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Table 3. Components of Asthma Control Test (ACT) and Score for Allergic Rhinitis (SFAR)

ACT Question 1, n (%)	1	4 (2.1)
	2	10 (5.1)
	3	42 (21.5)
	4	63 (32.3)
	5	76 (39.9)
ACT Question 2, n (%)	1	3 (1.5)
	2	12 (6.2)
	3	40 (20.5)
	4	86 (44.1)
	5	54 (27.7)
ACT Question 3, n (%)	1	3 (1.5)
	2	24 (12.3)
	3	15 (7.7)
	4	31 (15.9)
	5	122 (62.6)
ACT Question 4, n (%)	1	1 (0.5)
	2	1 (0.5)
	3	20 (10.3)
	4	33 (16.9)
	5	140 (71.8)
ACT Question 5, n (%)	1	3 (1.5)
	2	11 (5.6)
	3	40 (20.5)
	4	66 (33.8)
	5	75 (38.5)
Asthma control, n (%)	Controlled	52 (26.7)
	Uncontrolled	143 (73.3)
Nasal symptoms, n (%)	0	51 (26.2)
	1	19 (9.7)
	2	83 (42.6)
	3	42 (21.5)
Months of the year, n (%)	0	31 (15.9)
	1	148 (75.9)
	2	16 (8.2)
Rhinoconjunctivitis, n (%)	0	75 (38.5)
	2	120 (61.5)
Triggers, n (%)	0	20 (10.3)
	1	5 (2.6)
	2	170 (87.5)
Perceived allergic status, n (%)	0	60 (30.8)
	2	135 (69.2)
Previous positive allergic tests, n (%)	0	169 (86.7)
	2	26 (13.3)
Previous medical diagnosis of allergy, n (%)	0	69 (35.4)
	1	126 (64.6)
Familial history of allergy, n (%)	0	99 (50.8)
	2	96 (49.2)
Allergic rhinitis according to SFAR, n (%)	Yes	132 (67.7)
	No	63 (32.3)
Persistent allergic rhinitis, n (%)	Yes	16 (8.2)
	No	179 (91.8)

ACT: Asthma control test, SFAR: Score for allergic rhinitis

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Table 4. The comparison of the laboratory results of the two groups

	Total(n=195)	Controlled Asthma (n=52)	Uncontrolled Asthma (n=143)	p-value
WBC, 10^3/µL, mean	8285.31	8113.08	8347.94	0.381
RBC, 10^6/µL, mean	4.95	4.96	4.94	0.823
Hemoglobin, g/dl, mean	14.20	14.22	14.19	0.843
Hematocrit, %, mean	42.77	43.06	42.66	0.426
MCV, fL, mean	86.52	86.96	86.36	0.382
MCH, pg, mean	28.69	28.70	28.69	0.984
RDW, %, mean	13.40	13.26	13.45	0.524
Platelet, 10^3/µL, mean	300892.3	296519.2	302482.5	0.786
Neutrophil count, 10^3/µL, mean	4889.64	4682.50	4964.97	0.141
Neutrophil percentage, %, mean	57.43	56.61	57.73	0.450
Lymphocyte count, 10^3/µL, mean	2574.07	2514.42	2595.92	0.728
NLR, mean	2.04	1.98	2.07	0.509
Lymphocyte percentage, %, mean	31.36	32.09	31.09	0.476
ELR, mean	0.098	0.09	0.10	0.315
ENR, mean	0.054	0.05	0.06	0.544
Monocyte count, 10^3/µL, mean	629.54	634.23	627.83	0.864
Monocyte percentage, %, IQR	7.59	7.97	7.45	0.105
Eosinophil count, 10^3/µL, mean	242.77	217.50	251.96	0.198
Eosinophil percentage, %, mean	2.84	2.67	2.90	0.547
Basophil, 10^3/µL, mean	50.41	50.19	50.49	0.586
mean	9.73	9.63	9.77	0.563
PCT, %, mean	0.30	0.30	0.30	0.851
PDW, fL, mean	11.73	11.48	11.82	0.382
Eosinophilia, n (%)	92 (47.18)	21 (40.4)	71 (49.7)	0.252

: Mann-Whitney U test WBC: White blood cell count, RBC: Red blood cell count, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, RDW: Red cell distribution width, NLR: Neutrophil to lymphocyte ratio, ELR: Eosinophil to lymphocyte ratio, ENR: Eosinophil to Neutrophil ratio, MPV: Mean platelet volume, PCT: Plateletcrit, PDW: Platelet distribution width

design of the aforementioned study differed from that of this study, the insignificant difference between patients in different GINA step categories was noteworthy. Leukotriene receptor antagonists (LTRA) were also found by Yasuo et al. to have a critical role in the treatment of asthma with rhinitis (2).

We used ACT, but there are many different tools to assess asthma control. Asthma control has been assessed using different tools in previous studies. In the observational cross-sectional study conducted by Magnan et al with 14,703 patients, AR was determined to be related to a significantly worsened quality of life, more severe asthma, and difficulties in controlling asthma (19). Magnan et al. assessed the asthma control statuses of the included patients using the Juniper Asthma Control Questionnaire, a measurement instrument questioning six aspects of asthma control (19). The worsening effect of AR on asthma control was shown in many studies with different study designs and assessment tools. That aspect makes our results and implications stronger.

Because a limited number of studies were conducted specifically about persistent AR and its impact on asthma control, we focused on persistent allergic rhinitis. The cross-sectional multi-center study performed by Oka et al. had a similar design to ours (9). 520 asthma patients were included, and uncontrolled asthma was identified in 40.8% of those with AR (n:142/348), while

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this rate was 11% (n:19/172) in patients without AR. The sample of the above-mentioned study was also divided into two groups controlled and incompletely controlled asthma cases. Similar to this study, the patients in the sample of Oka et al. were mostly female similar to our findings, and 25.4% (n:132) had persistent AR (9). Persistent AR was not evaluated as an independent variable and was mentioned just as a subgroup in tables. The uncontrolled asthma group had significantly higher persistence and severity of rhinitis. The authors showed an increased degree of significance with their multi-center design and high number of persistent AR cases, even though persistent AR was not an independent parameter alone.

In the case-control study by Silva et al. it was reported that patients with moderate-to-severe persistent AR (n:20) had an increased ratio of abdominal muscles to chest wall volume than the control group (n:20) (10). The former group of patients also had a significantly decreased strength of the respiratory muscles and diaphragm. The inflammatory processes in persistent AR were determined to underlie changes in the respiratory muscles. Asthma control status was not compared in the study by Silva et al, but the crucial role of respiratory muscles in breathing has already been known (10). The inability to breathe would cause increased rates of dyspnea, as well as poor asthma control, which also presents mostly in the form of dyspnea. Our results were in indirect agreement with the findings of the limited number of studies reported in this section.

Few studies were conducted to explain this strong link between persistent AR and asthma. The biomarkers that are associated with the processes at the cellular level allow us to obtain evidence-based results. Objective criteria such as biomarkers were used to obtain a definitive implication. Downie et al. measured exhaled nitric oxide (eNO) values and found the seasonal variation of eNO in intermittent AR cases with intermittent symptoms due to exposure to pollen. A significant relationship between persistent AR and bronchial symptoms and bronchial hyperresponsiveness was shown (20). Similarly, fractional exhaled nitric oxide (FeNO) and nasal nitric oxide (nNO) values were measured in a healthy group, an AR group, and an asthma and AR group. The three observational groups had higher FeNO levels than the healthy group, and the AR-asthma group had higher FeNO levels than the AR and asthma groups. The results demonstrated the worsening impact of AR on the management of asthma through objective biomarkers of inflammatory processes (21).

Th17 lymphocytes and IL17A were shown to have a crucial role in pathological immune reactions in persistent AR and asthma cases (22). Gorska-Ciebiada et al. researched soluble intercellular adhesion molecule 1 (sICAM-1) and tumor necrosis factor-α (TNF-α) and found that patients with persistent AR and asthma together had higher levels of sICAM-1 and TNF-α than patients with AR alone. In the same study, sICAM-1 was found to be correlated with disease severity in AR (23).

The limitations of this study were that there were no patients with persistent AR in the controlled asthma group and that skin prick testing was not performed in all patients. To obtain clear implications and prevent the negative effects of the unavailability of skin prick tests, SFAR was used as a validated assessment tool. According to our evidence-based evaluation, we expect that more patients with persistent AR can be included by designing a larger cohort, but the significant results would lead to the same implications.

CONCLUSION

The sample of this study was divided into two groups "controlled" and "uncontrolled" asthma like other samples in similar studies in the literature. This multi-center cohort study was remarkable in that it employed a design that allowed us to obtain more definitive implications. Patients with persistent allergic rhinitis constitute a vulnerable subgroup of allergic rhinitis cases and the presence of persistent allergic rhinitis is associated with poor asthma control. Most asthma patients who are admitted to policlinics have persistent AR because of long-term symptoms. Patients with intermittent allergic rhinitis are admitted less frequently to the pulmonology policlinics. Those patients with persistent symptoms of rhinitis cause major problems in public health with the increased healthcare costs. Patients with asthma and concomitant persistent allergic rhinitis should be treated and followed up considering their higher risk

of poor asthma control. This study may help physicians manage the optimal treatment and follow-up of asthma.

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